# Conference Day Two

## SATURDAY, SEPTEMBER 20, 2014

<table>
<thead>
<tr>
<th>TRACK A</th>
<th>TRACK B</th>
<th>PARA-PROFESSIONAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>White River E</td>
<td>White River F</td>
<td>White River D</td>
</tr>
</tbody>
</table>

### BREAKFAST in Exhibit Hall
- **7:45 – 8:25 am** Cat Friendly Practice Panel: In Our Experience – White River G
- Included in your registration

### NETWORKING REFRESHMENT BREAK in Exhibit Hall
- **10:15 – 10:45 am**
- Included in your registration

### LUNCH in Exhibit Hall
- **12:15 – 1:15 pm** Lunch & Learn: Chronic Kidney Disease – White River G
- *Separate registration required*
- *Included in your registration*

### FUN RUN / FREE TIME
- **6:30 – 10:30 pm**
- Separate registration required

---

- **7:30 – 8:30 am**
- Nutraceuticals in Feline Liver Disease
  Dr. Sharon Center

- **8:30 – 9:20 am**
- Chronic Diarrhea: What’s the Cause?
  Dr. Kenneth Simpson

- **9:25 – 10:15 am**
- Managing Cats with Chronic Gastrointestinal Disease
  Dr. Kenneth Simpson

- **10:15 – 10:45 am**
- ICU Boot Camp: What You Should Know on Day One!
  Paula Plummer

- **10:45 – 11:35 am**
- Feline Friendly Handling & Restraint
  Paula Plummer

- **2:00 – 2:50 pm**
- Diagnosis & Management of Feline Diabetes Mellitus
  Dr. Catharine Scott-Moncrieff

- **2:55 – 3:45 pm**
- Diabetic Ketoacidosis: Understanding Pathophysiology is Critical to Treatment
  Dr. Catharine Scott-Moncrieff

- **3:45 – 6:30 pm**
- Nutraceuticals in Feline Liver Disease
  Dr. Sharon Center

- **6:30 – 10:30 pm**
- Fibropolyctic Feline Liver Disease Syndromes
  Dr. Sharon Center

- **7:45 – 8:25 am**
- Stem Cell Therapy in Feline Chronic Enteropathy: In Theory – Bench Top Research
  Dr. Craig Webb

- **8:30 – 9:20 am**
- Stem Cell Therapy in Feline Chronic Enteropathy: In Practice – Clinical Application
  Dr. Craig Webb

- **9:25 – 10:15 am**
- Diagnosis & Management of Feline Diabetes Mellitus
  Dr. Catharine Scott-Moncrieff

- **10:15 – 10:45 am**
- Diabetic Ketoacidosis: Understanding Pathophysiology is Critical to Treatment
  Dr. Catharine Scott-Moncrieff

- **10:45 – 11:35 am**
- The Feline Diabetic: Understanding the Disease
  Heather Lynch

- **11:40 – 12:30 pm**
- The Feline Diabetic: Successful Management
  Heather Lynch

- **12:30 – 2:00 pm**
- LUNCH in Exhibit Hall
  Included in your registration

- **2:00 – 2:50 pm**
- Diagnostic Testing for Hyperthyroidism in Cats: More Than Just T4
  Dr. Mark Peterson

- **2:55 – 3:45 pm**
- What’s the Best Treatment for Hyperthyroidism? Antithyroid Drugs, Surgery, Diet, or Radioiodine?
  Dr. Mark Peterson

- **3:45 – 6:30 pm**
- The Unstable Feline Diabetic Patient
  Paula Plummer
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 (Tecirlioglu 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


NOTES:
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 immunomodulatory 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 T cell 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 immunomodulatory 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 regulatory 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, 1-2x10⁶ 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 (1.5x10^6 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® Regenerative 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 an 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 Regenerative 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 improvement 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.

**Suggested Reading**


**NOTES:**
NOTES:
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 (eg., 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 T4 concentration that is clearly high.1-3 Serum total T3 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 T4 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 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 T4 concentrations between all of these assay methods is generally good, any of these different assays can occasionally provide serum T4 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 T4 value. Although most T4 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 T4 values) in euthyroid cats.3 If a high serum T4 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 T4 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 T4 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 T4 (or free T4) concentration.

Hyperthyroid Cat but Normal Serum T4 Concentration

Although serum total T4 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 T4 within the reference range.
limits.\textsuperscript{1-3} Such T\textsubscript{4} values are usually within the mid- to high-end of the reference range. Thus, finding a single reference range T\textsubscript{4} value does not preclude such a diagnosis.

In general, there are 2 possible reasons why a hyperthyroid cat could have a normal T\textsubscript{4} value. (1) In early or mildly affected cats, serum total T\textsubscript{4} concentrations can fluctuate in and out of the reference range.\textsuperscript{3} 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\textsubscript{4} concentrations. In early or mildly hyperthyroid cats (no concurrent illnesses), serum total T\textsubscript{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\textsubscript{4} concentrations to below the reference range in euthyroid cats.\textsuperscript{1,10,11} Similarly, marginally elevated serum total T\textsubscript{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.\textsuperscript{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\textsubscript{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 T\textsubscript{4}, measure free T\textsubscript{4} or TSH, perform dynamic thyroid function testing, or do thyroid scintigraphy.

**Repeat Total T\textsubscript{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\textsubscript{4}, confirming the diagnosis. On the other hand, in cats without overt underlying disease, simply repeating the serum T\textsubscript{4} concentration in 2 weeks may be diagnostic if the T\textsubscript{4} is fluctuating in and out of the reference range.\textsuperscript{13} Again, the veterinarian should never hesitate to repeat the serum T\textsubscript{4} test using a different technique, with RIA or CEIA being preferred in such cats.\textsuperscript{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.\textsuperscript{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\textsubscript{4} values.\textsuperscript{13,14}

With thyroid imaging (scintigraphy), hyperthyroid cats usually exhibit increased thyroidal uptake of radioisotope administered, either radioactive iodine (\textsuperscript{123}I or \textsuperscript{131}I) or technetium-99M as pertechnetate (\textsuperscript{99m}TcO\textsubscript{4}\textsuperscript{-}). Percentage uptake or increased thyroid:salivary ratio may be calculated; both are strongly correlated with circulating T\textsubscript{4} concentration and provide a sensitive means of diagnosing hyperthyroidism.\textsuperscript{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\textsubscript{4} Concentration**

In cats with mild hyperthyroidism and normal T\textsubscript{4} values, free T\textsubscript{4} concentrations can aid in diagnosis. In support of that, serum free T\textsubscript{4} concentrations measured by equilibrium dialysis were more consistently elevated in hyperthyroid cats (over 98\% of cases).\textsuperscript{1-3} Although the free T\textsubscript{4} was more sensitive than the total T\textsubscript{4} for diagnosing hyperthyroidism, the test specificity for free T\textsubscript{4} was poor, with up to 20\% of sick euthyroid cats having false-positive free T\textsubscript{4} results.\textsuperscript{1,15} These sick cats generally have corresponding total T\textsubscript{4} values in the lower half or below the reference range.

Caution is therefore advised in using serum free T\textsubscript{4} measurements by equilibrium dialysis as the sole diagnostic test for hyperthyroidism. It is more reliable if interpreted with a corresponding total T\textsubscript{4} measurement. A T\textsubscript{4} value within the mid- to high-normal reference range combined with a high free T\textsubscript{4} concentration is consistent with hyperthyroidism, whereas a low or low-normal T\textsubscript{4} with a high free T\textsubscript{4} is usually associated with non-thyroidal illness.\textsuperscript{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 T\textsubscript{4} assay situation further, unpublished results indicate that the present free T\textsubscript{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\textsubscript{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\textsuperscript{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\textsubscript{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\textsubscript{4} assays, most of which do not have the equilibrium dialysis step that we believed was important.\textsuperscript{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 T₄ assays over the use total T₄ estimations alone.

Many veterinarians mistakenly believe that the finding of a high free T₄ 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 T₄ test can never be considered to be a "gold standard" diagnostic test.⁴ Use of free T₄ 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 T₄ is elevated. However, caution is advised in over interpreting undetectable TSH values in cats, since the current cTSH assay has poor 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 T₄ concentrations, identification of concurrent disease, repeat total T₄ analysis, or simultaneous measurement of free T₄ allows confirmation of the diagnosis. Further diagnostic tests are rarely required. Dynamic thyroid function tests (T₃ 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 T₄ concentration remains within reference range, when the free T₄ 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 T₄ concentration is the biochemical hallmark of hyperthyroidism and is extremely specific for its diagnosis. False positive results (ie, a high T₄ 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 T₄ values, sometimes together with high free T₄ concentrations, turn out to be euthyroid.²,³,¹⁵ 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 T₄ concentration is measured in a cat without the characteristic signs of hyperthyroidism, one should always repeat the cervical palpation and verify the T₄ 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.¹⁵,¹⁴ It’s extremely important to remember that hyperthyroidism is a clinical diagnosis and should never be based on a serum T₄, free T₄, 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

**References**


NOTES:
Introduction

Hyperthyroidism can be treated in four ways: medical management with methimazole or carbimazole, nutritional management (low-iodine diet), surgical thyroidectomy, and radioactive iodine \(^{131I}\). 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 \(^{131I}\) are “permanent” or curative treatments. 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

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). 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 ¹³¹I 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. 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 ¹³¹I therapy to determine the effect of restoring euthyroidism on renal function.

However, medical management has many disadvantages. 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 T₄ values. 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. 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. 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.

Temporary hypothyroidism develops in most cats after unilateral thyroidectomy, with serum T₄ and T₃ 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-T₄ is recommended starting on the day of discharge. In these cats, life long replacement therapy is generally recommended.

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.

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. 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).

References

11. Peterson ME. Treatment of hyperthyroidism and concurrent renal disease: is the "Tapazole trial" necessary? In: 29th Annual Veterinary Medical Forum (American College of Veterinary Internal Medicine) 2011;104-106.
25. Peterson ME. Diagnosis and management of iatrogenic hypothyroidism. In: Little SE, ed. August's Consultations in Feline Internal Medicine, Elsevier; 2014:in press.
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, 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 pathomechanisms 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
- Partial obstruction- intussusception, foreign object, neoplasia, congenital anomalies
Structural
- 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
Laboratory Evaluation of Chronic Small Bowel Diarrhea

Fecal Analysis

Giardia (cysts-ZNSO4, IFA, ELISA), Cryptosporidium (IFA), Coccidia, Trichomonas faves (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 been 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, eosinophilic enteritis or hypereosinophilic syndrome. Neutrophilia ± a left shift may be encountered in inflammatory or infectious conditions. Lymphopenia may be associated 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/O 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 hypoalbuminemia 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 concentrations 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 hypoalbuminnaemia in patients with intestinal signs.

Serology and hormone assays

T₄, 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 (at 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

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 hepatobiliary 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 morphology, 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.
References


NOTES:
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 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 Siamese. Culture based studies have shown fewer luminal 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 intestinal 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? corticosteroids? 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, inappetence 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 rare 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 hepatobiliary disease and pancreatitis - "triaditis" - so the clinician must consider these disorders (Ultrasoundography 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 cobalamin tends to support a diagnosis of severe IBD or GI lymphoma.

Ultrasonographic 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 or 3) 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 (21 days) 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 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
prognosis for lymphoplasmytic enteritis is variable and depends on its severity and the presence of concurrent 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 systems, 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 inappetance 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 absence 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 “lymphoplasmytic 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 lymphadenopathy 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 FeLV 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, perioral 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 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

References and Further Reading


NOTES:
NOTES:


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.

References


NOTES:
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.

\[ \text{Osmolality} = 2 \times (\text{Na} + \text{K}) + 0.05 \times (\text{Glucose}) + 0.33 \times (\text{BUN}) \]

(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).
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 1. Electrolyte Supplementation**

<table>
<thead>
<tr>
<th>Serum Potassium Concentration (mEq/L)</th>
<th>Potassium Chloride Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3.5 (maintenance)</td>
<td>0.05–0.1 mEq/kg/H</td>
</tr>
<tr>
<td>3–3.5</td>
<td>0.1–0.2 mEq/kg/H</td>
</tr>
<tr>
<td>2.5–3</td>
<td>0.2–0.3 mEq/kg/H</td>
</tr>
<tr>
<td>2–2.5</td>
<td>0.3–0.4 mEq/kg/H</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>0.4–0.5 mEq/kg/H</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum Phosphorus Concentration (mg/dL)</th>
<th>Potassium Phosphorus Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–2.5</td>
<td>0.03 mmol/kg/H</td>
</tr>
<tr>
<td>1.5–2</td>
<td>0.06 mmol/kg/H</td>
</tr>
<tr>
<td>1–1.5</td>
<td>0.09 mmol/kg/H</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>0.12 mmol/kg/H</td>
</tr>
</tbody>
</table>
### 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 complications 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 CO₂ 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 identify 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.

### References


NOTES:
NOTES:
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 asymptomatic 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/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. 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). 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.

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.

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.

References

NOTES:
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. 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.

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. 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. 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.

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. 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. 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. 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.

References

NOTES:
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 is 40% then a PaO2 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 “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
✓ 1 gram (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

References
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.

NOTES:
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)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Concentration</th>
<th>Route of Administration</th>
<th>Approximate Duration of Action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butorphanol</td>
<td>0.2-0.04 mg/kg</td>
<td>10 mg/ml</td>
<td>SQ, IM or IV</td>
<td>45 minutes</td>
<td>IM administration takes 15 minutes to take effect and IV administration takes 2-5 minutes to take effect.</td>
</tr>
<tr>
<td>Dexmeditomidine</td>
<td>0.002-0.01 mg/kg</td>
<td>0.5 mg/ml</td>
<td>IM/IV</td>
<td>30-45 minutes</td>
<td>Lower doses to be used in conjunction with other drugs or if giving IV.</td>
</tr>
<tr>
<td>Ketamine</td>
<td>2-5 mg/kg</td>
<td>100 mg/ml</td>
<td>IM/IV</td>
<td>30-45 minutes</td>
<td>Lower doses to be used in conjunction with other drugs or if giving IV.</td>
</tr>
<tr>
<td>Acepromazine</td>
<td>0.025-0.05 mg/kg</td>
<td>10 mg/ml</td>
<td>SQ, IM or IV</td>
<td>30 minutes</td>
<td>Use only if indicated in the patient. Better results are seen when used in conjunction with butorphanol. Decrease dose in older, compromised patients.</td>
</tr>
</tbody>
</table>

*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

References:
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. In cats, the incidence is 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. 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. 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. 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. 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. 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. 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. 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. 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. 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. 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.

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. 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.

Standard Presentation/Clinical Signs

There are four Standard Clinical Signs that are present with both primary presentation and poorly controlled diabetics:

- **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. 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 treatment2. 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.3

- **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 of all species. 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**
  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. 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. Cats with fasting blood glucose 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.

**References**

1. 2011 Diabetes Fact sheet. CDC
8. Rand – Remission VE CLLIN NA
11. MK Reeve-Johnson, JS Rand, D Vankan, et al. Diagnosis of Prediabetes in cats: Cutpoints for Impaired Fasting Glucose and Impaired Glucose Tolerance in Cats 8 Years and Older Usine Ear or Paw Samples and a Prortable Glucose Meter Calibrated for Cats. ACVIM Forum 2013
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 confident: 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 < 60mg/dL, should not receive insulin
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. 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 confident: 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 ≤ 60mg/dL, should not receive insulin

American Association of Feline Practitioners
2014 Conference ● September 18 - 21, 2014 ● Indianapolis, IN

The Feline Diabetic: Successful Management
Heather Lynch, LVT

Para-professional
- 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. Likely 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**

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, 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.
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\textsuperscript{10,11}


<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>Eats all food</th>
<th>Eats less than</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500 (&quot;Hi&quot;)</td>
<td>units</td>
<td>units</td>
</tr>
<tr>
<td>450-500</td>
<td>units</td>
<td>units</td>
</tr>
<tr>
<td>375-449</td>
<td>units</td>
<td>unit</td>
</tr>
<tr>
<td>300-374</td>
<td>units</td>
<td>unit</td>
</tr>
<tr>
<td>250-299</td>
<td>units</td>
<td>unit</td>
</tr>
<tr>
<td>200-249</td>
<td>units</td>
<td>unit</td>
</tr>
<tr>
<td>150-199</td>
<td>units</td>
<td>unit</td>
</tr>
<tr>
<td>*120-149</td>
<td>units</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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**

**Parameter used for dosage adjustment**

<table>
<thead>
<tr>
<th>Step 1: Initial dose and first 3 days</th>
<th>Initial Dose on Insulin Dosage Chart - Veterinarian Directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>Try not to increase dose for 1 week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2 : Post induction changes</th>
<th>Change Insulin Dosage Chart - Veterinarian Directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketonuria or history of Ketones &amp; &gt;300 mg/dL (16.7mmol/L) (after 24-48 hours of treatment)</td>
<td>Start at 0.5 IU/Kg of ideal body weight BID</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2 : Post induction changes</th>
<th>Change Insulin Dosage Chart - Veterinarian Directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase every 3-5 days by 0.5-1.0 IU/cat BID</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2 : Post induction changes</th>
<th>Change Insulin Dosage Chart - Veterinarian Directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase every 5-7 days by 0.5 IU/cat BID</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3: Dosage Maintenance Goal glucose 80-200 mg/dl (4.4-11mmol/L)</th>
<th>Change Insulin Dosage Chart - Veterinarian Directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase dose by 0.5-1.0 IU/cat BID depending on dose of insulin and the degree of hyperglycemia</td>
<td></td>
</tr>
</tbody>
</table>

**ADDITIONAL STEPS FOR REMISSION GOAL CATS**

<table>
<thead>
<tr>
<th>Step 4: Dosage Reduction</th>
<th>Change Insulin Dosage Chart - Veterinarian Directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Dosage chart insulin not given if glucose &lt; 110mg/dL (6.1mmol/L)</td>
<td>Insulin dosage chart phases out insulin administration with normoglycemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 4: Dosage Reduction</th>
<th>Change Insulin Dosage Chart - Veterinarian Directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change the insulin dosage chart back to only administer insulin if blood glucose 150mg/dL (8.3mmol/L) or greater</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 5: Remission Euglycemia for a minimum of 14 days without insulin.</th>
<th>Change Insulin Dosage Chart - Veterinarian Directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose checked before feeding once a week, if glucose &gt; 180 (8.3 mmol/L) restart insulin at last effective dose</td>
<td></td>
</tr>
</tbody>
</table>
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.

**References/Suggested Reading**

**NOTES:**
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 diuresis 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 euvoletic 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 ml of the solution should be run 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 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)

References

7. Small Animal Critical Care Medicine, Silverstein and Hopper, Saunders, Elsevier, St. Louis, Missouri, 2009.

NOTES:
What Every Technician Should Know about Feline Hyperthyroidism
Paula Plummer, LVT, VTS (ECC, SAIM)

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 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 a 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.

**References**


**NOTES:**

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
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. 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 straightforward 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. SDMA increases in older cats as GFR declines and is not influenced by lean body mass; therefore, unlike creatinine, it is a sensitive indicator of renal function in older cats as they lose muscle. 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). A 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Renal Azotemia</th>
<th>Creatinine</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 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 Proteinuria in Cats with CKD

<table>
<thead>
<tr>
<th>Urine Protein:Creatinine Ratio (UPC)</th>
<th>Substage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.2</td>
<td>Non-proteinuric (NP)</td>
</tr>
<tr>
<td>0.2-0.4</td>
<td>Borderline proteinuric (BP)</td>
</tr>
<tr>
<td>&gt;0.4</td>
<td>Proteinuric (P)</td>
</tr>
</tbody>
</table>

Table 3: IRIS Substaging by Blood Pressure in Cats with CKD

<table>
<thead>
<tr>
<th>Systolic BP in mm Hg</th>
<th>Diastolic BP in mm Hg</th>
<th>Substage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>&lt;95</td>
<td>Minimal risk (N)</td>
</tr>
<tr>
<td>150-159</td>
<td>95-99</td>
<td>Low risk (L)</td>
</tr>
<tr>
<td>160-179</td>
<td>100-119</td>
<td>Moderate risk (M)</td>
</tr>
<tr>
<td>&gt;180</td>
<td>&gt;120</td>
<td>High risk (H)</td>
</tr>
</tbody>
</table>

*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. Results from one study are summarized in the table 4 below. 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.

Table 4: Survival time by IRIS Stage

<table>
<thead>
<tr>
<th>IRIS Stage</th>
<th>2b*</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (days)</td>
<td>1,151</td>
<td>778</td>
<td>103</td>
</tr>
<tr>
<td>Range (days)</td>
<td>2 – 3,107</td>
<td>22 – 2,100</td>
<td>1 – 1,920</td>
</tr>
</tbody>
</table>

*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). 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.

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 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. 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.

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.\textsuperscript{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

<table>
<thead>
<tr>
<th>IRIS Stage</th>
<th>Target serum phosphate conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.7 – 4.6 mg/dL 0.9-1.5 mmol/L</td>
</tr>
<tr>
<td>2</td>
<td>2.7 – 4.6 mg/dL 0.9-1.5 mmol/L</td>
</tr>
<tr>
<td>3</td>
<td>2.7-5.0 mg/dL 0.9-1.6 mmol/L</td>
</tr>
<tr>
<td>4</td>
<td>2.7-6.0 mg/dL 0.9-1.9 mmol/L</td>
</tr>
</tbody>
</table>

Potassium Supplementation

Approximately 20% to 30% of cats with CRF are hypokalemic.\textsuperscript{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\textsuperscript{14} and the IRIS treatment guidelines\textsuperscript{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.\textsuperscript{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.\textsuperscript{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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Frequency</th>
<th>Route</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal diet</td>
<td>Achieve and maintain ideal body weight</td>
<td>Ad libitum or meal feed 2 to 3 times daily</td>
<td>PO</td>
<td>Slow progression, prolong survival, control hyperphosphatemia</td>
</tr>
<tr>
<td>SQ fluid therapy</td>
<td>75–150 ml/cat</td>
<td>q 24–48h</td>
<td>SQ</td>
<td>Maintain hydration</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>2 mg/cat</td>
<td>BID</td>
<td>PO</td>
<td>Stimulate appetite</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>1/4 of 15-mg tablet or 1.88 mg (compounded)</td>
<td>Every 3rd day Every other day</td>
<td>PO</td>
<td>Stimulate appetite Antiemetic</td>
</tr>
<tr>
<td>Miropitant citrate (Cerenia®)</td>
<td>4 mg (1/4 of 16-mg tablet)</td>
<td>Once daily</td>
<td>PO</td>
<td>Antiemetic</td>
</tr>
<tr>
<td>Aluminum hydroxide and Aluminum carbonate</td>
<td>30–90 mg/kg/day (can go higher)</td>
<td>Dose divided and given with meals</td>
<td>PO</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Lanthanum carbonate (Fosrenal®, Renalzin®)</td>
<td>200 mg</td>
<td>TID with meal</td>
<td>PO</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Calcium carbonate and magnesium carbonate (Pronefra®)</td>
<td>0.25 ml/kg</td>
<td>BID with meal</td>
<td>PO</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Sevelamer hydrochloride (Renalgel®)</td>
<td>200 mg</td>
<td>TID with meal</td>
<td>PO</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Chitosan and calcium carbonate (Epakin®)</td>
<td>1 gm/5 kg</td>
<td>BID with meal</td>
<td>PO</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Potassium gluconate</td>
<td>2 mEq/4.5 kg</td>
<td>BID with food</td>
<td>PO</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>40–60 mg/kg</td>
<td>BID or TID with food</td>
<td>PO</td>
<td>Hypokalemia Metabolic acidosis</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>8–12 mg/kg</td>
<td>BID to TID</td>
<td>PO</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>0.625 mg in cats &lt;4 kg; 1.25 mg in cats &gt;4 kg</td>
<td>q 24 hr</td>
<td>PO</td>
<td>Hypertension</td>
</tr>
<tr>
<td>r-HuEPO</td>
<td>100 U/kg</td>
<td>3 X weekly*</td>
<td>SQ</td>
<td>Anemia</td>
</tr>
<tr>
<td>Darbopoetin (Aranesp®)</td>
<td>0.5–1.0 µg/kg</td>
<td>Weekly*</td>
<td>SQ</td>
<td>Anemia</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>50 mg</td>
<td>q 3 – 4 weeks</td>
<td>IM</td>
<td>Iron supplementation</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>50–100 mg</td>
<td>Once daily</td>
<td>PO</td>
<td>Iron supplementation</td>
</tr>
<tr>
<td>Benazepril</td>
<td>0.5 – 1 mg/kg</td>
<td>SID</td>
<td>PO</td>
<td>Proteinuria, hypertension</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>2.5-3.5 ng/kg</td>
<td>SID</td>
<td>PO</td>
<td>Prevent or treat renal 2° hyperparathyroidism</td>
</tr>
</tbody>
</table>

*Decrease dosing interval once target hematocrit has been achieved.

References


NOTES: