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Metabolic Encephalopathies (Part II): It's More Than Just HE

Ann Bilderback, DVM, DACVIM (Neurology)

Metabolic encephalopathy is a clinical syndrome resulting from disorders of metabolism. Due to the extremely high metabolic demands of the brain, systemic abnormalities that interfere with its energy metabolism may result in clinical signs of encephalopathy. The majority of metabolic diseases lead to diffuse, symmetrical forebrain signs because the cerebral cortical neurons are the most susceptible to dysfunction of energy metabolism. Clinical signs can be acute or chronic in onset and signs may wax and wane. Although the most well known metabolic encephalopathy is hepatic encephalopathy (HE), there are numerous other metabolic causes of encephalopathy. Treating the clinical signs of encephalopathy in these patients generally depends on treating the underlying metabolic disease. The topics of hepatic, renal and hypoglycemic encephalopathies were introduced in Part I of this two part series. In this article electrolyte, endocrine, thiamine deficiency, hypertensive, organic aciduria, and mitochondrial encephalopathies will be discussed. This article is meant as an introduction to the various causes of metabolic encephalopathies; an in-depth discussion, particularly diagnosis and treatment, is beyond the scope of this article.

Electrolyte-Associated Encephalopathy

Sodium (Na+) and calcium (Ca++) imbalances can cause encephalopathy, with severity typically correlating with how rapidly the imbalance develops. The prognosis for reversing the encephalopathy due to electrolyte disturbances is favorable. However, the overall prognosis for the individual patient varies and depends on the underlying disease process responsible for the electrolyte imbalance. There are many possible causes of these electrolyte disturbances and treatment for the underlying disorders which is beyond the scope of this article.

Calcium

Hypercalcemia can cause decreased excitability of neuronal cell membranes as well as direct toxic damage to neurons. Neurologic signs of hypercalcemia can include listlessness, dullness, and lethargy.

Hypocalcemia may lead to increased excitability of neuronal cell membranes as well as abnormal neurotransmission. Neurologic signs of hypocalcemia include facial rubbing, muscle twitching, cramping, tremors, ataxia and seizures.

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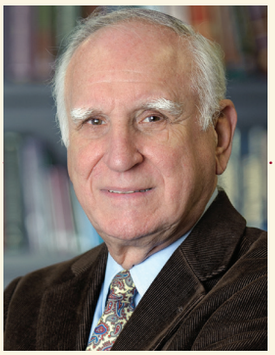
A Note from the Editor



Last month, LIVS celebrated its twenty first year as the first specialty referral hospital on Long Island and it continues to uniquely offer Medical Infrared Imaging, 3 Tesla MRI, Brachytherapy and Nano/ Micro Total Hip replacements among its services to the veterinary community. It is with great pride that we continue to offer these services in support of the regional veterinary community.

Summer brings on accidents and injuries of many kinds and LIVS remains open for any emergencies that may arise no matter the day or hour. Our regular appointment hours remain as before with each service ready to serve the needs of our clients and those patients referred to LIVS. Our contact number remains (516) 501-1700

A few days of temperature in the high nineties should remind us to be careful when walking our pets outside. If it feels hot enough to fry an egg on pavement, it probably can. When the air temperature is 90 degrees, the asphalt can reach a blistering 150 degrees — more than hot enough to cause burns and permanent damage with scarring in under one minute of contact. Hot sidewalks, pavement and parking lots can not only burn paws, they also reflect heat onto dogs' bodies, increasing their risk of heatstroke. Fresh water should be provided to pets ad libitum, yet some still seem to find the water accumulated in a flower pot base quite attractive though it often contains toxic traces of the fertilizer found in plant food.

Additionally, both pets and children left in cars for even a few moments can be life threatening in 10 to 20 minutes as temperatures reach unbearable levels, as high as 160 degrees in 10 minutes when the temperature outside is 90. Law enforcement officials are permitted to break windows to rescue pets or children when found inside locked vehicles. If civilians come upon this situation, they should call the police first, and check to see if the car is unlocked before going for the glass.

We've seen the surge in flooding incidents and subsequent power outages right here on Long Island, especially after the June 30 "tornado" which laid waste to trees that came down on roads we all need to travel on get to our destinations. Electrical lines came down with the trees. Our generator at LIVS can supply the whole complex with electricity in any power emergency.

Our Jeanne O'Brien just participated in a visit to the local "Ronald McDonald House" where she entertained the children being treated at the children's hospital next door, LIJ/Northwell. She brought lots of coloring books and stories to share and was a big hit. This month she will return with other LIVS' members to bake cupcakes and cookies for those in residence. At a camp for kids (5-21) with special needs, the "Henry Kaufmann Campgrounds" in Wheatley Heights, Jeanne told the story of LIVS, what the different personnel do, and showed pictures of pets treated including birds, reptiles, dogs, even a Llama. All the participants were thoroughly enthralled.

The news is full of political stories and I quote from the "Letter from the Editor" during the last presidential primary in 2016—"After the fireworks celebrating the nation's birth, things got even more fiery as the number of candidates for the presidency "exploded."

The unexpected happened and now we are again seeing an "explosion" of candidates but only on the Democrat side. No lack of spirited commentary on either side but rivalling the ambient heat is the political scene with all candidates doing his, her or "their" best to demonize the others. A quote from the past is a propos…

"Under democracy one party always devotes its chief energies to trying to prove that the other party is unfit to rule - and both commonly succeed, and are right." — H.L. Mencken

Back to school preparations are in order and besides pens, pencils and notebooks or rather computers, backpacks and credit cards, we add inspecting and servicing the cars some of the college kids are taking back.

Dr. Meghan Umstead has extended hours to offer services to our clients and referring veterinarians and is available to consult in cases that need direction and appropriate allergic management. The Internal Medicine Department under Dr. Joshua Tumulty's direction, has expanded appointment availability for elective and emergency internal medicine consultations and ultrasound evaluations Monday through Saturdays. Dr. Curtis Dewey, associate professor and section head of Neurology/Neurosurgery at the College of Veterinary Medicine at Cornell is at LIVS regularly for consultation. Appointments can be made at 516 501-1700. Feel free to contact any of the aforementioned staff members about how they may be of service.

As before we welcome all comments, please submit them to lmarino@livs.org

Leonard J. Marino, MD, FAAP, LVT

Metabolic Encephalopathies (Part II): It's More Than Just HE

➤ *Continued from Front Cover*

The underlying cause of both hyper- and hypocalcemia should be identified and treated. However, the electrolyte imbalance itself should only be treated if clinical signs are present

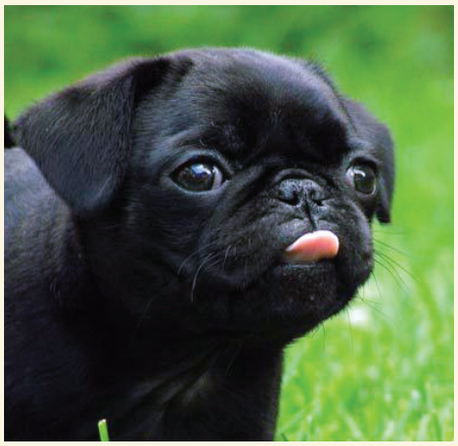
Sodium

Most sodium imbalances result from disorders of water balance and can be synonymous with hyperosmolality (hypernatremia) and hyposmolality (hyponatremia). In both instances neurological dysfunction can occur due to alterations in neuronal cell volume and function. Clinical signs typically indicate forebrain dysfunction (behavior changes, obtundation, head pressing, seizures, blindness) but can progress to involving the brainstem (ataxia, coma).

Hypernatremia can result in shrinkage of neurons due to intracellular dehydration (movement of water out of the neuron). Neuronal shrinkage can secondarily result in stretching and tearing of intracranial blood vessels and hemorrhage. Both intracellular dehydration and intracranial hemorrhage can contribute to clinical signs of encephalopathy. In cases of chronic hypernatremia (greater than 2-3 days), neurons compensate for the increased extracellular osmolality by creating intracellular substances, known as idiogenic osmoles, to prevent intracellular dehydration.

Hyponatremia can result in swelling of neurons (due to movement of water into the neuron) resulting in intracellular edema and subsequent brain edema. Neurons compensate for chronic hyponatremia (greater than 2-3 days) by extruding osmotically active intracellular components, such as potassium and amino acids, to prevent edema.

Small changes in sodium concentration that occur rapidly can cause more profound neurological dysfunction than larger more gradual changes, due to the subsequent pathology described previously (i.e. intracellular edema, intracellular dehydration, intracranial hemorrhage). Slow, gradual changes in sodium concentration can be tolerated, due to intracellular compensation described previously, with the patient not showing any signs of encephalopathy until concentrations become extreme. Some patients may remain neurologically normal with their sodium imbalance; however, rapid correction of either chronic hypernatremia or hyponatremia can subsequently result in severe encephalopathic signs. In patients with chronic hypernatremia, rapid correction can result in neuronal edema, due to the presence of idiogenic osmoles and osmotic gradient reversal inducing water to move into neurons. In patients with



chronic hyponatremia, rapid correction can result in neuronal and axonal shrinkage, due to the relative lack of intracellular osmolality inducing water to move out of the neurons/axons, and subsequent demyelination in the brainstem (especially the thalamus) which is similar to central pontine myelinolysis (CPM) in people. Clinical signs of CPM may no t become evident until days after the patient's hyponatremia has been corrected (see **Figure 1**).

The underlying cause of the sodium imbalance should be identified and both the underlying cause and the sodium imbalance itself should be treated. How rapidly the imbalance is corrected depends on whether the imbalance is acute (less than 2 days duration) or chronic (longer than 2-3 days duration). If the sodium imbalance is acute, the imbalance can be corrected rapidly. If the sodium imbalance is chronic, the rate of sodium correction should not exceed 0.5 mEq/l/hour (usually corrected over 48-72 hours) with sodium concentration monitored every 4-6 hours to avoid rapid correction and the secondary encephalopathy that can develop.

Endocrine-Associated Encephalopathies

There are numerous endocrine disorders that can lead to brain dysfunction including parathyroid disease, hyperthyroidism, hypothyroidism, diabetes mellitus, and hyperadrenocorticism. Dogs and cats with endocrine-related encephalopathy typically exhibit signs of forebrain dysfunction.

Hyperthyroidism can cause signs of encephalopathy by altering the balance of neurotransmitters. Thyroid hormones may also directly increase neuronal membrane excitability. Systemic hypertension can be seen with hyperthyroidism and may also contribute to signs of encephalopathy (see "Hypertensive Encephalopathy" later in this article). Clinical signs of hyperthyroid encephalopathy can include behavioral changes, agitation, seizures and coma.

Hypothyroid encephalopathy can be caused by a number of proposed mechanisms, including decreased neuronal oxygen consumption, accumulation of water-retaining extracellular mucopolysaccharide substances in the brain (myxedema), and atherosclerosis of major blood vessels resulting in vascular compromise to the brain. Encephalopathic signs include obtunded mental status and central vestibular signs. A rare form of hypothyroid encephalopathy can produce severe alterations of consciousness and even coma, called myxedema stupor or coma; Doberman Pinschers may be more predisposed to this syndrome than other breeds.

Both ketoacidotic and nonketotic hyperosmolar diabetes mellitus can lead to clinical signs of encephalopathy. In both forms of the disease, the pathogenesis of diabetic encephalopathy is believed to be due to the hyperosmolarity present. The predominant encephalopathic sign is obtunded mentation but these patients can progress to becoming comatose.

Excessive circulating glucocorticoids in hyperadrenocorticism may lead to neurotransmitter imbalance. Systemic hypertension is commonly associated with hyperadrenocorticism and may also lead to vascular compromise of the brain. Hyperadrenocorticoid-related encephalopathy can result in either obtundation or hyperexcitability. Central vestibular signs or forebrain signs can also be present secondary to vascular compromise

Primary hyperparathyroidism (PHPTH) is characterized by elevated PTH concentration, hypercalcemia, hypophosphatemia, and hyperphosphaturia. Clinical signs of encephalopathy secondary to PHPTH can include listlessness, depression, and lethargy. This is likely due to reduced CNS excitability secondary to the effects of hypercalcemia on the neuronal membrane. In a small percentage of patients with PHPTH, seizures may occur secondary to hypercalcemia, cerebral thromboembolic event or vasospasm.

Diagnosis of an endocrine-related encephalopathy is made by documenting clinical signs of brain dysfunction in a patient with an endocrinopathy that improves or resolves with treatment and control of the underlying endocrine disorder. Treatment of endocrine-related encephalopathies involves controlling the underlying endocrine disorder. The prognosis varies and depends on the endocrinopathy. With the exception of hypothyroid myxedema stupor/coma syndrome, the overall prognosis

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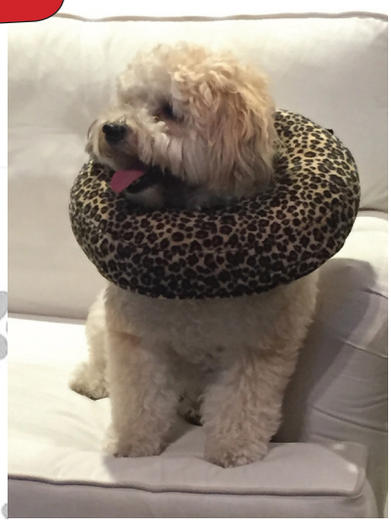

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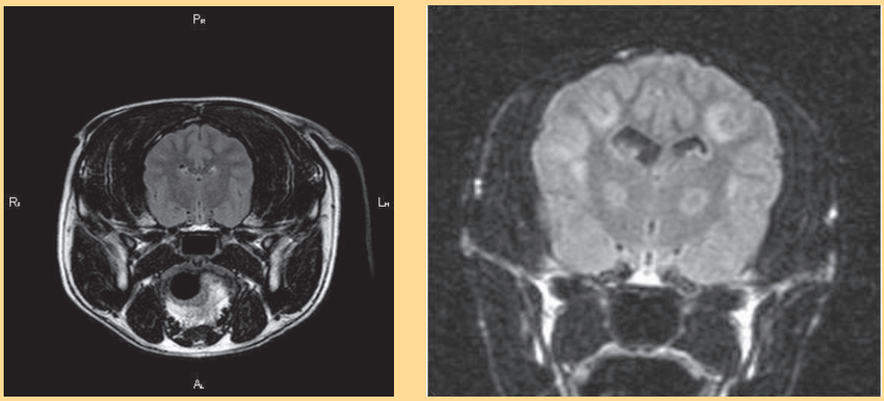

Figure 1: *Brain MRI at level of thalamus (FLAIR sequence). A) Normal Brain. B) 2.5 yr MI Shetland Sheepdog with severe hyponatremia (secondary to GI foreign body) which was corrected within 24 hours. Patient was neurologically normal while hyponatremic and at time of correction. Within 3 days of resolution of hyponatremia he was neurologically inappropriate. MRI reveals bilaterally symmetrical hyperintense (bright) lesions within the thalamus secondary to CPM. Clinical signs resolved with time and patient was neurologically normal within 2 weeks.*

for the reversal of encephalopathic signs is good with appropriate treatment and control of the underlying endocrine disorder.

Thiamine Deficiency

Thiamine (Vitamin B1) is an essential dietary requirement in small animals as it is a necessary component of carbohydrate metabolism. Thiamine deficiency results in impaired cerebral energy metabolism, focal lactic acidosis, neuronal excitotoxicity, and blood-brain barrier breakdown. This can result in polioencephalomalacia (i.e. cerebrocortical necrosis) with bilaterally symmetrical edema, necrosis and hemorrhage of brainstem nuclei.

The clinical signs differ between dogs and cats with thiamine deficiency. Dogs typically present with dilated unresponsive pupils and mild ataxia progressing to abnormal mentation, hyperesthesia, tetraparesis, seizures and opisthotonus. Cats, on the other hand, present with central vestibular signs, head tremors, mydriasis, and cervical ventroflexion (e.g. appearing as if they cannot lift their head).

Thiamine deficiency can be due to decreased intake, impaired absorption secondary to gastrointestinal disease, hepatic disease, increased use of thiamine due to fever or infection, or increased urinary loss. Thiamine deficiency has been reported in dogs and cats fed thiamine deficient diets, fresh fish diets containing thiaminase, or sulphur dioxide-preserved meat.

Thiamine deficiency can be suspected based on signalment, clinical signs, and dietary history. Deficiency can be confirmed with thiamine metabolite assays of blood, by measuring erythrocyte transketolase activity or a presumptive diagnosis may be made with a urinary organic acid profile analysis. Resolution of clinical signs following treatment with thiamine supports the diagnosis. MRI findings in dogs and cats reveal non-contrast enhancing bilaterally symmetrical thalamic and brainstem nuclear hyperintensity on T2-weighted and FLAIR images.

The prognosis for resolution of neurologic signs with thiamine deficiency is good if the diagnosis is made early and treatment with thiamine supplementation is initiated rapidly. The long-term prognosis is dependent on the underlying disorder which should be ascertained and managed appropriately.

Hypertensive Encephalopathy

Hypertension is defined as consistently elevated blood pressures, i.e. sustained systolic pressure >160-180 mm Hg. Hypertension can be either primary or secondary (due to an underlying disease). The most common causes of secondary hypertension in dogs and cats include renal disease, hyperadrenocorticism, corticosteroid administration, diabetes mellitus, pheochromocytoma, hyperthyroidism, hyperaldosteronism, and hepatic disease.

Hypertensive encephalopathy is believed to be caused by vasogenic edema, leakage of fluid from blood vessels into the brain tissue, due to impaired vascular autoregulation and endothelial/blood vessel injury. Autoregulatory mechanisms regulate intracranial blood flow and protect local microcirculation but can only function when blood pressure is maintained between 50 mm Hg to approximately 150-180 mm Hg. Hypertension can result in hyperperfusion, breakdown of blood-brain barrier, subsequent edema with resultant elevations in intracranial pressure (ICP) and hypertensive injury to the brain, especially in acute hypertension. The edema can be severe enough to result in brain herniation, which can be fatal. With chronic hypertension, intracranial blood vessels may be chronically vasoconstricted which can result in fibrous changes and degeneration of the vasculature, predisposing to blood vessel rupture and microhemorrhages.

The most common clinical signs associated with hypertensive encephalopathy include depressed mentation, ataxia, blindness, seizures and abnormal behaviors (e.g. circling, head pressing, mentally inappropriate, etc). Diagnosis is based on the documentation of consistently elevated systemic blood pressures with appropriate neurologic signs and MRI findings of either generalized edema or hemorrhagic/ischemic vascular event.

Treatment is aimed at addressing the underlying cause (if secondary hypertension) and symptomatic treatment of the hypertension (for both primary and secondary hypertension) with antihypertensive therapy. In severely neurologic patients who are rapidly deteriorating, hyperosmolar therapy (e.g. mannitol) may aid in reducing cerebral edema and ICP. However, it is possible that mannitol can result in a transient increase in ICP; therefore, it would be ideal to try and stabilize blood pressure if possible prior to mannitol therapy. Correction of hypertension can result in improvement of clinical signs. Long-term prognosis is dependent on the ability to manage both the underlying disease process and the hypertension itself.

Mitochondrial Encephalopathy

Abnormal mitochondrial function, due to a number of potentially heritable defects, can result in various encephalopathies resulting in progressive or episodic signs of CNS dysfunction. Several breeds have been reported including Alaskan Husky, Australian Cattle Dog, Shetland Sheepdog, Yorkshire Terrier, Jack Russell Terrier, and English Springer Spaniel, although any breed can be affected. The majority of reported dogs begin to develop neurologic signs within the first year of life but there are reports of onset of neurologic signs as late as 2.5 or 6 years of age. Seizures or acute onset ataxia are typically the initial clinical signs but can subsequently progress (i.e. behavioral changes, visual deficits, tetraparesis, visual deficits, vestibular dysfunction, cerebellar dysfunction, etc) depending on the nature of the mitochondrial encephalopathy.

Antemortem diagnosis can be difficult to

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make in cases of mitochondrial encephalopathy, especially if not already suspected based on signalment. MRI may reveal bilaterally symmetric, cavitary lesions in the brain and/or spinal cord. Cerebrospinal fluid (CSF) analysis is generally normal in these dogs. Diagnosis of these disorders is based on gross and histopathologic features of CNS at necropsy. The prognosis with mitochondrial encephalopathy is poor with no known treatment. Most, if not all, cases are euthanized, usually within 2-7 months of onset of neurologic signs, due to either progression or recurrence of neurologic dysfunction.

Organic Acidurias

Organic acidurias represent a group of diseases in which there is a defect in cellular metabolism resulting in the accumulation of one or more organic acids detectable in the serum, CSF and/or urine. Most of these disorders are due to inherited deficiencies of mitochondrial enzymes with reported breeds including Staffordshire Bull Terrier, West Highland White Terrier, Maltese, Standard Poodle, Cavalier King Charles Spaniel, Labrador Retriever, and Shetland Sheepdog. Organic acidurias overlap with mitochondrial encephalopathies, with the exception that organic acidurias produce identifiable accumulated organic acids in bodily fluids. In some cases, an organic aciduria is an acquired disorder, due to a malabsorptive disorder (e.g. exocrine pancreatic insufficiency[EPI]) or a toxin (e.g. propylene glycol toxicity). Not only have dogs been reported with acquired organic acidurias but also cats with one cat developing D-lactic acidosis secondary to EPI and subsequent intestinal bacterial overgrowth and another cat with organic aciduria secondary to cobalamin (vitamin B12) deficiency.

With organic acidurias, encephalopathy develops secondary to abnormal cellular energy metabolism, toxic effects of the accumulated organic acid(s), or a combination of these two processes. Furthermore, altered oxidative cellular energy metabolism may lead to increased anaerobic energy pathways which can lead to other metabolic derangements (ketoacidosis, hypoglycemia, lactic acidosis, hyperammonemia) which can contribute to encephalopathy. Clinical signs are variable with their severity and progression, even within a specific organic aciduria disorder. In general, multifocal or diffuse CNS dysfunction is present and may be progressive and/or episodic.

Organic acidurias are diagnosed by demonstrating abnormally high levels of specific organic acids in urine, serum, and/or CSF. MRI lesions in these patients are similar to mitochondrial encephalopathies with bilaterally symmetrical lesion noted. CSF protein concentration and cytology are generally normal.

Treatment is based primarily on manipulating diet and adding vitamin supplementation to compensate for abnormal metabolic pathways. Although specific dietary changes are tailored to the needs of the patient, general recommendations include high-carbohydrate, low fat (mostly medium-chain triglycerides), low protein diet, and supplementation with L carnitine and several B-vitamins (cobalamin, thiamine, riboflavin). In cases of acquired organic aciduria, treatment involves addressing the underlying cause of the organic aciduria (e.g. EPI, toxin, cobalamin deficiency, etc). The prognosis is variable, depending on the specific organic aciduria, but overall guarded. Acquired organic acidurias have a better prognosis with the resolution of neurologic signs in some patients with treatment of the underlying disorder. ❑

Immunosuppressive Therapy - Part 1

Joshua W. Tumulty, DVM, Diplomate ACVIM (SAIM), Dept. of Internal Medicine

Glucocorticoids are the most commonly used drugs for immunosuppression in dogs and cats with immune-mediated diseases. Prednisone in particular induces rapid, nonspecific inhibition of the immune system by reducing inflammation-associated gene transcription, inhibiting intracellular signaling pathways, down-regulating cell membrane expression of adhesion proteins, and slowing cell proliferation. Systemic immunosuppression is required to treat most small-animal autoimmune diseases; however, glucocorticoids, unfortunately, modulate metabolic pathways in many nonimmune-system cell populations as well, possibly resulting in life-threatening side effects. Several potent immunosuppressive drugs developed over the past few decades in human medicine have recently made the leap to our small-animal patients, and our use of them is growing. This two-part article will review their use in veterinary patients.

In recent years the technology used to construct prosthetic limbs for humans has been applied to animals. Prosthetics are made using thermosetting laminate plastic and closed cell thermo-foams, providing a snug fit for weight bearing comfort and functional use. Prosthetic paws have a rocker bottom surface for a smoother gait, and a rubber grip on the bottom that allows for good traction on slippery surfaces and longer use of the prosthetic paw. Custom colors and cosmetic designs are available (**Fig 1**). Current technology provides a prosthetic limb for the front or hind limb so long as 40 to 50% of the radius/ulna or tibia/fibula are present.

Cyclosporine

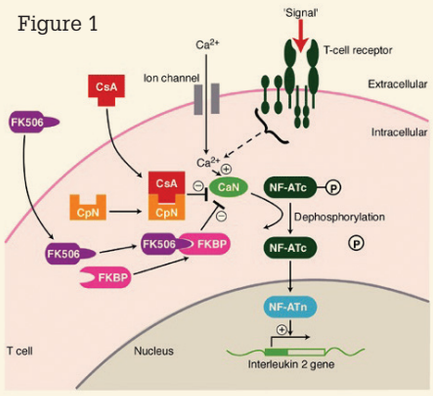
Cyclosporine is a potent immunosuppressive drug indicated for the treatment of inflammatory and immune-mediated diseases, and for organ transplantation. Cyclosporins are cyclic polypeptide macrolides originally derived from the soil fungus Beauveria nivea. Cyclosporine A is the molecule developed for commercial use. The use of cyclosporine to prevent rejection of renal allografts in people was first described in the 1970s. In veterinary medicine, oral cyclosporine received FDA approval in 2003 for treatment of canine atopy, and was recently also approved for allergic skin disease in cats. Cyclosporine has been used in an extra-label fashion for many years for renal transplantation in dogs and cats, and for a range of inflammatory and immune-mediated conditions.

Cyclosporine's primary immunosuppressive mechanism of action is inhibition of T-cell function (**figure 1**). Cyclosporine acts to inhibit calcineurin, an intracellular protein phosphatase that activates gene transcription factors. Activation of T-cells results in activation of calcineurin, which dephosphorylates inactive nuclear factor (NFAT). NFAT translocates into the nucleus, where it upregulates transcription of genes coding for several important cytokines, including IL-2, IL-4, TNF- and INF- . Calcineurin inhibitors, including cyclosporine, act by binding to intracellular cyclophilins, which are proteins that facilitate protein folding. Binding of cyclosporine to cyclophilin A creates a complex with high affinity for calcineurin. Through inhibition of calcineurin, cyclosporine specifically inhibits T-cell function and thus, cell-mediated immunity, but has little immediate impact on humoral immunity. Decreased IL-2 expression in CD4+ Th1 cells associated with cyclosporine therapy leads to inhibition of proliferation and activation of both T-helper and T-cytotoxic lymphocytes, and blunting of the immune response. Cyclosporine has also been shown to have many other local anti-inflammatory and immunosuppressive effects, especially in the skin.

Cyclosporine is a large lipophilic molecule, which must be solubilized prior to intestinal absorption. Commercial cyclosporine is available as two very different types of oral formulations. Cyclosporine was initially approved in humans as a vegetable-oil based preparation (Sandimmune®), but poor oral bioavailability caused marked variability in blood drug concentrations. A more recent formulation, an ultramicronized preparation approved in 1996 (Neoral®), forms a microemulsion upon contact with aqueous fluids, resulting in more predictable absorption. Oral bioavailability of the microemulsion is improved by up to 50% compared to the oil-based preparation. Because of the marked variability in bioavailability of the non-ultramicronized preparation, it is not recommended for oral use in small animals. Cyclosporine has a high binding affinity for red blood cells and plasma lipoproteins. Because up to 50% of the drug in blood is located in red cells, whole blood is recommended for therapeutic drug monitoring (TDM). Once in the circulation, cyclosporine distributes widely, accumulating in skin, liver, kidneys and fat, resulting in a large volume of distribution. Tissue levels exceed levels in serum by a factor of 3 to 14. Peak blood concentrations generally occur approximately 2 hours after oral administration. Blood concentrations then rapidly decrease over the remainder of the dosing interval. Extensive metabolism by the hepatic cytochrome P-450 system yields many different metabolites, some of which may retain therapeutic efficacy. Drugs that inhibit P-450 enzymes have been given concurrently with cyclosporine in order to decrease the dose needed to maintain adequate blood drug concentrations. Ketoconazole, in particular, has been used to decrease in oral cyclosporine dosages in dogs by as much as 75%.

The complexities of cyclosporine disposition in normal animals contribute to markedly variable blood drug concentrations both between patients and even within the same patient. Therapeutic management may therefore be facilitated by monitoring blood cyclosporine concentrations. Currently available methods for TDM include HPLC and a specific monoclonal RIA. HPLC has the advantage that the parent drug can be discriminated from metabolites. Since RIA measures metabolites as well as the parent drug, blood cyclosporine concentrations will therefore be higher by a factor of 1.5 to 1.7 compared to the same sample analyzed by HPLC. HPLC is labor intensive, and so methods such as RIA are most often employed in clinical situations, with the laboratory performing the assay typically providing recommendations regarding ideal target drug concentrations. In human medicine, trough blood levels were the initial basis for adjustment of drug dosages. Many studies in people have since suggested that area under the plasma drug concentration time curve or 2-hour peak drug concentrations are preferred. With peak cyclosporine concentrations requiring only a single sample, adjusting drug doses to attain target peak drug levels

Figure 1



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Immunosuppressive Therapy - Part 1

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has become the single best blood concentration measurement for use during human organ transplantation. In veterinary medicine, measurement of trough cyclosporine concentrations also prevailed for many years based on initial work done in canine and feline renal transplant studies. Recommendations from laboratories offering TDM have often involved measurement of both peak and trough cyclosporine blood levels, although target peak concentrations have not been well established in small animals.

Pharmacodynamic assays investigate a drug's effect on target cells. Many pharmacodynamic markers of the immunosuppressive effects of cyclosporine have been studied in human medicine, including lymphocyte proliferation, calcineurin enzyme activity, lymphocyte surface antigen expression, and intracellular cytokine quantification. Through pharmacodynamic monitoring, human studies have shown individually distinct degrees of calcineurin inhibitor sensitivity in patients. Pharmacodynamic monitoring shows great promise for optimizing cyclosporine therapy and delivering individualized therapy.

Cyclosporine is FDA-approved for the treatment of canine atopic dermatitis and feline allergic skin disease, and has also been used to prevent transplant rejection and to treat sebaceous adenitis, pemphigus foliaceus, anal furunculosis, feline stomatitis, inflammatory bowel disease (IBD), myasthenia gravis, noninfectious, inflammatory meningoencephalitis, pure red cell aplasia, immune-mediated hemolytic anemia (IMHA), immune-mediated thrombocytopenia (IMT), and immune-mediated polyarthritis in dogs and cats. Recent pharmacodynamic research has confirmed that canine responses to the drug are comparable to the response profile that is well recognized in people: individual responses are extremely variable from dog to dog, both in dogs receiving the same standard oral dose, and in dogs with oral doses adjusted to attain comparable blood levels. Given this high degree of variability of individual responsiveness to cyclosporine in dogs, dosing protocols should be tailored to allow for this patient-to-patient variability. In my opinion, recommended dosing protocols in dogs with chronic, non-life-threatening inflammatory skin and gastrointestinal diseases should be quite different from the protocols used in dogs with more acute and life-threatening immune-mediated diseases.

In chronic diseases that are typically not life-threatening, such as skin conditions, anal furunculosis, and mild IBD, cyclosporine is often effective at a standard, relatively low starting dose. Cyclosporine is typically given long term, with doses adjusted upwards if needed 'to effect,' based predominantly on clinical signs.

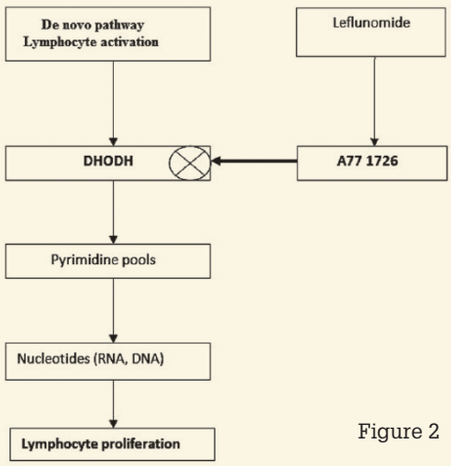

Figure 2

Typically, however, starting doses do not need to be increased and, in the long term, the drug is tapered to the lowest effective dose needed to maintain remission. Recommended starting cyclosporine doses in dogs are 5 mg/kg once daily for most skin diseases and IBD, and 5 mg/kg once to twice daily for anal furunculosis. In cats with skin conditions such as allergic skin disease, eosinophilic granuloma complex and pemphigus foliaceus, a starting cyclosporine dose of around 5 mg/kg daily is recommended. Blood concentrations are usually not necessary for treatment of these conditions, as remission of disease is the main criterion used to decide whether drug therapy is adequate. In fact, for many of these conditions, cyclosporine blood levels have been shown to have minimal correlation with remission, perhaps because the drug is selectively concentrated in tissues such as the skin. Even at standard low FDA-approved doses, some dogs can still develop significant suppression of T-cell biomarkers of immunosuppression despite very low trough cyclosporine concentrations. This could explain the phenomenon reported by some dermatologists, that individual dogs treated for atopy can develop severe secondary infections.

In dogs suffering from more life-threatening diseases such as severe IMHA and IMT, in contrast, cyclosporine must be targeted to attain effective immunosuppression as rapidly as possible. In these patients, starting cyclosporine at a low dose and adjusting doses upwards 'to effect' is not recommended. Attaining effective oral doses as rapidly as possible is essential for ensuring adequate immunosuppression whilst avoiding overdosage. Currently recommended starting cyclosporine doses for life-threatening diseases range from 5 mg/kg to 10 mg/kg twice daily. Subsequent measurement of blood drug levels and/or assessment of activated T-cell mRNA IL-2 and IFN- expression using qRT-PCR within a week of starting therapy, with dose adjustments as needed, are the best methods that are currently available to assess adequacy of therapy, and are strongly recommended in dogs with severe disease.

Side effects are uncommon with cyclosporine, with the exception of GI signs such as vomiting, diarrhea, anorexia and nausea. Giving the drug frozen and/or with food can reduce GI side effects, although such measures may also alter drug absorption profiles. Uncommonly, cyclosporine can cause an idiosyncratic hepatotoxicity, which does not seem to be dose dependent. Gingival hyperplasia and hypertrichosis have also occasionally been reported with cyclosporine. Chronic cyclosporine therapy may also predispose to neoplasia such as lymphoma. One advantage of cyclosporine is that it is not myelosuppressive. Experimentally, cyclosporine has been shown to increase some markers of platelet activation in dogs, which may be a concern in patients with IMHA, where hypercoagulability and resultant pulmonary thromboembolism can be a major contributor to patient mortality. However, to date, it has not been demonstrated whether this phenomenon is clinically relevant in IMHA patients with naturally occurring disease.

Cyclosporine is an expensive drug, and clinicians are therefore tempted to explore cheaper forms of the drug. There are many approved human generic microemulsion preparations similar to Neoral®, and these have been shown to have therapeutic equivalency in people. Studies investigating the pharmacokinetics of these preparations in dogs have not been performed, and it is not safe to assume that a generic formulation is therapeutically equivalent to the approved canine product (Atopica®). Neoral® currently costs around $2 for a 25-mg capsule and $6 for a 100-mg capsule, while the generic equivalents cost around $1 and $2 for the 25-mg and 100-mg capsules respectively. The veterinary product is priced comparably to the human proprietary products, but has the advantage of being FDA-approved and available in capsule sizes that are convenient for dosing accuracy (10 mg, 25 mg, 50 mg and 100 mg), as well as a 100 mg/ml oral suspension. Unfortunately, transdermal cyclosporine has been shown to be inadequately absorbed in cats.

Leflunomide

Leflunomide is an isoxazole derivative, immunosuppressive drug that was developed within the past two decades for treatment of

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rheumatoid arthritis and prevention of transplant rejection. Leflunomide is a prodrug for its primary active malononitriloamide metabolite, A77 1726 (teriflunomide). Malononitriloamides reversibly inhibit the mitochondrial enzyme dihydroorotate dehydrogenase, a key enzyme in pyrimidine synthesis, with resultant inhibition of the pyrimidine ribonucleotide uridine monophosphate (rUMP), and decreased DNA and RNA synthesis and G1 cell cycle arrest (**figure 2**). Leflunomide inhibits B- and T-cell function, suppresses antibody production and has anti-inflammatory effects, possibly via inhibition of de novo pyrimidine biosynthesis and cytokine-associated and IL-2-stimulated tyrosine kinase activity.

Prior to commercial development, leflunomide was made available to the transplant research group at UC-Davis. This group described treatment of small number of canine patients with refractory inflammatory and immune-mediated diseases such as IMHA, IMT, noninfectious inflammatory meningoencephalitis, systemic histiocytosis, immune-mediated polymyositis, immune-mediated polyarthritis, and pemphigus foliaceous with leflunomide, typically with promising success rates. Unfortunately, when these results were reported in the late 1990s, the drug was no longer commercially available. When leflunomide did become available as the proprietary product Arava®, drug cost limited its use in small-animal clinic patients. Only recently did an affordable generic equivalent become available and, as a result, preliminary reports of leflunomide use in small-animal patients are beginning to surface. There are still currently very few published reports discussing the use of leflunomide in dogs and cats. Recently, a case series describing the use of leflunomide in 14 dogs with immune-mediated polyarthritis reported a high response rate with few side effects.

Leflunomide appears to be very well tolerated in dogs although, if the drug attains more common usage, it is likely that less frequent but more serious side effects will be recognized. The most common side effect seen with leflunomide in dogs is occasional inappetance, lethargy and vomiting. Serious side effects occasionally reported in people include myelosuppression, cutaneous drug reactions and hepatotoxicity. In humans, traces of teriflunomide can persist for many months after drug discontinuation, and in the instance of drug reactions, cholestyramine or activated charcoal are needed to rapidly reduce drug levels. In dogs, the terminal half-life of teriflunomide is much shorter than in humans, so the potential for persistent side effects is probably significantly less. Complete blood counts and serum biochemistry (especially ALT) should be regularly monitored in small-animal patients on leflunomide.

The initial recommended starting oral dose for leflunomide in dogs is 2–4 mg/kg daily, with doses adjusted to attain a plasma trough teriflunomide levels of 20 µg/ml within a few weeks of commencing therapy. Measurement of leflunomide levels is available through Auburn University. For cats with immune-mediated polyarthritis, a leflunomide dose of 10 mg (total dose) orally, once daily, combined with methotrexate, has been suggested, with dose reductions to effect. Leflunomide comes in tablet sizes (10 and 20 mg) that are convenient for dosing our smaller patients. Proprietary leflunomide costs about $40 for a 10-mg or 20-mg tablet, while the generic equivalent is priced at around $1 for a 10-mg tablet and $1.50 for a 20-mg tablet. Leflunomide generics have an 'AB' rating by the FDA, meaning that the generic is 'equivalent' to Arava®. However, since 'equivalence' is often determined by pharmacokinetic data in healthy individuals, an AB rating does not guarantee identical performance in clinical patients.

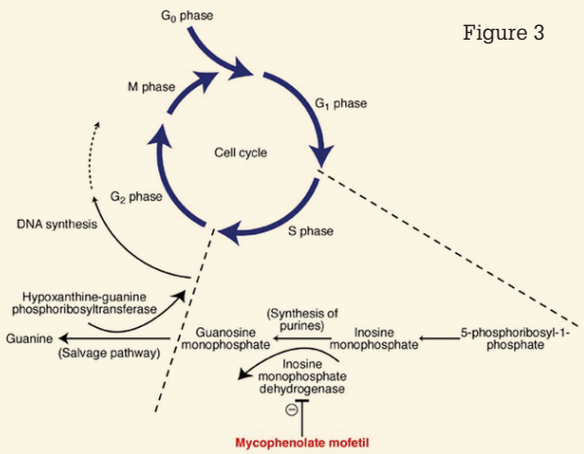

Figure 3

Mycophenolate

Mycophenolate is the synthesized prodrug form of mycophenolic acid, a selective inhibitor of inosine monophosphate dehydrogenase, an enzyme that controls the rate of synthesis of guanine monophosphate in the de novo pathway of purine synthesis (**figure 3**). Mycophenolate is a fermentation product derived from Penicillium fungi. Mycophenolic acid inhibits B- and T-cell proliferation, and decreases antibody production. Mycophenolate is primarily used in human medicine for prevention of rejection of transplanted organs, although it is also used to treat immune-mediated diseases such as systemic lupus erythematosus, IMHA, IMT and pemphigus vulgaris.

The original proprietary mycophenolate mofetil, CellCept®, and the related mycophenolate sodium, Myfortic®, were expensive, and as a result the products only achieved limited usage in small-animal medicine. However, recently, the availability of cheaper generic alternatives has led to increased usage of mycophenolate in small-animal patients. A 250-mg CellCept® capsule currently costs around $7, whereas the equivalent generic 250-mg capsule costs less than 50c. An oral suspension version of mycophenolate mofetil (200 mg/ml) is available for more convenient dosing in smaller patients. The successful use of mycophenolate mofetil in a small-animal patient with naturally occurring disease was first described in a dog with myasthenia gravis. Much of the subsequent anecdotal usage of mycophenolate for a variety of different immune-mediated diseases used dosing similar to that reported in this original paper. Mycophenolate mofetil is also available in an injectable form, and its IV use has been described during the successful stabilization of 3 dogs with myasthenia that could not tolerate oral medications. Ironically, a recent case report of 15 dogs with myasthenia gravis treated with mycophenolate mofetil reported that the drug was ineffective at attaining clinical remission.

A recommended starting dose for mycophenolate mofetil in dogs is 10–20 mg/kg once daily or divided twice daily, although sometimes GI signs (particularly vomiting and diarrhea) at the high end of the dose rate will necessitate dose reductions. Mycophenolate mofetil has variable oral bioavailability in dogs, so variability in response to therapy should also be expected. Mycophenolate has not been used widely enough to establish the frequency of serious side effects in dogs but, in people, GI signs and, less commonly, marked myelosuppression and a rare and fatal neurologic disease (progressive multifocal leukoencephalopathy) have been reported. Complete blood counts should therefore probably be regularly monitored in dogs receiving mycophenolate. In humans, GI side effects can be reduced by replacing mycophenolate mofetil with mycophenolate sodium. Mycophenolic acid in humans is primarily excreted conjugated to glucuronide and, since cats lack the glucuronyl transferases needed for glucuronidation, the drug should be used with caution in this species, although the use of mycophenolate mofetil has been described at a dose rate of 10 mg/kg twice daily, with no obvious side effects, in two cats with IMHA. ❑

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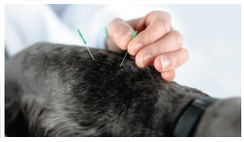

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