

Koret School of Veterinary Medicine
The Robert H. Smith Faculty of Agriculture, Food and Environment
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CLINICAL APPROACH TO THE BLEEDING PATIENT

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Bleeding is commonly encountered in critically ill veterinary and human patients. While blood transfusions are increasingly used in veterinary medicine, availability of blood products is often limited and administration is not risk free. Potential side effects of blood transfusions include transfusion reactions, hemolytic reactions, infectious agents transmission, bacterial contamination, microembolic disease, volume overload, acute lung injury and electrolyte abnormalities. When multiple transfusions are required, price is often a limiting factor. Identifying the specific cause for bleeding and use of component therapy will decrease side effects. This lecture deals with clinical approaches to the bleeding patient with emphasis on the pathophysiology, clinical assessment, diagnosis and therapy.

A diagnostic plan should include anamnesis, travel history and history of litter mates or other relatives. A thorough physical exam should follow, with special attention given to possible areas of hemorrhage. The presence of tumors or endocrine disease that may affect hemostasis should be assessed.

Evaluation of a blood smear is essential. A normal smear will have 10-20 platelets per high power field. Platelet dysfunction of primary hemostasis is most reliably assessed using a buccal mucosal bleeding time (BMBT). Activated Clotting Time (ACT) evaluates the intrinsic and common coagulation pathways. Activated Partial Thromboplastin Time (APTT) is also used to evaluate the intrinsic and common pathways. Prothrombin Time (PT) is used to evaluate the

extrinsic and common pathways.

For animals with defects of primary hemostasis secondary to vWD, desmopressin acetate (DDAVP) may be used to increase plasma vWF concentration. A transfusion of cryoprecipitate (which contains a high level of vWF) may be given, especially if bleeding is anticipated as part of a planned event (e.g., elective surgery). Cryoprecipitate is available from some animal blood banks, and should be ordered in advance. Platelet concentrate transfusions are not yet readily available for veterinary patients, but platelet-rich plasma (PRP) may be prepared from fresh whole blood for transfusion to thrombocytopenic animals in crisis. Fresh whole blood will contain viable platelets for about 8 hours after collection in CPDA.

Animals that are lacking specific coagulation factors, or who have antagonized the vitamin K-dependent coagulation factors may be treated with either fresh frozen plasma or stored plasma to restore these factors. Vitamin K may be supplemented parenterally via subcutaneous injection, or orally, if the animal is able to eat. Intravenous vitamin K may result in anaphylaxis and is not recommended. Vitamin K may be given orally until the anticoagulant has been cleared from the system (up to 2-3 months, depending on the type of rodenticide).

The therapy of DIC is a controversial one, but can involve the replacement of deficient coagulation (and anticoagulant) factors via FFP transfusion, among other therapies (such as anticoagulation).

CONGENITAL SUBAORTIC STENOSIS AND TRICUSPID VALVE DYSPLASIA IN DOGUE DE BORDEAUX DOGS

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The Dogue de Bordeaux (DdB) breed has historically gone through several bottle neck effects and its population is relatively small. The local basis for importing new DdB breeding animals is limited to only a handful of European breeders, further compromising the already limited national gene pool. Frequent, unaccounted for inbreeding is therefore likely, triggering prevalent inherited congenital defects in the local DdB population. The aim of this study was to identify a probable mode of inheritance of congenital cardiac disease in the local DdB population using pedigree analyses.

Twenty one DdB dogs have been diagnosed with subaortic stenosis (SAS) and/or tricuspid valve dysplasia (TVD) between 2004 and 2007, reflecting an over-representation relative to DdB dogs presenting to the Koret School of Veterinary Medicine over that same period of time with non-cardiac pathologies. The most probable mode of inheritance appeared to be autosomal recessive. Thirteen patients with a valid pedigree documentation descended from at least one of 3 registered sires. Thus, pedigree analyses helped identify specific ancestors which directly introduced these two genetic defects to the Israeli DdB population.

This information can be used to 1) recommend which individual dogs should be avoided for breeding purposes and 2) recommend which offspring dogs are potential carriers or actually affected and should be directly screened, accordingly, for cardiovascular defects that may exclude them from further breeding. These two activities may reduce the frequency of congenital SAS and/or TVD in the local DdB population.

A literature search revealed several genes that were postulated as contributing to normal cardiomorphogenesis. The NKX2-5 and GATA4 genes appeared as potentially important role players in the pathogenesis of SAS, TVD, and/or other congenital heart defects.

As evidence of involvement of genes in congenital heart disease is rapidly accumulating, future use of DNA samples from these as well as from prospective DdB patients may assist in identifying genetic differences between control and sick DdB dogs.

A key factor for fruitful future research in this field is tight collaboration and cooperation between owners, breeders, clinicians, and molecular biologists.

A NOVEL SUSTAINED-RELEASE GASTRO-RETENTIVE SWELLING TABLET CONTAINING AMOXICILLIN FOR COMPANION ANIMAL TREATMENT

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Beta lactam antibiotics are amongst the most commonly prescribed drugs in small animal medicine. The short biological half-life of beta lactam antibiotics and their pharmacodynamic properties indicate the need for prolonged exposure of the pathogen to an effective drug concentration in order to guarantee its elimination. Whereas the most common treatment protocol in veterinary medicine is based on immediate release orally administered dosage forms, this treatment engages rapid elimination, and a short biological half life. According to this

protocol, effective antimicrobial therapy requires multiple daily drug administration during the treatment period. As a result, one of the common reasons for treatment failure is the pet owner's low compliance to the treatment regime.

Purpose: The purpose of the present study was to design a sustained-release gastro-retentive swelling tablet containing amoxicillin for companion animals. This tablet will gain its gastro-retentivity by incorporating swelling properties when reaching the gastric medium, thereby limiting its evacuation

through the pyloric sphincter. The potential tablet will enable continuous antibiotic release in the stomach over a 5 day period following oral administration, thereby preventing the need for daily administration- Single Dose Swelling Tablet (SDST).

Materials and methods: Production of tablets was based on direct compression of amoxicillin-polymer blends. Tested SDSTs consisted of several formulations, differing in characteristics including tablet content (ratio and type of polymers), dimensions and geometric shape. Polymers used in tablet preparation differed in two main parameters: solubility (regulation of liquid absorption, leading to tablet swelling), and rigidity (endurance facing gastric contractions).

The study consisted of several sequential stages. During the first stage, different *in vitro* analytic tests were conducted in order to evaluate solubility and stability of amoxicillin, as well as drug dissolution rate from different formulations in two pH buffers. During the second stage,

tablet gastro-retentivity was evaluated *In vivo* in mature beagle dogs, using sequential X-ray radiographs. Next, pharmacokinetic profiles were determined based on plasma antibiotic concentration measurements over time.

Results: Three of the tested formulations exhibited remarkable gastro-retentivity (average retention of 52±hr). These formulations combined two types of polymers (K-100M and polycarbophil) and exhibited prolonged gastric retention compared to single polymer formulations. Tablets of a globoid geometrical shape showed prolonged gastric retention compared to cylinder-shaped tablets. A 12 hour fasting period preceding tablet administration contributed to the prolongation of gastric retention time. One of the tested tablets was characterized by a distinguishable pharmacokinetic profile, displaying steady mean antibiotic concentrations over a 5 day period. This formulation was characterized by the addition of polyethylene glycol to the polymeric matrix.

NEUROMUSCULAR DISEASES

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Neuromuscular diseases are diseases of the peripheral nerves, the neuromuscular junction and the muscles. The typical clinical presentation is abnormal gait and weakness. Although neuromuscular diseases are frequent they are underdiagnosed. Reaching the correct diagnosis is challenging due to the difficult localizing the problem to the nerve – muscle components. Many animals will be diagnosed mistakenly as a central nervous system lesion in the spinal cord. This will lead to different diagnostic procedures that will not enable diagnosis and appropriate treatment.

Polyneuropathies can involve the peripheral nerves anywhere along their pathway from the cell body in the spinal cord to the small nerve roots that emanate from the spinal cord to the lengthy peripheral nerves until they reach the muscle fiber. There are many causes for polyneuropathies, among them are immune mediated disease like polyradiculoneuritis, infection with *Toxoplasma gondii* and *Neospora caninum*, metabolic diseases like hypothyroidism and diabetes mellitus, chronic organophosphate intoxication, paraneoplastic syndrome and more.

Junctionopathies are diseases that interfere with normal synapse function like myasthenia gravis and botulism.

Polymyopathies are diseases that involve the muscle fibers: Causes include electrolyte imbalance, metabolic disorders like hypothyroidism, hyperthyroidism (cats), hyperadrenocorticism and immune mediated disease like polymyositis. History, physical and neurological examination will direct the localization to the neuromuscular system. Owners frequently will describe in addition to weakness,

coughing, regurgitation, vomiting, dysphonia and dysphagia which should raise the suspicion of cranial nerves involvement. This finding does not support focal spinal cord lesion but rather a diffused peripheral lesion. Information on vaccination history, the possibility of poison exposure, and an accurate description of the gait are also important to obtain. Physical examination helps to rule out orthopedic problems or systemic diseases that might induce weakness. Muscle pain or atrophy should also be examined. Neurological evaluation will enable in the most cases correct localization. Typically the animal will not demonstrate mental changes. Cranial nerves are often affected (mainly 7,9,10). Gait evaluation will reveal weakness usually without ataxia. The stride is usually short and stiff and sometimes tremor of the affected limbs is observed. In most cases of polyneuropathies the spinal reflexes are weak or absent. This finding cannot be explained with spinal cord lesions and indicates a diffused peripheral nerve involvement. Decreased muscle tone and severe muscle atrophy are also common findings. In polymyopathies however the animal can demonstrate normal spinal reflexes and mild muscle atrophy. Cervical ventroflexion is a common finding in cats with neuromuscular disease.

Diagnostic workup usually begin with blood hematology and biochemical profile along with urine analysis. Further diagnostic tests are commonly required. Such tests include thyroid and adrenal function, thoracic radiographs, abdominal ultrasound, serology for toxoplasma and neosporan organisms, cholinesterase blood levels, antibodies against acetylcholine receptors, Tensilone test, EMG, muscle and nerve biopsy and

CSF analysis.

The correct localization is imperative for the diagnosis of neuromuscular diseases and it can be achieved by combination of history, physical and neurological examination. Much of the

diagnostic workup does not require special equipment and can be done at the clinic. Accurate diagnosis of the disease will enable suitable treatment which will lead in many cases to the animal's recovery.

DIAGNOSTIC IMAGING OF CANINE SPIROCERCOSIS: WIDE RANGE OF PATHOLOGIC FINDINGS.

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Introduction: *Spirocerca lupi* is a nematode parasite of dogs and other carnivores. It has worldwide distribution but is most prevalent in warm climates. Dogs are the definite host and become infected by ingesting the corpophagous beetle intermediate host. After being released in the stomach of the final host (e.g. dog), the larvae penetrate the stomach wall and migrate in the wall of the arteries to the thoracic aorta, where they remain for three months. The worms reach the oesophagus from this site by direct migration through the thoracic cavity. Typically, the worms become encapsulated in nodules (granulomas) within the esophageal wall where they reach their sexual maturity.

Pathogenesis: Migrating larvae cause hemorrhages, inflammatory reactions, necrosis and abscesses in the tissues in which they migrate. Most of these lesions are not serious and heal rapidly. Larvae migrating in the walls of the thoracic aorta cause purulent panarteritis with thickening of the intima and granuloma of the adventitia. Degeneration of the elastic tissue may lead to thromboembolism, stenosis or formation of aneurysm with possible rupture of the vessel. Calcification and

ossification of the aortic wall is often seen using CT imaging.

The adult worms live in nodules in the esophageal and sometime stomach wall. These nodules eventually reach the size of a pigeon egg, in which several worms are embedded in a pus-like, crumbly, brownish mass. Large nodules in the oesophageal wall may cause obstruction and thereby interfere with prehension of food. Massive infestation may lead to esophageal rupture with consequent of mediastinitis, pneumothorax and pyothorax.

Spondylitis involving the thoracic vertebrae is often associated with the infection. *S. Lupi* appears to be an important factor in malignant tumourigenesis (oesophageal fibrosarcoma and osteosarcoma).

Affected dogs may present with lameness and thickening of the distal limbs due to hypertrophic osteopathy (HO). Aberrant migration via arterial or venous walls or possibly via a hematogeneous route may lead to the formation of nodules in the pleura, mediastinum, diaphragm, lung, trachea, bronchi, thymus, heart, lymphatics, subcutaneous tissues, stomach, spinal cord, renal capsule, urinary bladder, small intestine and rectum.

RENAL RADIOLOGY IN PET RABBITS (*ORYCTOLAGUS CUNICULUS*)

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Urinary tract disease is a common clinical presentation in pet rabbits and abdominal radiographs are used routinely for patient assessment. In other species, it is accepted that renal disease can induce changes in the radiographic size of the kidneys. Currently, such measurement in rabbits is subjective. The ratio of kidney length to the length of the second lumbar vertebra (L2) is the most widely used quantification of normal kidney size in dogs and cats, but is not well documented in rabbits. This study was designed to establish standards for the radiographic renal size in rabbits

and to determine the best radiographic measurement to use as a standard. Radiographs from 59 rabbits with presumed normal renal function were retrieved. Kidney measurements on radiographs were tested for possible association with age, weight, sex and reproductive status. This study reveals that differences in kidney size related to sex and reproductive status are detectable on radiographs and suggests that reproductive status should be considered when evaluating kidney size in rabbits. With the establishment of baseline values, abnormal kidney size can be assessed in a more objective manner.

TWO NOVEL TECHNIQUES FOR THE RELIEF OF TENSION DURING REPAIR OF LONG URETHRAL DEFECTS IN DOGS. A CADAVERIC STUDY

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Introduction: Long urethral defects unamenable to primary repair may result from any of a number of etiologies. The aims of this study were to develop a model of urethral defect unamenable to primary repair without tension, and to examine two strategies aimed at relieving the tension at the site of the anastomosis.

Materials and Methods: This study was performed on young adult male dog cadavers, weighing between 25kg and 35kg, and euthanized for reasons unrelated to this study. All dissections were performed as soon as possible after euthanasia. The caudal abdomen and the ventral aspect of the pelvis were approached by caudal reflection of the prepuce and incision of the linea alba caudal to the umbilicus. The floor of the pelvis was exposed by sharply incising and reflecting the adductor muscles.

The membranous urethra was exposed by removal of the cranial aspect of the pelvic floor. This was achieved by performing a sagittal osteotomy of the cranial ramus of the pubis at the cranial aspect of the obturator foramen, bilaterally, and a transverse osteotomy through the caudal ramus of the pubic bones at the medial aspect of the obturator foramen. The bladder and prostate were fixed cranially to prevent caudal movement of these structures. This was achieved by drilling a 2mm diameter hole in the body of the pubis, bilaterally, and passing a single strand of 1mm nylon with a swaged on needle through both holes and through the trigone of the bladder. Care was taken not to distort the locations of these structures by placing this suture.

The length of the prostatic and membranous urethra was then measured from the trigone of the bladder, cranially, to the bulb of the penis, caudally. A full thickness urethral defect was then created caudal to the prostate, in the center of the window created by removal of the pubic bone flap. The length of the urethra to be removed was initially marked by making small incisions in the urthralis muscle. Once the length between the marks had been confirmed the segment of urethra was removed by sharply incising the tissue with a scalpel. Immediately after cutting the urethra there was a retraction of the cut edges and this distance between the cut edges was measured. The urethra was then sutured by preplacing 4 full thickness sutures dorsal, ventral, medial and lateral in the urethral wall. The sutures were individually tightened and the tension on the sutures subjectively evaluated. In a pilot study performed prior to initiating this study, it was found that, in this model, 15% of the urethral length could be removed before tension at the site of the anastomosis was encountered.

The specimens were then assigned to undergo either a crural release (CR) or an ischial osteotomy (IO) in order to relieve the

tension at the anastomosis. The CR was performed by careful dissection of the origin of the crura of the penis on the ischial tuberosity. Once visualized the crural attachment was sharply incised, bilaterally. Blunt dissection was performed between the bulb of the penis and the ischial arch until the ischiourethralis muscle was observed. The muscle was elevated by sharply incising its attachments to the ishium. Blunt dissection was continued ventral to the urethra, cranially, to the level of the osteotomy. The IO was performed by identification of the origin of the crura of the penis on the ischial tuberosity. An osteotomy of the ischium was then performed in the sagittal plane. The osteotomy was performed lateral to the crura of the penis and was initiated at the obturator foramen and terminated at the ischial arch. By performing the osteotomy bilaterally, the crura of the penis and their origin on the ischium was isolated. The segment of bone with the penis attached could then be slid cranially.

After performing the procedures the cut edges of the urethra were again opposed by tightening the preplaced sutures and the tension of the sutures was subjectively evaluated. In the IO group the bone segment was moved cranially until the anastomosis could be performed without tension and the amount of cranial displacement was noted.

Three repetitions with 15% of the urethra removed were performed in each group. In addition, in both groups, urethral defects of 20% and 25% of the urethral length were performed in order to determine the maximum urethral defect that could be closed without tension using these techniques.

Results: Both CR and IO were both effective in relieving the tension encountered at the anastomosis after the removal of 15% of the urethral length. A maximum of 25% of the intrapelvic urethral length could be removed while still achieving a tension free anastomosis after performing either of the tension relieving techniques. Urethral defects longer than 25% resulted in tension at the anastomotic site subsequent to performing both CR and IO.

Discussion: Anastomosis of the urethra, without tension, can be achieved even in long urethral defects. The clinical application of these techniques is beyond the scope of this study. The application of these techniques, in clinical cases, can perhaps be considered in situations in which the alternate techniques are associated with high morbidity and mortality. It is possible that urethral defects longer than 25% of the urethral length could be approximated without tension by cranial traction on either the crura in the CR technique or the ischium in the IO technique, however, this was not evaluated in this study.

TREATMENT OF ENAMEL HYPO CALCIFICATION IN A DOG

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Enamel is the hardest and most dense structure in the body. It is produced by ameloblasts. During the period of enamel development a few deficiencies may occur which may be noted on clinical, radiological or histological examinations. In enamel hypocalcification (demineralized enamel) the enamel may be soft, poorly mineralized to the extent which it may appear yellow to brown in color. This type of deficiency is qualitative. A normal amount is produced but is deficient in mineralized substance(hypomineralized). In enamel hypoplasia (hypoplastic enamel) less enamel is produced resulting in a thinner than normal layer of enamel. This deficiency is a quantitative one. Enamel hypoplasia will appear immediately once the tooth erupts in contrast to enamel hypo-calcification which might not be visible till the abnormal enamel wears away or becomes stained. This case report describes the diagnosis and treatment of enamel hypocalcification in a dog by use of new generation restorative material.

The patient, a one year old female Pomeranian, weighing 3.35 kg was referred on the 11/27/2007 due to the discoloration of her teeth which was observed by the referring veterinarian.

Pre-operative intra oral dental radiographs were performed to determine the root formation status of the affected teeth and of the missing teeth. Based on the patient's age, clinical and radiographic examination a diagnosis of exogenous enamel hypo-calcification was made.

Treatment options for enamel hypocalcification are either restorative or exodontic. When choosing the restorative option, the defects can be restored by etching, bonding and placement of a composite restoration or, instead, topical application of fluoride if an enamel layer is still present. All options were discussed with the owner who requested conservative treatment and restorative therapy for the enamel defects whilst keeping the teeth under radiological observation to monitor for future periapical changes and or periodontal disease.

REGIONAL ANESTHESIA – NEW WEAPON FOR OLD ENEMY

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Continuous regional anesthesia provides superb analgesia for various painful conditions. In addition to its use for a wide spectrum of surgical procedures, it is also very efficient in relieving chronic and cancer pain.

Techniques for delivering this type of analgesia vary. The most important component of a system for drug delivery is a soaker or diffusion catheter that is a specially designed fenestrated catheter. These catheters can be purchased commercially or constructed homemade in a sterile manner during the surgery. A disadvantage of homemade soaker catheters is that they can only be introduced with surgical intervention. Fenestrated areas can differ in length and are designed to provide analgesia of diameter of 30 mm up to 450 mm. Catheters are placed as close as possible to the source

of pain with the fenestrated portion within the tissue. For the nerve block continuous regional anesthesia a nerve stimulator can be used to insure catheter placement close to the nerve to be blocked.

Delivery systems can vary from single dosage of a chosen drug to the syringe pumps or sophisticated elastomeric pumps. The decision of which system is to be used is based on the type of treated condition, drugs used, ease of delivery and cost factors. Drugs choice is balanced between opioids, local anesthetic drugs or combination of both.

Altogether, this type of analgesia is very effective and easy to provide with a wide range of options and can be used in long term treatment of surgical and non-surgical conditions.

PASSIVE SMOKING AND PLACE OF RESIDENCE AS RISK FACTORS FOR LYMPHOMA IN DOGS

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Background: Several case-control studies have tried to evaluate the role of cigarette smoking as a risk factor for lymphoma in humans with inconsistent and inconclusive results. Environmental tobacco smoke has not been studied as a risk factor for lymphoma in humans. Few studies have identified other environmental exposures as risk factors for lymphoma and mortality rate from lymphoma in humans. These risk factors included living in proximity to industrial plants, living in an urban county rather than a rural county, exposure to various pesticides and herbicides, and levels of solar ultraviolet radiation.

Neoplasia in household pets has been used as a model for several human cancers. As pet dogs live in close association with people and share domestic exposures with them, dogs can serve as sentinels of environmental cancer risk. Pet epidemiology studies could act as a tie-breaker when the results from traditional approaches are at odds.

We examined the relationship between passive smoking and canine lymphoma, whether residence in an urban area is a risk factor, and if there were any clusters of cases that might suggest proximity to an environmental hazard.

Methods: A hospital-based case-control study, examining the smoking habits of owners of dogs diagnosed with lymphoma compared to those of owners who brought their dogs for reasons other than lymphoma, using telephone interviews. Cases for this study include all lymphoma-diagnosed dogs which

were treated at the KSVM VTH during the years 2002-2008. Controls include dogs randomly chosen which arrived at the hospital for reasons other than cancer during 2007 and were older than 4 years of age. We also collected and compared information regarding their place of residence.

Results: 68 cases and 82 controls were included in the study. The percentage of smokers amongst the lymphoma dog owners was 50% compared to 39% amongst the controls. The odds ratio is 1.56. This difference was not statistically significant ($p=0.19$). Environmental tobacco smoke home index and the environmental tobacco smoke people index were used to reflect the intensity of cigarette smoke the dogs were exposed to. Both indexes were higher for the lymphoma group compared to the controls but this was not a statistically significant difference ($p=0.24$, $p=0.69$).

The geographic distribution of the cases and the controls was similar. There were no clusters of cases in any specific area.

Discussion: There were no statistically significant differences between the lymphoma and control groups regarding exposure to tobacco smoke or place of residence. However we did observe a trend towards higher exposure to tobacco smoke in the lymphoma group. With the accumulation of additional lymphoma cases in our hospital in the future maybe a larger survey will be able to prove our hypothesis.

THE USEFULNESS OF CREATINE KINASE AS A DIAGNOSTIC AND PROGNOSTIC FACTOR – RESULTS OF A RETROSPECTIVE STUDY OF 304 CATS

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Serum creatine kinase (CK) activity is routinely used to assess skeletal muscle damage in companion animals. Due to its short half-life, increased CK activity mostly reflects acute muscle damage. There are no large-scale studies evaluating CK as a diagnostic and prognostic marker in cats. The aim of this study was to investigate the clinical and clinicopathological findings and outcome of 3 groups of cats with markedly, moderately and mildly increased serum CK activity compared

to cats with normal CK activity (>30 -fold upper reference limit [URL], 10-30-fold URL, <10 -fold URL and within reference interval, respectively, groups 4, 3, 2 and 1, respectively). Data were retrieved from medical records of cats that were consecutively presented to the hospital and had their serum CK activity measured routinely at presentation. A total of 304 cats (103, 137, 31 and 33 cats, in groups 1, 2, 3 and 4, respectively) were included in the study. Increased serum CK

activity was common in ill cats (66%). Based on the human medicine definition, 30% of the cats had rhabdomyolysis (increased serum CK activity $> X 5$ URL). Cats that were injected within 24 hrs prior to presentation had significantly ($P<0.001$) higher median CK activity compare to cats that did not receive injections. Trauma and saddle thromboembolism (STE) were significantly more prevalent in-group 4 vs. the other groups ($P<0.001$), while pancreatitis was significantly more prevalent in-group 1 vs. the other groups ($P=0.038$). There

were significant differences between groups in hospitalization length and treatment cost. The mortality rate (natural death and euthanasia) was significantly ($P=0.017$) different in the in-group 4 vs. the other groups. In summary, serum CK activity was found to be a negative prognostic indicator, but only when extremely increased (>30 fold). It was also associated with a higher disease severity, as reflected by longer hospitalization period and higher treatment cost in cats with increased CK activity.

ANTEMORTEM DIAGNOSIS OF INTRACRANIAL AND OCULAR METASTASES OF A MIX MALIGNANT MAMMARY TUMOR.

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A 9-year old, spayed, female cocker spaniel was presented with three weeks of progressive blindness, exophthalmos and circling. Surgical excision of a recurrent malignant mixed mammary tumor was performed two months earlier. Neurological examination revealed depression, circling and leaning to the left, head turn to the same side and ambulatory tetraparesis with hypermetria of all four limbs. Bilateral, dilated, non responsive pupils, severe corneal edema and elevated intra ocular pressure (IOP) were also recorded. Neuro-anatomic localization suggested a multi-focal lesion involving the cerebral cortex, cerebellum and the eyes. Post contrast computed tomography (CT) revealed enlargement of the left lateral ventricle, an intra-axial enhancement (7-10mm) in the Diencephalon - Mesencephalon junction and cerebellar meningeal enhancement. Cerebrospinal fluid (CSF) had a markedly increased total nucleated cell count (1550 cells/ μ L, normal ≤ 3 cells/ μ L) and elevated protein concentration (49 mg/dL, normal ≤ 25 mg/dL). Cytology of the CSF revealed high number of markedly large (20-200 microns) round to

polyhedral cells of varying size, containing large nuclei with loose-chromatin and 2-5 nucleoli. These cells showed marked anisocytosis and anisokaryosis and extensive cytoplasmic vacuolation. Cytology of the aqueous humor (AH) samples showed a high cellularity of cells similar to those in the CSF. Based on these findings a tentative diagnosis of brain and ophthalmic metastases of a malignant mammary tumor was made and the dog was euthanized. Gross pathology showed multiple nodular masses of variable size (range 0.3cm to 2 cm) in the mammary lymph node, lungs and brain. Histopathology of all masses showed dense cellularity of neoplastic epithelial cells arranged in nodular to solid sheets that were cytokeratin-positive. The concurrent presence of these similar epithelial cells in the mammary lymph nodes, lungs, CNS and eyes with the history of a malignant mammary tumor led to the diagnosis of a malignant mammary tumor with distant metastasis. To the best of our knowledge, this is the first report of an *antemortem* diagnosis of CNS mammary tumor metastases based on cytological evaluation of the CSF.

RENAL AMYLOIDOSIS IN DOG: COMPARISON BETWEEN CHINESE SHAR-PEI AND NON-SHAR-PEI DOGS

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Renal amyloidosis (RA) is a heterogeneous spectrum of fibrillar diseases, characterized by extracellular deposits of insoluble β -pleated sheet proteins in the kidney, designated as amyloid. This retrospective study aimed to characterize the clinical and clinicopathologic signs and mortality of dogs with a light microscopy diagnosis of RA; we further compared these parameters between Chinese Shar Pei (CSP) and non Shar Pei (NSP) dogs. Data were retrieved from medical records of dogs presented to the teaching hospitals of UC Davis and the Hebrew University (1986-2007). Ninety dogs including 40 males and 50 females, and 15 CSP and 75 NSP were studied. Shar Peis [4.5 years, (range, 3.6-17 years)] were younger vs NSP [9.0 y, (range, 2.4-10 years); $P<0.001$]. Fifty-eight dogs (64%), including 7 CSPs (47%), and 51 NSPs (68%), had predisposing neoplastic or inflammatory (infectious and non-infectious) diseases. Five CSPs (33%) had historical familial Shar Pei fever. Infectious diseases were more prevalent in NSPs vs CSPs (75% vs 27%, respectively, $P<0.001$). Proteinuria was detected in 96% of all dogs, and the urine protein to creatinine ratio was greater in CSPs [15.9, (range, 0-75)] than NSP [6.9, (range, 0.4-23); $P=0.04$]. Correspondingly, hypoalbuminemia was more prevalent in CSPs (98%) than NSPs (71%, $P=0.004$),

and median serum albumin, was lower in CSPs [1.4 g/dL, (range, 0.5-3.1) vs NSPs [2.0 g/dL, (range, 1.0-3.8); $P<0.001$]. Median serum creatinine was 4.9 mg/dL (range, 0.6-27 mg/dL) for all dogs, but was 2-fold higher in CSPs [9.8 mg/dL, (range, 1-27.1)] vs NSPs [4 mg/dL, (range, 0.6-23.5); $P=0.03$]. Increased serum ALT ($P=0.004$) and ALP ($P=0.037$) activities were more prevalent in CSPs vs NSPs. Hyperbilirubinemia was documented in 44% of all dogs, and was more common in CSPs (80%) vs NSPs (36%; $P=0.012$). Median serum bilirubin was 0.2 mg/dL (range, 0-5.5) in NSPs vs 0.7 mg/dL (range, 0-9.7) in CSPs ($P=0.005$). Histoopathology revealed glomerular amyloid deposition in 95% of all dogs (95% in NSPs and 90% in CSPs). Medullary RA was more common in CSP (89%) vs NSP (35%; $P=0.02$), as was extra RA, detected mostly in liver (36%), pancreas (27%), and spleen (15%). Median survival time was 5 and 2 days in CSPs and NSPs, respectively, mainly due to euthanasia, with no difference between groups. In conclusion, RA is a fatal disease. CSP with RA are younger and have more severe azotemia and generalized disease vs NSP. Although renal medullary involvement was more common in CSP, as previously described, glomerular involvement and proteinuria are invariably present in CSPs in late disease stages.

EMERGING ZOONOTIC DISEASES - FACTORS AND DISEASES.

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Currently, we recognize 1415 human pathogens. 61% of these pathogens are zoonotic, e.g. animals are the reservoir, and transmission occurs directly by contact with the reservoir or indirectly by an arthropod vector (mosquitoes, ticks, fleas). 73% of the emerging diseases are zoonoses. Emerging diseases are defined as entirely novel pathogens which emerge in different circumstances (SARS, Hendra virus), diseases which have not been detected for prolonged periods and emerged in recent years (plague outbreak in Algeria after 50 years without outbreaks), pathogens which changed their characteristic animal reservoir, diseases which emerge in a new given geographical region, and pathogens, mainly speaking of bacteria present with multiple antibiotic resistant patterns, such as MRSA.

Many factors influence the emergence of specific pathogens and diseases.

Changes in land use and specifically deforestation, is the main driving force pushing toward the emergence of Nipah virus (RNA virus, family Paramyxoviridae) in Malaysia. Outbreaks also occurred in Singapore, India and Bangladesh, reaching a case fatality rate of 40-60%. The main reservoir of this virus is frugivorous bats.

The increased demand and consumption of bush terrain and as a result the increased hunting of wildlife (apes, Duiker antelopes, bats) mainly in the Congo basin (Central-West Africa) resulted in the emergence of two hemorrhagic fever viruses (Ebola and Marburg). The main reservoir of these 2 deadly viruses was recently found to be the Egyptian

Fruit bat.

Climate change appears to be one of the most distinctive factors influencing the emergence of zoonoses. Extreme weather conditions are the net result of these changes. Rift-Valley fever and Hantavirus, are two examples of diseases which emerged as a result of ENSO phenomenon (El-Nino Southern Oscillation), a major contributor to these extreme events (mainly expressed in unusual rainfall).

Many other conditions appear to influence the emergence of various pathogens and diseases. **Exotic animal trade** had brought the monkeypox virus into the U.S, carried asymptotically by African rodents. **The dramatic increase in global tourism** has exposed many travelers to entirely new zoonotic pathogens such as Simian Foamy Virus encountered by travelers when coming in contact with temple-monkeys found mainly in South-East Asia.

DEMOGRAPHIC AND BEHAVIOURAL INFLUENCES OF TNR (TRAP-NEUTER-RETURN) ON FREE-ROAMING CAT POPULATIONS IN AN URBAN ENVIRONMENT

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Continuous abandonment of pet cats to the streets, the high fecundity of the cats themselves and the abundance of vital resources in the urban environment have enabled free-roaming cat populations to reach densities as high as 1000-2500 cats per km² in this environment. These high densities can lead to public health hazards, predation on wildlife and extremely impaired welfare of the cats themselves. During the last decade, the trap-neuter-return (TNR) method has gradually become the main method of control and in many places in Israel the only method of control. In contrast to its popularity of use, TNR has been studied only in isolated or rural environments and on a relatively small scale. Indeed, only one study has examined the demographic influences of TNR in an urban environment. That study, however, was performed without control and the TNR was combined with significant rates of kitten adoption.

Over a one-year observational study, we examined four groups of free-roaming cats (n=260) that were routinely fed in the urban environment. Seventy-five percent of the cats in two groups (experimental group) were initially trapped, neutered and returned to the feeding sites; cats in two other groups (control) were left untreated.

The number of adult cats in the experimental groups increased significantly along the study period, whereas in the control groups it decreased significantly. This increase in the experimental groups was due to higher immigration and lower

emigration rates in comparison to the control groups. In the experimental (initially neutered) groups, annual presence of neutered cats was significantly higher than that of intact cats; kitten survival was significantly higher than their survival in the control groups; and a lower rate of agonistic interactions was observed compared to the control groups. It was also found that intact male cats participated in more agonistic male-male encounters than castrated cats.

Targeting the TNR method mainly at feeding groups located in urban residential neighborhoods may thus result in an increase in group size. This is the consequence of two major changes in group dynamics: on the one hand, intact cats immigrate into the neutered groups more readily; while on the other hand, neutered cats reduce their emigration rates, possibly due to a reduction in reproductive and competitive pressures. In the context of food delivery, we found the feeding groups to be time and place dependent, exhibiting non-random social interactions. In comparison to the control groups, we found less aggression in the experimental groups and, specifically, fewer agonistic neutered-neutered male encounters. This is a first report of such a phenomenon, which may contribute to a reduction in territorial behavior, and thereby conduce to the higher immigration rates of adult cats from the surroundings that was found in these groups.

METHICILLIN RESISTANT *STAPHYLOCOCCI* IN DOGS

A ZOONOTIC THREAT?

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The genus *Staphylococci* is composed of aerobic gram positive bacteria which are comensal on mucosal membranes of different animals including human. The members of the genus are usually divided by their coagulase activity, the coagulase positive members are also known for the inflection opportunism features they posses. Among them can be found the species *S. aureus*, *S. Intermedius*, *S. pseudointermedius*.

The Penicillin resistance among *Staphylococci* bacteria is a very common phenomenon among human and other animals and widely researched in recent years.

The molecular mechanism is based on genetic encoding (mecA gene). Encoded protein blocks the Penicillin linkage site to the bacteria cell wall and in this way prevents its degeneration.

One of the greatest challenges of the human medicine currently is coping with Methicillin resistant *S. aureus* (MRSA). Its prevalence in medical institutes of developed countries can reach up to 40%. However, in recent years there has been an incline in the number of MRSA carriers in non-hospitalized populations (community associated MRSA).

Recent reports show MRSA a prevalence of 1% among canine populations in the USA. Other members of the *Staphylococci* such as *S. pseudointermedius* have also been found to be resistant in dogs. Furthermore, these members were found to be zoonotic and dangerous.

To the best of the author's knowledge the prevalence of

Methicillin susceptible or resistant *Staphylococci* among dogs in Israel is unknown. Moreover no risk factors have been defined for these *Staphylococci*.

Ninety six dogs admitted the VMTH or a private clinic was sampled. The sampled dogs suffered from a variety of illness and some of them came for a routine check up or vaccination. *Staphylococci* isolated from the samples and their Methicillin resistant was tested by their ability to present the mecA gene using PCR methods.

Twenty seven percent of the study population was found to be carriers of *Staphylococci* with the mecA gene. Most of them belonged to the species *S. pseudointermedius* (73%). The risk factors possessing Methicillin resistant *Staphylococci* were calculated by a multivariable model.

These risk factors included dogs that were hospitalized over one day ($p<0.003$, OR=5.6). Pure breed dogs ($p<0.01$, OR=5.6) and dogs who presented illnesses such as pancreatitis, chronic kidney disease etc.) ($p<0.002$, OR=6).

It appeared there was a high percentage population of Methicillin resistant *Staphylococci* among dogs in Israel. The main *Staphylococcus* in this group was *S. pseudointermedius*.

However, at this stage it doesn't seem this presents a zoonotic danger from carrier dogs of Methicillin resistant *Staphylococci* since no MRSA has been isolated at this point and there are no reports of *S. pseudointermedius* infections in Israel.

PREVALENCE OF CAMPYLOBACTER AT RETAIL – COUNTER – A PRELIMINARY STUDY

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Campylobacter is considered today to be the primary cause of food borne gastroenteritis. But while other bacteria such as *Salmonella* and *E. coli* usually manifest themselves in large outbreaks, Campylobacter is usually the cause of sporadic outbreaks

There are many ongoing international research projects ongoing in order to understand the scope of the problem and design ways to deal with it on all the levels of the food chain. Due to the fact that the disease is not registered as a listed disease in many countries its influence on reported rate does

not influence statistical reports. Until today no survey of Campylobacter was done in Israel on any level of the food chain. This fact stands as a major contrast to the interest and funds invested worldwide in Campylobacter research.

The aim of this work was to access the burden of Campylobacter at the retail point in Israel. The retail point was chosen for financial reasons as well as out of the fact that this is the last possible intervention point of the Public health Authorities

CLUSTERS OF *CAMPYLOBACTER* STRAINS FROM HUMANS, POULTRY AND CATTLE IN ISRAEL – A MOLECULAR EPIDEMIOLOGY STUDY.

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Campylobacter is a zoonotic pathogen and one of the most common causes of food-borne bacterial gastroenteritis in developed countries including Israel. The *Campylobacter* family consists of over 16 different species, *C. jejuni* is responsible for most human cases (~ 80%), followed by *C. coli* (~20 %).

Campylobacter is a gram negative rod, thermo-tolerant, microaerophilic and can be found as commensal bacteria in poultry, swine, sheep, cattle, dogs, cats, shellfish and rodents. Our current understanding of the epidemiology of *Campylobacter* infection remains incomplete. Most of the cases occur as sporadic events and common risk factors include consumption of raw poultry meat, raw milk, untreated water, work in a slaughterhouse and contact with pets and livestock.

The high incidence of clinical disease associated with this organism, its low infective dose and its potentially serious complications, confirm its importance in public health considerations. The main aim of this study was to

track the sources of *Campylobacter* contamination by genetic fingerprinting of *C. jejuni* isolates from poultry, cattle, and human clinical cases.

Samples from poultry (n=33) and dairy cows (n=19) were taken using a rectal swab, and human isolates (n=55) were sampled from the *Campylobacter* National Reference Center. Genetic fingerprinting was performed using Pulse Field Gel Electrophoresis (PFGE) with the *Sma*I enzyme

The data analyzed by the BioNumerics software, revealed 6 clusters of identical genotypic fingerprints from human, poultry and cattle.

The results of this study indicate that similar to the situation in other countries, the source of campylobacteriosis in humans may be either cattle or poultry and several common clones were revealed. Strain differentiation as performed in this study is essential for identification of contamination sources and determination of routes of transmission and pathogenesis.

HACCP: WHERE DID WE GO WRONG?

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Ever since Dr. Paul LaChance of NASA and Dr. Howard Bauman of Pillsbury pioneered the use of CCPs (critical control points) in food production 50 years ago, HACCP (hazard analysis and critical control points) has become the most widely accepted system for managing food safety in the world.

HACCP is a regulatory requirement for many industries in many countries and is the basis for managing food safety in a variety of international management systems (ISO 22000, BRC, IFS, GlobalGAP, SQF, etc.).

There is no argument as to the effectiveness of the system when it is applied properly. However, poor implementation or abuse of the system can be devastating. Indeed, many of the recently widely publicized food safety incidents were caused by products originating from HACCP certified plants.

This lecture highlights some of the weaknesses of HACCP, not for the purpose of discouraging manufacturers, but rather to offer a better understanding of the system, thus enabling industry to apply and maintain more effective food safety management programs.