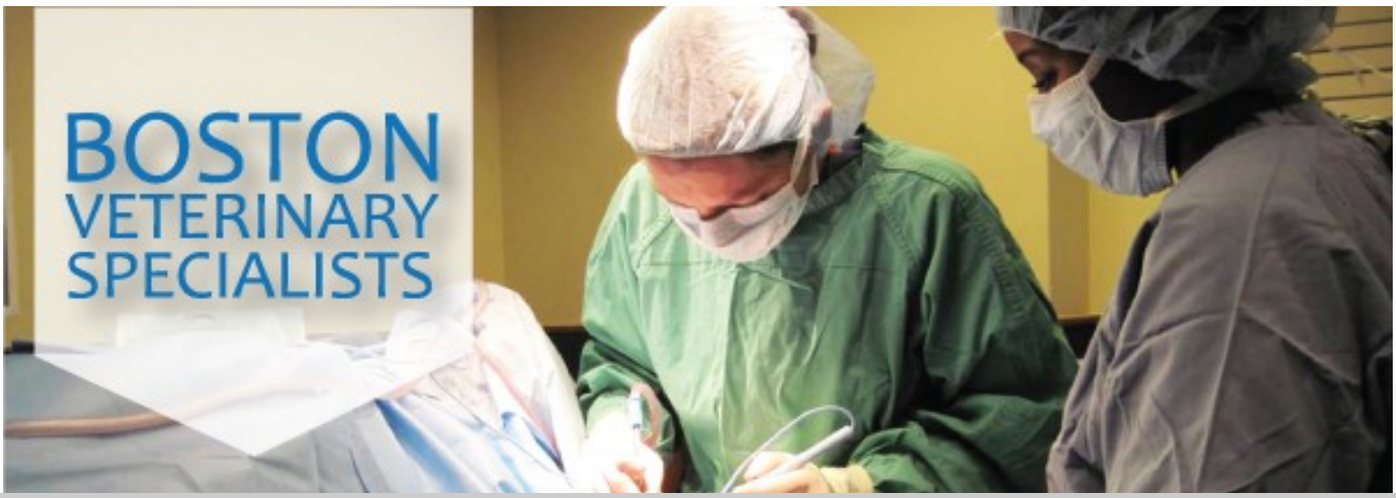


Monthly Update **November 2012**
Issue Contributor: William B. Henry DVM, DACVS
Editor: William B. Henry DVM, DACVS

PART ONE: CURRENT KNOWLEDGE (PART TWO: DECEMBER NEWSLETTER, CASE STUDIES USING PAMIDRONATE)

INTRODUCTION: Osteogenic Sarcomas (OS) are tumors we frequently see in our referral practices. As general practioners you often recognize them first.The reason I chose this subject is we now have research data that better defines this incurable tumor. Because it is a common tumor in the dog and in man the dog has been used as a research model for the disease. As we all recognize certain breeds seem very predisposed to OS, Golden Retrievers, Greyhounds, and Rottweilers.[13] With the genome of the dog sequenced more knowledge about why there appears to be a breed predisposition may be discovered in the near future. With better evidence based medicine we can now refute many of the past assumptions and prognostications about OS.

OSTEOSARCOMA (OS): OS is a relatively common, highly metastatic primary bone tumor that accounts for 5% of all tumors and has been reported to be responsible for up to 98% of all primary bone tumors in dogs.[1, 2, 3]

CURRENT STANDARD OF CARE: Amputation and adjuvant chemotherapy are the standard of care with a reported median survival time MST of 262-366 days.[1, 2, 3] Limb-sparing proceedures (allografts, metallo-bone prosthesis) with adjuvant chemotherapy are also performed with the intent to cure.[4] Palliative treatment options for dogs with primary bone tumors include, analgesia and radiation therapy[2]; analgesia and amputation without chemotherapy[4]; analgesia and aminobisphosphonates alone have become more recently used in veterinary and human medicine.[15]

AMPUTATION AND ADJUVANT CHEMOTHERAPY:The agents commonly used are carboplatin, cisplatin, and doxorubicin.[5,6] With the availability of CT scans for metastatic disease it is now almost mandatory to recommend this prior to investing in this treatment. CT scans and adjacent lymph node aspirates are a minimum pretreatment protocol. Following those examinations an adequate biopsy sample should be obtained to determine the Grade of the OS. Some owners may decline this recommendation because it is invasive, in their mind. However it is worth it when considering the further cost of amputation and chemotherapy. Some owners decline biopsy because of the age of their dog. Some veterinarians discourage this option either because of the age of the patient, concomitant disease, or relying on out dated belief on there prognostic value.

PROGNASTIC SIGNIFICANCE OF HISTOLOGIC GRADING: The prognostic significance of histologic grading for canine osteosarcoma can be divided into several morophologic subclasses: osteoblastic, chondroblastic, fibroblastic, and telaangectatic ie mixed osteoblastic/fibroblastic/chondroblastic.[7]

FREQUENCY OF DIFFERENT HISTOLOGIC SUBTYPES OF 166 PRIMARY AND 34 METASTATIC CANINE OS: Osteoblastic 87 (52.4); Chondroblastic 5 (3.0%); Fibroblastic 5 (3.0%) Mixed fibro- and osteoblastic 26 (26%); Mixed chondro and osteoblastic 17 (10.2%); Mixed fibro, chondro, and osteoblastic 9 (5.4%); Other mixed combinations 17 (10.2%).[7]

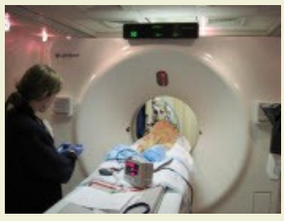
Continued next page

Tech Tips

The discussion this month gives you the dosages for the various commonly used fluids and the general basis for their use. From this, a chart can be easily constructed for use in the OR, if the surgeon wants quick dosage calculations for the various fluids available. A quick " cheat sheet" taken from this months TECH TIP discussion is often helpful when emergencies arise in the OR.

Read more on page 3.

CT Corner



The CT CORNER this month demonstrates the value of it's use in the pretreatment decision process when dealing with Osteogenic Sarcomas.

View video: William, male Doberman, Front Limb Lameness at:
http://www.youtube.com/watch?v=0VYiH6vot_U&feature=youtu.be

Continuing Education Opportunities

Drs. Henry and Briere lead CE courses throughout the year for practicing veterinarians on a wide range of topics in veterinary surgery.

January 16, 2013 -
Dr. Henry, *"Osteogenic Sarcoma: Newer Treatment Options"*

March 6, 2013 - Dr. Briere, *"Hip Dysplasia"*

Register online at:
http://www.bostonvetspecialists.com/vets.html#CE

BASIS OF HISTOLOGIC GRADING SYSTEM: Histologic variables including tumor cell pleomorphism, amount of tumor matrix, tumor cell density, tumor necrosis, estimated number of multinucleated giant cells, estimated whirl formation, number of mitosis, tumor growth into vessels ie vasvular invasion.[7]

THE THREE MOST SIGNIFICANT PROGNOQSTIC INDICATORS: 1) Vascular invasion 2) Mitosis,Grade 1 (< 10/ hdf); Grade 2 (10-20/hdf); Grade 3 (> 20/hdf), plus multinucleated giant cells > 3 /hdf.[7]

HISTOLOGIC GRADES IN 166 OS CASES: Grade 1, 4.2%; Grade 2, 20.5%; Grade 3, 75.3%[7]

LYMPH NODE METASTASIS: In those 166 OS cases 54 lymph nodes were available for evaluation; 24 had metastatic disease.[7]

PROGNOSTIC SIGNIFICANCE OF ALKALINE PHOSPHATASE in OS: In both human and veterinary medicine a NORMAL ALK. PHOS. level provides a much better long term survival prognosis.[8,9]

ACCURACY BIOPSY TECHNIQUES: In this study of 166 OS cases when a Michele trephine was used it was accurate 77% of the time (7 out of 9 cases). Classification of OS is made easier by large biopsy specimens including the edge of the tumor. An incisional biopsy of the softer outer parts of the OS combined with a core biopsy from the calcified inner part will result in the best chance for an accurate diagnosis. Blind Fine Needle Aspiration Biopsy (FNAB) obtained in this study in 35 cases was accurate in 63% of the cases.The advantages of FNAB over core biopsy is the relative ease of obtaining the samples, thus lower cost and less invasive, resulting in less post-op pain. However, there is less information about the tumor subtype and grade if obtained by FNAB when compared to core biopsies. Earlier biopsy technique studies were more accurate 82-94%, however this was prior to Grading of OS as they were making only an OS diagnosis.[16,17]

DECISION MAKING/TREATMENT OPTIONS: Generally OS occurs in young dogs that are 2-4 years old and older dogs. In the recent past the general belief was that most OS had metastasized at the time they were initially diagnosed. Before that, in the 1960-1970's most were prognosed to die in 4-6 months and often euthanized because of probable metastatic disease or severe pain in 4-6 months following the initial diagnosis. Because of the poor prognosis for long term survival amputation was often not recommended. Now that we have better means of determining lung metastasis and relatively in expensively via CT, one can better judge prior to major investments in time and money for chemotherapy, radiation, or amputation.

NEWER PALLIATIVE TREATMENTS: Another more recent assumption was that in those dogs who were poor candidates for amputation because of age, size/weight, and/or other orthopedic diseases in their forelegs or rear legs (CHD OA, Untreated ACL's or Elbow OA) that perhaps palliative radiation was the only pain management option. It appears that BISPHOSPHONATES may be useful in the dogs with OS to manage pain.

BISPHOSPHONATES: WHAT ARE THEY? They are synthetic analogs of inorganic pyrophosphate. Bisphosphonates have been intensively investigated in human medicine as novel antineoplastic agents and randomly reported in veterinary medicine before 2005.[18, 19] At low concentrations, bisphosphonates inhibit bone resorption (osteoclast function) without inhibiting the process of bone mineralization, resulting in enhancement of bone density. Although there are several aminobisphosphonates commercially available, pamodronate has been used most extensively in human medicine for the management of tumor induced hypercalcemia, Paget's disease, osteolytic bone metastasis in breast cancer, osteolytic lesions of multiple myeloma, metastatic prostate cancer, and osteogenic sarcoma.[15] They increase bone mineral density (BMD) which in turn results in pain relief and prevention of pathologic micro fractures and catastrophic macro long bone fractures.

PAMODRONATE: Is commercially available and recently became much less expensive. ($194.85 for 10 ml bottle, 9mg/ml)

PAMODRONTE DOSEAGE: 1.0 mg/kg IV q28d as a 2-hour constant rate infusion (CRI). Higher doses; 3mgs./kg have been found to be nephro-toxic.[15] The 1mg/kg dose was empirically derived from clinical toxicity studies in the humans and thus used in the dog. The q28-30d interval was the conventional dosing intervals used in human patients with cancer.[15]

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Read our October newsletter article about the Pediatric Emergencies by visiting our newsletter archive: http://archive.constantcontact.com/fs032/1109892572426/archive/1110184841979.html

ANCILLARY PALLIATIVE TREATMENT; NSAIDs: Carprofen (Rimadyl) appears to be helpful in managing the pain associated secondary to OS as would be expected. The clinical association between the use of NSAIDs and delayed bone healing has led to increased concern regarding their routine use in human orthopedics because decreased blood supply to healing bone. A published report in the veterinary literature subjectively suggested rimadyl slowed the growth of OS. A recent study using Carprofen significantly down regulated vascular endothelial growth factor (VEGF) in vitro without significantly changing alkaline phosphatase.[12] No studies are available using the NSAID Deramaxx, but because it's similar mechanism of action as Carprofen it appears to helpful for OS pain management. One could interpret, due to down regulation of VEGF, that Carprofen slows the neovascularity to the tumor thus slowing, it's rate of growth. Tumors need a lot of oxygen to grow rapidly. Recognition of this has stimulated a lot of research in human medicine for methods of interrupting tumor neovascularity.

PALLIATIVE TREATMENT PROTOCAL USING PAMODRONATE AND CARPROFEN/DERAMAXX: Pretreatment complete blood panel; UA; radiographs of the affected bone initially and monthly or bimonthly thereafter depending on the degree of lameness; standard three chest radiographs initially and single view monthly or bimonthly depending on clinical signs; monthly liver and kidney enzymes. Treatment Protocal: Pamodronate 1mg/kg IV q28-30d as a CRI in 250 ml 0.9% sodium chloride.

PART TWO: CLINICAL EXPERIENCE OF A SURGEON, CASE STUDY EXAMPLES AND WHAT HAVE WE LEARNED: December 2012 Newsletter.

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Tech Tips

ADVANCED FLUID THERAPY

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The first consideration of fluid therapy is based on patient status as each patient is an individual with specific needs. What is the patient's current physical condition based on physical exam and evaluation of lab work? What is the scheduled procedure? What is the speed of your surgeon?

The goal of fluid administration should be the support of oxygen delivery, systemic blood pressure whether due to hypotension or hypovolemia, prevention of, or correction of electrolyte imbalances, metabolic or acid-base disorders.

As we all know, total body fluid composition is divided into extracellular fluid and intracellular fluid. Approximately 1/3 of the body's fluid is distributed into the extracellular space and the remaining 2/3 considered to be intracellular fluid. Of the extracellular fluid this is further divided between the interstitial fluid which contains 3/4 of the extracellular fluid and plasma containing the remaining 1/4 of the extracellular fluid. To put this in a different perspective, approximately 605 of the patient's body weight consists of fluid with 20% of the body weight being extracellular fluid and the remaining 40% of the body weight being intracellular fluid.

Going back to our patient status, evaluate hydration, electrolyte balance, renal and hepatic function. What are we working with and what do we have in our armory to effect correction? Fluid therapy is critically important during the perioperative period. The most important goal is to maintain hemodynamic stability and protect vital organs from hypoperfusion (heart, liver, brain, kidneys). All sources of fluid losses must be accounted for. Good fluid management goes a long way toward preventing problems.

- Conventional Crystalloids
- Colloids
- Hypertonic Solutions
- Blood/blood products and blood substitutes

Conventional crystalloid is combinations of water and electrolytes. Combination of water and electrolytes. These are balanced salt solution with electrolyte composition and osmolality similar to plasma. The most commonly used crystalloids are lactated Ringers, Plasmalyte, and

Normosol. They have a short intravascular retention as the fluids equilibrate with intracellular and interstitial compartments. They contain a base source (Na++CO3-): lactate: liver metabolism acetate: muscle metabolism and gluconate: metabolism in most body tissue. Crystalloids are comprised of small molecules. These fluids are good for volume expansion. However, both water and electrolytes will cross a semi-permeable membrane into the interstitial space and achieve equilibrium in 2-3 hours. It is important to remember: 3mL of isotonic crystalloid solution are needed to replace 1mL of patient blood. This is because approximately 2/3rds of the solution will leave the vascular space in approximately 1 hour or less. A major disadvantage is that it takes approximately 2-3 times the volume of a crystalloid to cause the same intravascular expansion as a single volume of colloid. Commonly calculated crystalloid rate of administration for surgical patients are 5 ml/kg for the first hour for anticipated procedures without significant blood loss and decreasing by ½ for each subsequent hour. If significant blood loss or extension surgical time is anticipated, this may be raised to 10/kg for the first hour and decreasing to ½ after the first hour.

Colloids are large molecular weight solutions (nominally MW > 30,000 Daltons)> these solutes are macromolecular substances made of gelatinous solutions which have particles suspended in solution and do NOT readily cross semi-permeable membranes or form sediments. Because of their high osmolarities, these are important in capillary fluid dynamics because they are the only constituents which are effective at exerting an osmotic force across the wall of the capillaries. These work well in reducing edema because they draw fluid from the interstitial and intracellular compartments into the vascular compartments. Initially these fluids stay almost entirely in the intravascular space for a prolonged period of time compared to crystalloids. These will leak out of the intravascular space when the capillary permeability is deranged or leaky. Albumin solutions are available for use as colloids for volume expansion in the setting of CHF however albumin is in short supply right now. There are other solutions containing artificial colloids available. The general problems with colloid solutions are:

- Much higher cost than crystalloid solutions
- Small but significant incidence of adverse reactions
- Because of gelatinous properties, these can cause platelet dysfunction and interfere with fibrinolysis and coagulation factors thus possibly causing coagulopathies in large volumes.
- These fluids can cause dramatic fluid shifts which can be dangerous if they are not administered in a controlled setting.

Common rates of administration for the canine patient are 3-5 ml/kg/hr with a daily total volume to remain within a 20-30ml/kg range. The feline rates are lower and may be calculated at 1-3 ml/kg/hr with a daily total volume of 20 ml/day. Should colloids be used in conjunction with IV crystalloid therapy, the rate of administration of the crystalloid may be reduced by up to 50%.

Hypertonic solutions are those containing sodium concentrations greater than normal saline. They are available in 1.8%, 3%, 5%, 7.5%, 10% solutions. Hyperosmolarity creates a gradient that draws water out of cells; therefore, cellular dehydration is a potential problem. These solutions are often used in veterinary medicine as a quick "band aid" for refractory hypotension until other interventions are made available. The most common calculated dose is 3-7 ml/kg IV bolus given over time up to 15 minutes. With the elevated sodium content, the patient must first be euvolemic prior to administration. It is recommended that only a single dose of hypertonic saline be administered due to the potential for cellular dehydration.

The decision to administer blood products preoperatively is often based on the packed cell volume and hemoglobin concentration. In veterinary medicine a packed cell volume of 20% is often considered the transfusion trigger. Whole blood may need to be administered in volumes of 10 to 30 ml/kg, depending on the magnitude of anemia and hypovolemia (cats: 5 to 15 ml/kg). These volumes should be halved if packed red blood cell products are used. The rate of administration depends upon the magnitude of the hypovolemia. The amount of blood to administer can also be calculated: (desired PCV - current PCV) x body weight (kg) x 2 ml whole blood (assumes a PCV of about 40%) (Or 1 ml packed red blood cells [assumes a PCV of about 80%]). Intraoperatively, the decision is based on the amount of acute blood loss with the initial packed cell volume being taken into consideration. Typically at TAMU, if there is significant observed blood loss and the packed cell volume has decreased by at least 25%, blood products are prepared for delivery. Bearing in mind that the entire patient status should be considered regarding the ability to deliver oxygen to the cells. Having said that, what is the blood pressure, what is the heart rate, has it raised as a compensatory response to a change in volume status, and has the end tidal CO2 decreased as a result of volume loss? Remember that the oxygen saturation estimated by the pulse Oximeter only tells you the percent of hemoglobin saturation which is not helpful in blood loss situation. Bottom line - if the hemoglobin has dropped to an unreadable level due to blood loss, the pulse Oximeter can still give you excellent % saturation readings. Look globally at the patient!