



Care Beyond a Cure: Oncologic Emergencies--

Help!!!!

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Care Beyond a Cure: Oncologic Emergencies-- Help!!!!

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Cancer is a word that is feared throughout the world, regardless of what species is affected. A diagnosis of cancer sets in motion feelings of fear and urgency which spur our clients on to demand rapid response by the veterinary health care team to their concerns. This heightened level of emotion is first witnessed during the initial diagnosis of cancer and decision-making process, but is often most apparent in the emergency situation. In addition,

dogs and cats hide their clinical signs until quite late in the disease, often facing cancer therapy in debilitated states; therefore, speed and decisiveness are key ingredients of successful emergency care. Therefore, canine and feline oncologic emergencies must be handled with extreme medical care and also with understanding. When an emergency or urgent situation is noted, the entire veterinary health care team should be equipped and prepared to provide timely compassionate care to meet the medical and non-medical needs of patient and caregiver alike. In some cases, this may mean referring the case to another facility. There are three types of emergencies:



“Therefore, speed and decisiveness are key ingredients of successful emergency care”

- True life-threatening emergencies
- Medical problems that are perceived as being life-threatening by well-meaning, concerned clients
- Emergencies of convenience, where the client would prefer to have the dog and cat evaluated immediately despite non-life-threatening emergencies, in order to accommodate the client's personal needs or schedule.

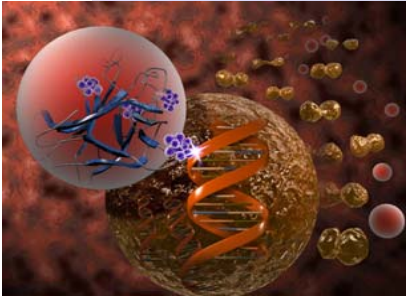
Regardless of the type of emergency, the following information should be obtained:

- A primary complaint

- Vital signs, including but not limited to:
 - Airway and breathing ability
 - Heart rate, rhythm and character
 - Body temperature
 - Mucous membrane color and capillary refill
- Complete physical examination
- Complete history, including prior cancer treatment

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When a dog or cat is presented for an emergency, blood and urine samples should be obtained and an intravenous catheter placed as soon as possible. The blood and urine can be submitted at any time to determine pre-treatment parameters

blood count, biochemical profile, activated clotting time, and urinalysis. Essential information that is rapidly obtained and vital for initial decision-making should include a urine specific gravity, packed cell volume, white blood cell count, and blood glucose. These should be obtained on admission. As soon as the diagnostic and therapeutic plan is initiated, the clients should be made aware of each and every aspect of the case. Measured, realistic information should be provided as soon as assessments are made

and the information is available. It is also important to provide a cost estimate for initial care, as well as updates for ongoing supportive care. Utilizing the team approach to care is vital in the event of an emergency. The client is an integral member of that team and, once empowered with information, is placed in a decision-making role that allows for optimal medical care of the patient, while meeting the emotional needs of the caregiver and family. Ongoing communication allows for an open dialogue between team members regarding financial limitations, philosophy for continuing critical care in the face of diminishing hope, and advanced strategies for crisis situations, such as cardiac or respiratory arrest. Oncologic emergencies, while rare, are an inevitable consequence of cancer and cancer therapy. Therefore, planning for these uncommon and unwanted problems is essential in order to result in positive outcomes. It is important to recognize that the true "first step" in handling oncologic emergencies is actually prevention. This step occurs prior to the initiation of treatment and is the result of time spent with the caregiver educating about the nature of disease, effects of any and all medication administered, and the early and often subtle symptoms that when acted upon often prevent a true emergency from ever happening. Similarly, instructions about what the client can do at home to support his or her dog and cat are also quite helpful. Always remember, the client is perhaps the most important member of the veterinary health care team.

The next step of planning includes educating and empowering the entire veterinary health care team to take an active role in supporting the patient and the client. The word cancer and cancer therapy often frightens veterinary health care team members as much as it does clients. There are a few common emergency situations that will be encountered. Developing a treatment strategy or "cookbook approach" to these emergency situations empowers the staff to intervene on behalf of the patient. In addition, providing the health care team with information that empowers them to respond to the emotional component of the emergency on the part of the caregiver is also essential. All members of the health care team must recognize that it is this emotional component of the disease cancer that magnifies the seriousness of almost any health problem.

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NEUTROPENIA AND SEPSIS

Emergencies are always frightening to clients/caregivers, but when an emergency occurs due to cancer or cancer treatment, the intensity of this fear is magnified by the emotional impact imparted by the cancer itself. Therefore, the canine and feline health care team must act swiftly to not only provide medical care for the patient, but also care for the emotional or non-medical needs of the client. Sepsis due to chemotherapy or cancer-related neutropenia is one of the more common emergencies handled in canine and feline cancer medicine. Bleeding due to thrombocytopenia is much less common. Both conditions are usually preventable by judicious monitoring and appropriate supportive care during cancer therapy. In addition, caregivers should be educated about the early clinical signs of neutropenia and thrombocytopenia induced by cancer treatment, thus empowering the client to assist in early detection and seek immediate treatment.

In humans, sepsis is a common cause of death in cancer patients, exceeding all other causes combined.¹⁻⁷ As the popularity of dogs and cats increases and the use of chemotherapy and radiation soar in private practice, this observation is likely to be repeated in canine and feline cancer medicine. Because dogs and cats tend to hide their symptoms until late in the disease, the condition of sepsis may be quite advanced when first recognized and requires prompt intervention by the canine and feline health care team.

Neutropenia secondary to malignancy or myelodysplasia, or as a result of the myelosuppressive effects of chemotherapy or radiation therapy, is a common predisposing factor for development of sepsis in dogs and cats. Septic shock is the state of circulatory collapse that occurs secondary to overwhelming sepsis and/or endotoxemia. This syndrome is frequently fatal, with a mortality rate of 40% to 90%. The profound systemic effects of septic shock include:

- Vasoconstriction leading to multi-organ failure
- Cardiac dysfunction, in part from lactic acidosis
- Increased vascular permeability, leading to hyperviscosity and hypovolemia

- Liver dysfunction from splanchnic vascular pooling and tissue ischemia
- Acute renal failure
- Worsening neutropenia and thrombocytopenia
- Coagulopathies
- Severe gastrointestinal damage
- Decreased insulin release
- Initial hyperglycemia followed by hypoglycemia

The bacteria that most commonly cause morbidity and mortality in canine and feline cancer patients arise from the dog and cat's own flora.⁸ The most important thing a clinician can do for the septic canine and feline cancer patient is to quickly identify the source and type of bacterial infection, and initiate therapy with broad-spectrum antibiotics as well as appropriate and aggressive supportive care. Factors such as prolonged hospitalization, the presence of urinary, venous, chest, endotracheal and other tubes or catheters, and antibiotic administration may result in increased susceptibility to increasingly resistant strains of organisms. These factors should be avoided or minimized wherever possible. Minimizing the chance for exposure to or the opportunity for development of, resistant strains of bacteria enhances the chance for rapid recovery in response to appropriate antibiotic therapy.



Predisposing Factors

The following are predisposing factors for neutropenia-associated sepsis:

- Defects in cellular immunity are a cause of sepsis in dogs and cats with cancer. Cellular immune dysfunction, while extraordinarily difficult to diagnose in the dog and cat, may be due to an underlying cause or the result of administration of antineoplastic agents and/or corticosteroids. These defects may result in various bacterial, mycobacterial, fungal, and viral infections. Humoral immune dysfunction is also associated with an increased prevalence of sepsis in human patients with cancer and may cause similar problems

in animals. Agammaglobulinemic or hypogammaglobulinemic dogs and cats are suspected as being susceptible to infections. Multiple myeloma and chronic lymphocytic leukemia are common neoplasms associated with humoral immune dysfunction in people, and are likely causes in the dog and cat as well.

- Neutropenia may be caused by the myelosuppressive effects of chemotherapy. The myelosuppressive effects of chemotherapeutic agents can be categorized as high, moderate, or mild. These drugs cause a nadir (lowest part of the white blood cell count) at different times after administration).
- Splenectomized dogs and cats are susceptible to overwhelming sepsis when infected with a strain of encapsulated bacteria against which they have not made antibodies.
- Indwelling vascular or urinary catheters have been associated with an increased prevalence of sepsis. The longer a catheter is present, the higher the probability for infection, especially in neutropenic dogs and cats.
- Frequent acquisition of blood samples greatly increases the risk of sepsis in dogs and cats with cancer.
- Prolonged hospitalization can result in serious consequences, in part because the patient is continually exposed to bacterial strains that are resistant to the antibiotics most commonly used in that practice.
- Malnutrition is a serious cause of debilitation and decreased resistance to bacterial infection, especially in those dogs and cats with neutropenia.
- Dogs and cats with neurologic dysfunction or nonambulatory patients from any cause are at increased risk for sepsis as well.

Whenever possible, these risk factors must be avoided or minimized, and associated problems recognized and corrected early to reduce the probability of sepsis. The first approach for clinician and client is to understand the myelosuppressive effects of various drugs. The myelosuppressive effects of chemotherapeutic agents can be categorized as high, moderate, or mild. These drugs cause a nadir (lowest part of the white blood cell count) at different times after administration. Clients and the

veterinary health care team should be encouraged to be more vigilant for the clinical signs associated with neutropenia and thrombocytopenia around the time of the nadir for the drug being used. With monitoring of CBCs at the appropriate times, especially early on in the course of chemotherapy, the veterinarian will have a general idea of how low the white blood cell count is actually dropping. If the count appears too low (less than 1000/ul), or the patient becomes even mildly symptomatic, subsequent dose reduction should be considered.

Further steps can be taken to minimize the risk of sepsis for the dog and cat with cancer. One logical step is to minimize the administration of immunosuppressive drugs, especially corticosteroids. Whenever a splenectomized dog and cat is treated for cancer, they should be watched carefully for complications, including sepsis. The risk of catheter-induced sepsis can be minimized by using aseptic technique and by placing a new catheter in a new site every 2 to 3 days. Strict aseptic procedures should be used, especially with dogs and cats that are myelosuppressed. The use of semipermanent indwelling catheters in patients with cancer may be safe if strict aseptic procedures are followed by caregivers and health care professionals. Proper aseptic technique and changing of catheters are especially important in dogs and cats with neurologic dysfunction, as these dogs and cats are at a much higher risk for sepsis. The duration of hospitalization should be limited whenever possible to limit exposure to resistant bacteria.



Diagnosis

Dogs and cats presented with septic shock secondary to neutropenia require immediate intervention and careful client support. Diagnostic and therapeutic interventions must begin concurrently for the patient's benefit. The differential list for neutropenia is quite extensive. Obviously, the diagnosis of septic shock begins with the physical examination as a catheter is placed and blood samples are acquired for initial diagnostics. Mucous membrane color can be difficult to identify in dogs and cats, however, in some dogs and cats with septic shock, brick-red mucous membranes may be noted. In addition, some of the following signs may be identified on physical examination in dogs and cats in the hyperdynamic state of septic shock:¹⁻⁶

- Tachycardia
- Short capillary refill time
- Gastrointestinal signs
- Altered mentation
- Decreased blood pressure

End-stage signs reflect a hypodynamic state and include:¹⁻⁶

- Hypothermia
- Mucous membrane pallor
- Marked mental depression
- Bloody diarrhea
- Signs of multi-organ failure

Thrombocytopenia and neutropenia are often identified during the course of septic shock. Hyperglycemia is an early finding that often is followed by hypoglycemia. Cultures of urine and blood should always be obtained, even though they may be negative and require a significant amount of time for turn around. Appropriate broad-spectrum antibiotics and combinations must be available immediately for parenteral administration. When positive, the results of cultures will guide follow-up oral antibiotic selection. Metabolic acidosis is commonly identified.

Blood and urine taken at the time of initial presentation can be very helpful for supporting a diagnosis of septic shock. At a minimum, samples should be obtained for a complete blood count (CBC), biochemical profile, and urinalysis on each dog and cat. These clinical pathologic findings are often combined with other tests.

The absence of circulating neutrophils affects many of the commonly used clinical, laboratory and radiographic findings that may normally suggest a localized or systemic infection. For example:

- Neutropenia results in a urinalysis without pyuria, despite infection.
- Without a neutrophilic infiltrate, which otherwise would be responsible for many of the radiographic changes associated with pneumonia, chest radiographs often

appear "normal" even in the presence of significant pneumonia.

Thus, any suspicious sites should be cultured. This includes, but is not necessarily limited to:

- Blood cultures: Two, and preferably four, sets of blood cultures (aerobic and anaerobic) should be acquired. However, extreme care should be taken to be cognizant of the total volume of blood taken, including blood for hemograms, biochemical profiles and other tests, because these dogs and cats almost always have some degree of anemia of chronic disease. The timing of the sampling intervals is controversial, however, sampling every 20 to 30 minutes prior to initiation of antibiotic therapy may be adequate. At least 2 ml of blood should be injected into appropriate culture containers.
- Catheter cultures: If central venous catheters are present, cultures of the port should be obtained. Ideally, culture bottles that contain an antibiotic-binding resin or other antibiotic-binding substance should be included with each culture for patients on antibiotics.
- Urine culture: A cystocentesis specimen for urine culture and analysis should be acquired in each case.
- CSF culture: When neurologic signs are present, a cerebrospinal fluid (CSF) tap should be obtained and cultured appropriately. CSF should be sent for Gram stain, bacterial culture, cell count and differential, and glucose and protein determination. A cryptococcal antigen titer or India ink preparation should be performed in suspect cases. Acid-fast stains and culture are probably not indicated routinely.
- Stool cultures: For dogs and cats with diarrhea, appropriate cultures should be done for clostridial bacteria, including appropriate assays for endotoxin.
- Lung cultures: Chest radiographs and a transendotracheal wash should be taken, especially when the patient shows any sign of respiratory difficulty such as increased respiratory effort or a cough.

Other diagnostic studies that should be considered include:

- Complete blood count with differential, biochemical profile, and urinalysis
- Chest and abdominal radiographs to look for signs of infection
- Abdominal ultrasonography looking for pancreatitis, abscesses, abdominal effusion, etc.
- Echocardiography to identify the presence of valvular endocarditis
- Bronchoscopy, if pulmonary disease is suspected
- Skin biopsy, if deep cutaneous infection is identified
- Bone marrow aspirate or biopsy to determine the cause and severity of neutropenia
- Percutaneous or laparoscopic-guided liver biopsy or aspirate to evaluate for hepatic infection or abscessation
- Exploratory laparotomy in select cases when other, less invasive tests are not successful, yet there is clinical evidence of disease in the abdomen
- Blood gas analysis

Treatment¹⁻⁸



Treatment for septic shock should begin as soon as the condition is suspected. This is usually at the time the dog and cat is initially presented for an acute, emergency condition.

Treatment for the septic, neutropenic dog and cat is primarily directed at:

- Restoring adequate tissue perfusion
- Improving the alterations in metabolism
- Controlling systemic infection



Restoring Adequate Tissue Perfusion: Standard therapy includes crystalloid solutions and antibiotics. Although the use of hypertonic solutions for the treatment of shock is being investigated, balanced electrolyte solutions are cited in most

canine and feline texts as "the first line of therapy." The initial infusion rate for critical dogs and cats is 40 to 60 ml/kg IV for 1 hour, then 10 to 12 ml/kg/hour thereafter. The fluid rate should then be adjusted to meet the needs of each dog and cat as determined by monitoring body weight, heart and respiratory rates, central venous pressure, ongoing losses (e.g., vomiting and diarrhea), and urine output. During that first hour of fluid administration, it is vitally important to monitor at 15-minute intervals for evidence of fluid overload and adjust appropriately.



Improving Alterations in Metabolism: When choosing the type of fluids, some authorities prefer a non-lactate containing fluid; lactate must be metabolized to bicarbonate by a functional liver that may be impaired during shock and sepsis. Normosol R® and Plasmalyte® are examples of non-lactate-containing fluids with acetate and gluconate as buffers. Dextrose should be included in fluids when systemic hypoglycemia is identified during constant patient monitoring.



Controlling or Preventing Infection: Asymptomatic dogs and cats with fewer than 1000 to 1500 neutrophils/ μ l should be started prophylactically on antibiotics. Trimethoprim-sulfa (7.5 mg/kg BID PO) is often recommended for prophylactic therapy in the asymptomatic, yet neutropenic, patient. Neutropenic dogs and cats in septic shock should be started on intravenous fluids and intravenous antibiotic therapy as soon as samples for bacterial cultures are acquired. Re-evaluation of the initial antibiotic regimen is mandatory when the identity and sensitivity patterns of the bacteria become available. For gram-negative infections, two antibiotics that are effective against the isolated organism are often recommended.

Initially, broad-spectrum antibiotic therapy, often combinations of an aminoglycoside plus penicillin or 2nd generation cephalosporin (e.g., cefoxitin, cefamandole, cefaclor, cefuroxime, cefonicid, ceforanide, cefotetan, ceftazidime), is commonly used in sepsis. If the infection doesn't respond within 12 to 24 hrs, the antibiotics should be changed. For gram-negative organisms, a different aminoglycoside, quinolone, or aztreonam may be used. Extended-spectrum penicillins (e.g., ticarcillin, carbenicillin, azlocillin, piperacillin sodium, and mezlocillin), 3rd generation cephalosporins (e.g., cefotaxime, moxalactam, cefoperazone,

ceftizoxime, ceftriaxone, ceftazidime, cefixime), or imipenem with cilastatin sodium have sufficiently broad spectrums to be used alone. Dogs and cats placed on aminoglycosides, particularly gentamicin, should be monitored for nephrotoxicity via urinalysis (urine sediment should be examined for the presence of casts) and measurement of BUN and creatinine concentrations.



Other treatments include:

- **Corticosteroids:** Steroids remain controversial in septic shock. Recommended doses in shock are hydrocortisone at 300 mg/kg, methylprednisolone or prednisone at 10-30 mg/kg, or dexamethasone at 4-8 mg/kg. Short-term use (i.e., less than 2 days of massive doses) does not result in as many adverse effects as long-term use.
- **Glucose:** If hypoglycemia is present, glucose at 0.25 g/kg IV bolus can be given, followed by infusions of 2.5-10% glucose solutions as needed to maintain normal blood glucose levels.
- **Bicarbonate:** Bicarbonate can be given if severe metabolic acidosis is present. The amount of bicarbonate to give can be calculated (i.e., base deficit x (0.3 x BW in kg)) or estimated (mild, moderate, or severe acidosis is treated with 1, 3, or 5 mEq bicarbonate/kg IV, respectively). Bicarbonate should be given slowly IV (i.e., over 20 minutes or more).
- **Neutrophil-Rich Transfusions:** These transfusions have not been associated with beneficial responses in controlled trials. In addition, transfusion reactions and allosensitizations to specific antigens of the granulocytes may occur, and increased prevalence of severe pulmonary reactions may also be noted.
- **Hematopoietic Growth Factors:** Canine recombinant granulocyte colony-stimulating factor (rcG-CSF, 5 µg/kg/day SQ) and canine recombinant granulocyte-macrophage colony-stimulating factor (rcGM-CSF, 10 µg/kg/day SQ) have been associated with an increased rate of myeloid recovery in dogs and dogs and cats with neutropenia. These hematopoietic growth factors increase cell numbers and enhance neutrophil function, but are not yet available commercially. Human recombinant G-CSF

and GM-CSF are commercially available; however, long-term use may induce antibody formation to the protein. Of the two human recombinant proteins, rhG-CSF induces the most profound increase in canine and canine and feline neutrophil numbers before development of antibodies is noted.

- **Transfusions** of Fresh, Whole Blood
- **Other Options:** Tumor necrosis factor antiserum, antibody to tumor necrosis factor, interleukin and interferon therapy, pooled immunoglobulin preparations, and monoclonal antibodies to neutralize endotoxin may be future treatments of choice.



THROMBOCYTOPENIA

The cytotoxic effects of chemotherapeutic agents, bone marrow infiltration by a malignant process, and canine and feline infectious peritonitis most commonly cause a decreased platelet count. If a chemotherapeutic agent induces bone marrow suppression that results in cytopenia, thrombocytopenia usually occurs a few days after neutropenia and before a decrease in red blood cell numbers. Commonly identified abnormalities include a mixed hemostatic defect compatible with disseminated intravascular coagulation (DIC), thrombocytopenia, isolated prolongation of the activated partial thromboplastin time (APTT), and prolongation of both the APTT and one-stage prothrombin time (OSPT).



Predisposing Factors

Thrombocytopenia can occur in any dog and cat with cancer that receives myelosuppressive chemotherapeutic agents. Drugs such as vincristine, bleomycin, and prednisone do not cause as significant a thrombocytopenia as do some of the more highly myelosuppressive agents (e.g., doxorubicin). Compared to many other myelosuppressive drugs, cyclophosphamide induces less suppression in platelet numbers. Dogs and cats with bone marrow infiltration by a malignant process are more sensitive to the cytotoxic effects of chemotherapeutic agents that can result in thrombocytopenia. Other conditions that affect the bone marrow are likely to make the marrow more sensitive to cytotoxic agents. Tumors that are frequently associated with coagulopathies may cause a consumptive thrombocytopenia. In addition,

hypersplenism and chronic bleeding of any cause can result in a decrease in the number of platelets.



Diagnosis

Dogs and cats are often presented late in the course of clinical disease due to their ability to mask the early symptoms of illness. This is true for diseases or conditions that result in thrombocytopenia. Clinical signs include, but are not limited to, bleeding diatheses, melena, and weakness. The blood loss can occur into any organ and result in multisystemic abnormalities. An acute decline in the number of platelets may result in the development of clinical signs at higher platelet counts than if the decline in platelets is much slower. Therefore, if there is any suspicion that thrombocytopenia may be present (gingival hemorrhage, petechia or ecchymotic hemorrhages, or any of the above mentioned symptoms), proactive interventional and diagnostic measures should be taken after the physical examination is performed. A catheter should be placed and blood obtained with a small gauge needle for routine blood work (CBC with platelet count, biochemical profile, T4 and FeLV/FIV testing), and a urinalysis should be performed as well to complete a minimum database. Diagnosis is confirmed by obtaining platelet counts and by examining bone marrow aspirate or biopsy specimens. Bone marrow evaluation is essential and helps the clinician determine the cause of the thrombocytopenia. Clotting profiles (e.g., APTT, OSPT, and fibrin degradation products [FDPs]) may help determine if the thrombocytopenia is the result of a coagulopathy, such as DIC.



Therapy

Thrombocytopenia-related clinical signs can be exacerbated when drugs that affect platelet function are administered during the time of overt or impending thrombocytopenia. Therefore, aspirin and aspirin-like drugs should be withheld from dogs and cats with thrombocytopenia. In addition, the use of heparinized saline for catheter maintenance can be a problem in some patients if multiple catheter "flushes" are performed.

Obviously, dogs and cats with thrombocytopenia should be kept quiet and care should be taken during handling. Vincristine (0.5 mg/m² body surface area) can be administered IV to induce

premature release of platelets from megakaryocytes.⁸ Platelet counts increase 4 days after vincristine is given. Where available, platelet transfusions may be administered to specific dogs and cats that are, or have a high likelihood of, bleeding uncontrollably. Administering each unit of platelets with 30 to 60 ml of plasma is recommended. In dogs and cats with acute bleeding that is not responsive to other treatments of procedures, hemostatic, epsilon aminocaproic acid (Amicar[®]) can be given IV or PO (250 mg/m² QID).⁹ Dose reduction should occur with the next administration of myelosuppressive chemotherapeutic agents.

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