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SEPTIC SHOCK: WHAT, WHEN AND HOW
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Sepsis and Septic shock are common complications in small animal practice and the most common cause of death in non cardiac intensive care units. In Human beings the American College of Chest Physicians /Society of Critical Care Medicine Consensus Conference, in 1990, agree some definitions of sepsis as the systemic inflammatory response due to infection due to bacteria, viruses, fungi and parasites. Therefore was recognized that sepsis is just part of a continuum ranging syndrome from Sepsis, SIRS, Septic shock and Multiple Organ Failure Syndrome.

Sepsis is defined as the systemic inflammatory response to infection. The systemic inflammatory response syndrome can occur as a result of sepsis and is currently defined as two or more of the following criteria:

1. Temperature > 103.5 or < 100.0°F (> 39.7 or < 37.8°C)
2. Heart rate > 160 bpm (dog) or > 250 bpm (cat)
3. Respiratory rate > 30 bpm or PaCO₂ < 32 mm Hg.
4. White blood cell count > 19,000 or < 4,000 or > 10% band neutrophils

The Center for Disease Control and Prevention in Atlanta, Georgia, report an incidence of sepsis in USA, of 164,000 cases in 1979 to 660,000 cases in 2000, being the 11th cause of death with a 9.3% of all human beings deaths.

Shock has been defined as “a critical imbalance between the delivery of oxygen and nutrients to the cell and utilization of oxygen and nutrients by the cell. Shock may be any syndrome, disease state, or injury that results in a critical decrease in effective blood flow. Lack of effective blood flow leads to derangement in cellular metabolism and ultimately cell death. When left unchecked, shock leads to multiple organ dysfunction and failure, culminating with death.” Shock has been divided into four classifications:

1. Hypovolemic: shock due to loss of circulating volume
2. Cardiogenic: pump failure
3. Distributive: vasogenic shock due to peripheral vasodilation
4. Obstructive: obstruction to flow

Many conditions contribute to the spread of infection, sepsis and associated septic shock. The overuse of corticosteroids, immunosuppressive therapies, the underestimation of nosocomial infections in veterinary practices, the inadequate use or proper maintenance of IV catheters are some of the reasons that septic shock has become more often for Veterinary practitioners.
Effective management requires prompt recognition of early clinical signs related to systemic inflammation. Although inflammation is the normal bodily response to infection, in severe sepsis, regulation of this response is perturbed, leading to an exaggerated response, showing clinical manifestations as: mental depression, hyper or hypothermia, tachycardia, elevated or abnormally decreased white blood cell count with or without shift to the left.

In response to the presence of pathogens, mononuclear cells (monocytes and macrophages) produce and release cytokines with strong proinflammatory actions, that assist the defense mechanism, attracting activated neutrophils. However, that mechanism can also produce a widespread activation of the coagulation and impair, even suppression of the fibrinolysis.

Patients that are in early septic shock may have “injected” or brick red mucous membranes with a shortened capillary refill time (CRT< 1 second), tachycardia, tachypnea, fever, bounding pulses and may feel warm to the touch due to peripheral vasodilation. As septic shock progresses, mucous membranes may take on a “muddy appearance, CRT becomes prolonged (> 2 seconds), pulses become weak and the extremities may become cool to the touch. Patients that present to a veterinary clinic with these signs should be evaluated quickly and resuscitative therapy begun immediately. A “team” approach helps to move this process along efficiently. While the clinician performs a physical exam, a technician can collect samples and place catheters and a receptionist can begin taking a history from the owner.

Owners of pets that present with any of the above clinical signs should be questioned closely to determine if there are predisposing factors in the patients history. Immunosuppressive therapy for immune-mediated disease and/or chemotherapy for various forms of cancer are common predisposing factors. Underlying diseases such as hyperadrenocorticism, diabetes mellitus and viral infections such as parvovirus can place an animal at risk for the development of sepsis. Owners of intact female pets should be questioned about recent pregnancies and estrus cycles. Additionally it should be determined if the animal is exposed to other animals (wild or domestic) and whether it has had any recent medical or surgical procedures (biopsies, foreign body removal, etc.).

Cytokines main effects

- **Histamine**: increase vascular permeability and smooth muscle contraction.
- **Serotonin**: causes the same action as histamine
- **PAF**: causes the release of platelet mediators, increase in vascular permeability, smooth muscle contraction and activation of neutrophils, there is some evidence that show it play a main role in bowel necrosis
- **Thromboxanes**: causes platelet and PMN aggregation, vasoconstriction
• IL-8: causes monocytes attraction.
• C3a: causes smooth muscle contraction and mastocytes degranulation.
• C5a: provokes smooth muscle contraction, increase in capillary permeability, attraction and activation of neutrophils and macrophages.
• Kinines: vasodilatation, smooth muscle contraction, increases in capillar permeability.
• Fibrynolitic system: increase in vascular permeability, attraction to macrophages and neutrophils.
• PgE2: vasodilatation increases histamine action.
• LtB4: neutrophil attraction, synergism with PgE2, enhance capillary leakage
• LtD4: smooth muscle contraction, increase in vascular permeability
• LtC4: depression os cardiac contractility

Sepsis cause disruption of homeostasis through a non-control cascade of inflammation, excessive coagulation with impaired fibrinolysis that contributes to the inflammatory condition, microvascular hypoperfusion, organ dysfunction and high mortality. The magnitude of this cascade of events, is influenced by the virulence of the pathogens and over all, for the host response capability.

Sepsis is currently defined as the systemic inflammatory response to infection. Therefore systemic inflammatory response syndrome (SIRS) is a complicate syndrome that may occur as a result of infection, but also from trauma, burning lesions, frozen stroke and so many other aggresions. Currently SIRS is defined as as a conditions in patients that show two or more of the following criteria:

Temperature > 39.7 or < 37.8 °C
Respiratory rate > 30 bpm
PaCO2 < 32 mm Hg.
Heart rate > 160 bpm (dog) or > 250 bpm (cat)
White blood cell count > 19,000 or < 4,000 or > 10% band neutrophils

In early stages of septic shock (hyperdinamic phase), patients may show dark red mucous membranes with a short capillary refill time (CRT<1 second), elevated heart and respiratory rate, fever, bounding pulses and signs associated to peripheral vasodilation. In more advanced stages mucous membranes may see grey and dry, Increased CRT, weak pulses. These patients need a Emergency Team Work approach, because the different procedures and exams that such a patient require.

Data about of septic patients, should be collected to determine if they have any predisposing factor in history as immunosuppressive therapy or chemotherapy, as well metabolic diseases such as Cushing’s Syndrome, Diabetes mellitus or viral infections as Parvovirus.

Blood samples should be obtained for culture, complete blood count, prothrombin time, partial thromboplastin time, clinical chemistry panel and
blood gas evaluation. In the same way, urine sample must be obtained by centesis for urinalysis and culture.

The aim of treatment in septic shock is care, improve and maximize oxygen delivery to the tissues to address their demands. Two or three largest possible catheter should be placed for fluid administration and if possible, a jugular catheter for assess central venous pressure.

The adequate fluid and administration rate choice for fluid therapy remains as a very controversial issue. Initially you can start with a crystalloid fluid at 70-90 ml/kg in dogs, 45-60 ml/kg in cats, looking forward a hemodynamic stability (Blood pressure, Capillary refill time, Central Venous Pressure, Good quality and rate Femoral Pulse, Mucous Membrane Color, Peripheral temperature).

If there is not adequate response to therapy, the remainder volume can be given as a colloid such as Haemacell, Dextran or Hetastarch (10-20 ml/kg/day). Therefore, colloids should also be considered if the total protein is less than 3.5 gm/dl. In cats, the best response is achieved with colloid bolus 5 – 10 ml per cat. If there is a glucose level less than 60 mg/dl, a bolus of 50% dextrose should be given at a volume of 0.5-1 ml/kg, diluted with and equal volume of saline, IV.

If the microorganism source can be identified, samples should be aseptically obtained and submitted for culture and sensitivity. While wait for the culture results, antibiotic therapy should be instituted. Broad-spectrum antibiotics should be selected based on the suspected pathogen organism.

Intravenous empirical antimicrobial therapy directed to all potential infections sources should be given as early as possible. Coverage should always include Staphylococcus, Streptococcus and E. Coli.

Infectious process requiring surgical drainage or debridement should be treated promptly. Cardiopulmanry unstable function is not an acceptable reason to delay surgical treatment if sepsis is the cause of instability.

Frequent complications associated to the Septic Shock patients are sepsis and GI ulceration. Use of Famotidine, Ranitidine may help to reduce the risk of ulceration. If there is evidence of GI hemorrhage, Sucralfate 1-5 ml TID is indicated by oral tube if needed.

Nutrition is the key to maximize the likelihood of healing in septic patients, and enteral nutrition is the best choice to feed both to the patient and to the enterocytes. If the patient do not eat despite adequate GI protective and antiemetic drugs, a farynge - esophageal tube can be placed for short-term enteral nutrition. Otherwise, total parenteral nutrition (TPN) is very expensive and does not provide nutritional support of the enterocytes.

Finally, good hospital care is very important for the patient’s well being, like prevention of decubital ulcers keeping patients on soft padded surfaces covered with absorbent material to prevent scalding by urine and feces.
Catheters must to be checked daily and the entrance point must be routinely desinfected.

There is something new in Sepsis Treatment

- **Drotrecogin alfa (activated):** Activated plasma protein C, Xigris®, Lilly, Germany, was developed in 2001 as recombinant human product. It been show to exert anti-inflammatory effects by inhibiting cytokine production in monocytes and reducing adhesive interactions between neutrophils and endothelial cells. Bernard et al, 2001, report that Xigris® substantially reduce the mortality in humans with sepsis. After a preliminary report of Healy, 2002, in November of 2001, Drotrecogin alfa, was approved for clinical use in USA, but still there is a intense debate about benefits and risks, specially in septic infants or lower risk groups.

- **Macrophage Migration Inhibitory Factor (MIF):** MIF is a cytokine produced by T cells, macrophages, pituitary cells, monocytes and some others. MIF can activate production of pro-inflammatory cytokines in macrophages and has been found in the plasma of patients with severe sepsis and septic shock. Mitechell in 2002, report that blockade of MIF improved survival in mice models and the it administration enhanced mortality in a LPS challenge model. However, certain evidences reported by Satoskar et al, 2001, suggest that inhibition of MIF can impair the macrophage activity against other aggresions like parasites and Salmonella infections.

- **Nitric Oxide Synthase Inhibitor:** Nitric oxide is widespread cell product that produce severe vasodilation and hypotension, despite of many other deleterous effects on sepsis patients. Bakker et al, 2004 report that using an specific inhibitor of the synthase enzyme, improve the resolution of shock conditions in patients with severe sepsis and septic shock.

- **Venous Filters:** Thromboembolism is well recognized complication in sepsis patients, and in multiple trauma or burned septic patients, coexists with venous thrombosis, means a contraindication for the anticoagulation therapy. Waknine, 2003, communicate that using a Vena Cava Filter in septic patients, obtain a considerable improve in the management of thromboembolism compare with regular anticoagulant therapy.

- **N-acetylcisteine (NAC):** NAC, an precursor of gluthatione, have many antioxidant capabilities. Many studies has shown that using NAC in sepsis patients, maybe beneficial due to improvement of liver function and reduction in adhesion of cytokines. Paterson, 2003 and Vargas, 2004, report results that support of using NAC in sepsis patients.
• **Vasopressin and its analogs:** The vasopressin stimulates V1a receptors in the vascular pathway (Vasoconstriction) and the V2 receptors (renal water reabsorption) in the kidney. Both can increase the mean arterial pressure during the vasodilatory shock in the late stage in sepsis. By the other hand, Tsuneyoshi and Boyle, 2003, describe that vasopressin has a fibrinolytic activity, that can be useful in the treatment of septic shock.

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