**SURVIVING SEPSIS: DOES ANYTHING MAKE A DIFFERENCE?**

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Key Points

- Sepsis is the systemic inflammatory response to infection.
- Early and aggressive resuscitation is accomplished with fluids and pressors/inotropes and should be completed as soon as possible after sepsis identification.
- Early antibiotic administration is consistently associated with better patient outcomes.

Sepsis is a common and potentially deadly consequence of severe infection. Fundamentally, sepsis is the systemic inflammatory response (SIRS) resulting from unbridled disseminated inflammation. The trigger for SIRS in sepsis is a microbial toxin such as endotoxin from gram-negative organisms or the release of exotoxins or peptidoglycans from gram-positive organisms. Fungi and protozoal organisms can also induce sepsis. White blood cells and platelets are recruited to sites of inflammation by cytokines, such as tumor necrosis factor and IL-1, and contribute to inflammation and local activation of the coagulation cascade. Normally, a balance of pro and anti-inflammatory cytokines keeps the inflammation and coagulation at a local level. Dysregulation of this local response leads to systemic inflammation and microthrombosis which can progress to organ dysfunction and failure.

The terminology associated with sepsis and SIRS can be confusing. In 1992 consensus definitions were established to assist with identifying sepsis patients.

- **SIRS** is the clinical syndrome associated with the systemic response to trauma or infection.
- **Sepsis** is SIRS secondary to infection.
- **Severe sepsis** is sepsis associated with organ dysfunction, poor perfusion, or hypotension.
- **Septic shock** is severe sepsis with hypotension that is unresponsive to fluid resuscitation.
- **Multiple organ dysfunction syndrome (MODS)**, is the abnormal function of organ systems associated with response to advanced SIRS.

The Surviving Sepsis Campaign

Sepsis has an extremely high mortality rate, estimated to be approximately 30% in people with severe sepsis and up to 50% of those in septic shock. Mortality in dogs is also approximately 50%, with increasing mortality rates for dogs with MODS. Based on the unacceptably high human mortality rate, a group of international experts in sepsis and critical care came together in 2001 and issued the “Barcelona Declaration” in an attempt to improve recognition and outcome for patients with sepsis. Their ultimate goal was to reduce worldwide sepsis mortality by 25% within five years via a 6 point action plan which included Awareness, Diagnosis, Treatment, Education, Counseling, and Referral of septic patients. Furthermore, the group began a critical evaluation of evidence to form a set of recommendations known as the “Surviving Sepsis Campaign (SSC)” which uses the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to help qualify the quality of evidence from high (A) to very low (D) and to clarify the strength of recommendations (1=strong, 2=weak). The first evidence-based recommendations were published in 2004 and these were revised and updated with new data in 2008. Yet another update is currently underway, with the new recommendations...
Recognizing Sepsis in Dogs and Cats

Paramount to success is appropriate early identification of the septic patient, which can be difficult, especially in the cat. Animals fulfilling the SIRS criteria (below) should be evaluated for the possibility of an underlying causative septic focus.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dog</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (beats/min)</td>
<td>&gt;120</td>
<td>&lt;140 or &gt;225</td>
</tr>
<tr>
<td>Respiratory Rate (resps/min)</td>
<td>&gt;40 or PaCO2 &lt;30 mmHg</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Temperature</td>
<td>&lt;100.4°F or &gt;104.0°F</td>
<td>&lt;100°F or &gt;104°F</td>
</tr>
<tr>
<td>Leukogram</td>
<td>&gt;18,000 or &lt;5000 WBC/μL</td>
<td>&gt;19,000 or &lt;5000 WBC/μL</td>
</tr>
</tbody>
</table>

Sepsis occurs as a continuum of clinical signs. Early stages are marked by a hyperdynamic response (except the cat) while later stages are marked by progressive SIRS and MODS. In the dog, early signs of sepsis include tachycardia, bounding pulses, rapid capillary refill time, red mucous membranes, fever, and decreased blood glucose. Tachycardia and an increase in cardiac contractility occur in response to tissue hypoxia. Bounding pulses result from the increase in cardiac output coupled with the systemic vasodilation. Vasodilation is also the cause of the injected (bright red) mucous membranes that characterize this early “hyperdynamic” phase of septic shock in the dog. Fever is induced by the effects of inflammatory mediators on the thermoregulatory centers in the brain. Signs of late sepsis include hypoglycemia, thready pulses, prolonged capillary refill time, pale mucous membranes, cool extremities, stupor, hypothermia and multiple organ failure. Distributive shock is caused by massive inflammatory mediator-induced systemic vasodilation and myocardial dysfunction.

The hyperdynamic phase of septic shock is not appreciated in cats; they do not develop injected mucous membranes, bounding pulses, or sometimes even tachycardia. Sepsis in cats is generally marked by lethargy, pale mucous membranes, tachypnea, weak pulses, hypotension, hypothermia, icterus, and diffuse abdominal pain (even in the absence of a primary abdominal problem). Cats may present with tachycardia or a relative bradycardia, a heart rate which is inappropriately low given the state of shock (e.g. 120-140 bpm).

Sepsis Therapy: Implementing Sepsis Bundles

Because the volume of data presented in the Surviving Sepsis Campaign was immense, the recommendations were simplified by grouping them into “severe sepsis bundles.” The bundles are defined as groups of therapies that may be more efficacious when implemented together, rather than individually. The two sepsis bundles include the Sepsis Resuscitation Bundle and the Sepsis Maintenance Bundle.

Resuscitation Bundle: Much of the resuscitation bundle is based on a landmark study by Rivers, et al which showed a marked reduction in mortality rate for patients treated with “Early Goal-Directed Therapy” during the first 6 hours in the emergency department. The goal is for the bundle to be applied 100% of the time within 6 hours for patients with severe sepsis, septic
shock, or a lactate ≥4 mmol/L. The resuscitation bundle includes 1) measuring serum lactate, 2) obtaining cultures prior to antibiotic administration, 3) broad spectrum antibiotic administration as soon as possible after identification of sepsis, 4) treating hypotension, and 5) maintaining adequate central venous pressure and central venous oxygen saturation.

**Management Bundle:** The management bundle includes 1) administration of low-dose steroids for septic shock, 2) administration of human activated protein C (rhAPC), 3) maintaining adequate glycemic control, and 4) preventing excessive inspiratory plateau pressures in mechanically ventilated patients.

**Individual Bundle Components**

**Fluid Therapy and Management of Hypotension:** Combinations of isotonic and hypertonic crystalloids and colloids are used for fluid resuscitation. Resuscitation should begin immediately upon identification of hypotension or hyperlactatemia. Fluid boluses should be used to treat hypotension as long as there is a response to the boluses. SSC recommends hemodynamic targets of a mean arterial pressure of >65 mmHg, a central venous pressure of 8-12 mmHg, central venous oxygen saturation of >70%, urine output >0.5 mL/kg/hr. After volume resuscitation, ongoing fluid therapy with crystalloids, synthetic colloids, and biologic colloids (plasma) is continued to address hypovolemia, dehydration, ongoing fluid losses, electrolyte imbalances, low oncotic pressure and coagulopathies (DIC).

Constant rate infusions of inotropes or pressors may be needed for hypotensive patients unresponsive to fluid resuscitation. The two SSC drugs of choice are dopamine and norepinephrine (GRADE 1C) and the goal is to titrate them to a mean arterial pressure of > 65 mmHg (Grade 1C). Vasopressin is considered a third line therapy, with addition of vasopressin to norepinephrine expected to yield an effect equivalent to norepinephrine alone. Dobutamine is recommended for patients with a high cardiac filling pressure and low cardiac output (1C).

Many studies exist looking at fluid types and responses in septic animals, with each fluid seeming to have pros and cons in different situations. Fluid overload has recently become a hot topic in human critical care, as it has been associated with increased mortality in many studies. Studies evaluating pressors and inotropes in veterinary species also show mixed responses to individual drugs.

**Lactate** production is a byproduct of anaerobic metabolism. Decreased oxygen delivery (oxygen content, blood flow, blood pressure) and decreased lactate metabolism (hepatic dysfunction) can contribute to lactate accumulation. Lactate levels are prognostic in human septic shock, particularly if hyperlactatemia is persistent despite therapy. Lactate is also a better prognosticator that oxygen variables and may be better at identifying patients with hypoperfusion that are not yet hypotensive. Studies in dogs have also shown an association between higher lactate levels and persistent hyperlactatemia with poorer prognosis. Several point of care devices can be reliably used for lactate measurement in small animals. Given its frequent association with prognosis, it makes sense to measure lactate in critically ill patients.

**Cultures and antimicrobial therapy:** Obtaining appropriate cultures is recommended as long as it does not interfere with timely starting of antibiotic therapy. (GRADE 1C) SSC recommends obtaining two or more blood cultures from septic patients; one or more should be percutaneous and one should be obtained from every vascular access device that has been in place for >48 hours. Other pertinent sites should also be cultured with the same caveat. Site of infection should be identified quickly (Grade 1C) and source control should be achieved as soon as possible after successful resuscitation (Grade 1C).
Intravenous antibiotics should be started within 1 hour of recognizing severe sepsis (GRADE 1D) or septic shock (GRADE 1B). Pending culture and sensitivity results, initial empirical antibiotic choice should be broad spectrum (GRADE 1B) and cover gram negative, gram positive and anaerobic organisms or cover the presumed organisms common at the presumed source of infection. Antibiotic choice must also take into account penetration at the site of infection, potential side effects, and underlying organ dysfunction in the patient. Once culture and sensitivity results have been obtained, antibiotic choices may need to be changed. If combination therapy is employed, the regimen should be reduced once susceptibilities are available (Grade 1D) or decreased once a noninfectious cause is identified (Grade 1D). Total duration of therapy is limited to 7-10 days unless the source cannot be drained or immune deficiencies are present (Grade 1D).

Multiple human sepsis studies looking at timing of antibiotic therapy have been published since the last SSC recommendations. Most support early administration of appropriate antibiotics. Worse prognosis has been reported for patients that start antibiotics after achieving septic shock. Patients at low risk of death receiving combination therapy had higher mortality than those receiving monotherapy in one study. One study showed mortality was no worse for patients started on the wrong antibiotic (organisms ultimately found not to be susceptible) as long as it was started early after sepsis identification. There are no veterinary studies critically evaluating antibiotic timing in sepsis.

Stereoids are essential for maintenance of vasomotor tone and vascular response to catecholamines, thus, physiologic doses of steroids may be indicated in patients with absolute or relative adrenal insufficiency. Relative adrenal insufficiency has been documented in humans and animals with sepsis. Patients are suspected of having sepsis-induced adrenal insufficiency based on persistent hypotension (septic shock) despite adequate fluid loading and lack of response to pressors and inotropes; these patients may benefit from a supraphysiologic dose of corticosteroids. SSC does not recommend ACTH testing in those thought to have adrenal insufficiency in sepsis. The drug of choice in human medicine is hydrocortisone for its glucocorticoid and mineralocorticoid effects. If using a steroid without mineralocorticoid effects, concurrent fludrocortisone may be used.

Recombinant human activated protein C has been shown to reduce mortality in patients with a high risk of death (APACHE II > 25 or multiple organ failure). Activated protein C is a vitamin K dependent serine protease which has both anticoagulant as well as cytoprotective and anti-inflammatory actions. Infusions of activated protein C (APC) were shown to decrease mortality (APC 25% mortality vs placebo 31%, relative risk 0.81P=0.005) and decreased organ dysfunction in patients at high risk of death (APC 31% organ failure vs placebo 44%). APC is not shown to be beneficial for early sepsis patients that are not at high risk for death. This drug is extremely expensive and not likely going to be a part of veterinary sepsis therapy any time soon.

References: