PART 2: STABILIZATION & TREATMENT

Systemic Inflammatory Response Syndrome & Sepsis

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Early recognition of patients with systemic inflammatory response syndrome (SIRS) and sepsis is imperative in order to optimize the chance of patient survival. Early intervention is then necessary to minimize further tissue ischemia, cellular damage, and organ injury.

Part 1 of this series—Systemic Inflammatory Response Syndrome & Sepsis: Recognition & Diagnosis (January/February 2015)—addressed early recognition. This article will discuss stabilization and treatment, focusing on:
- Rapid circulatory support
- Appropriate antimicrobial choices
- Goal-directed supportive measures.

STABILIZATION WITH FLUID THERAPY

Patients with SIRS or sepsis commonly have decreased systemic oxygen delivery. Optimizing cardiovascular function helps support tissue perfusion and minimizes further ischemic damage.

While early aggressive fluid therapy is essential to help increase cardiac output, tailoring fluid requirements to individual patient needs is important to avoid the detrimental effects of fluid overload. Patients with SIRS/sepsis may be resuscitated and supported with one or more of the following fluids:
- Isotonic crystalloids
- Hypertonic crystalloids
- Synthetic colloids
- Blood component therapy.

Isotonic Crystalloids

Isotonic crystalloids are the cornerstone for resuscitation and treatment of patients with SIRS/sepsis.

In patients with severe cardiovascular shock (noncardiogenic), the safest way to administer these fluids, and tailor fluid resuscitation to the patient, is to:
1. Administer and repeat small 10 to 20 mL/kg boluses
2. Then closely monitor patient response to each bolus.

In normal animals, approximately 30% of the volume administered remains in the vasculature 30 minutes after isotonic crystalloid administration, with the remainder lost into the interstitium and via the kidneys. However, patients with SIRS/sepsis often have vascular leak syndrome, which can lead to even more fluid loss from the intravascular space. Therefore, judicious fluid therapy is especially important in these patients.1

In addition, excessive isotonic crystalloid administration may quickly lead to intravascular fluid overload and subsequent cardiogenic pulmonary edema.2 Thus, these patients require close monitoring of physical examination parameters and their response to fluid therapy.

The practice of delivering a “shock dose” of fluids—90 mL/kg (dogs) and 50 mL/kg (cats)—as a single bolus is no longer recommended due to predisposition to volume overload.

Hypertonic Crystalloids

Administration of hypertonic (7%–7.5%) sodium chloride, also known as hypertonic saline (HTS), causes a transient osmotic shift of water from the extravascular to the intravascular compartment in interstitially hydrated animals.

Evidence suggests that HTS may also aid in:3–5
- Increasing cardiac contractility
- Reducing endothelial swelling
- Mildly vasodilating the peripheral vasculature
- Modulating the inflammatory response.

A 3 to 5 mL/kg IV bolus of HTS may be administered at a rate not to exceed 1 mL/kg per minute, which avoids dangerous adverse effects, such as vagally mediated hypotension, bradycardia, and bronchoconstriction.6,7 The volume-expanding effects of HTS are greatest 30 minutes after infusion; then gradually decline over the following 2 to 4 hours.1

Signs of Positive Patient Response to Isotonic Crystalloids
- Improved pulse quality
- Decreased lactate level
- Decreased heart rate
- Improved mentation
Because osmotic diuresis results after HTS administration, additional therapy with isotonic crystalloids or colloids is indicated to prevent interstitial dehydration and maintain volume expansion. However, HTS therapy should not be repeated due to risk for hypernatremia.

**Synthetic Colloids**

Colloids are large molecules (molecular weight > 10,000–20,000 Da) that, theoretically:

- Do not leave the vascular space
- Are hyperoncotic to normal animals
- Help pull fluid to, and keep it within, the vascular space.

Synthetic colloids may be useful in patients with SIRS/sepsis, especially if they are hypoproteinemic.

**Hydroxyethyl starch solutions**, such as hetastarch (Hextend, hospira.com), are commonly used and are suspended in an isotonic crystalloid solution. **Tetras starch solutions**, such as VetStarch (abbotanimalhealth.com), have been more recently studied, and at standard doses may have less of a tendency to cause coagulopathies than hetastarch.

The recommended dose for hydroxyethyl starch solutions is up to 20 mL/kg Q 24 H in dogs and cats. However, this dose is frequently exceeded when deemed clinically necessary; close monitoring for adverse effects is recommended.

Bolus therapy for hydroxyethyl starch solutions in dogs should be delivered in 5-mL/kg increments up to 20 mL/kg; in cats, 3- to 5-mL/kg increments up to 10 mL/kg should be used.

Constant rate infusions (CRIs) of hydroxyethyl starch solutions of 1 to 2 mL/kg/H can be administered to increase oncotic pressure in stable, hypoproteinemic patients.

Adverse effects of excessive synthetic colloid use may include volume overload, hemodilution, coagulopathy, platelet dysfunction, and acute kidney injury.

Even though evidence is lacking in veterinary patients, there is serious concern in human medicine that colloid solutions may be associated with an increased need for renal replacement therapy. As a result, use of synthetic colloids in humans has been dramatically reduced in recent years.

**Blood Products**

The need for blood products in patients with SIRS/sepsis depends on the disease process and individual characteristics of the patient.

**Red blood cell (RBC) transfusion** may benefit patients with:

- Recent blood loss (or RBC lysis)
- Requirement for general anesthesia and surgery

1. **Use transfusion therapy** to help maintain PCV > 25% in animals with acute anemia secondary to loss or lysis of RBCs.
2. **Use colloids and/or plasma therapy** in animals with acute hypoproteinemia to maintain colloid osmotic pressure > 16 mm Hg or total solids > 4.5 g/dL. Note: Synthetic colloid therapy makes refractometer readings inaccurate.
3. **Consider plasma therapy** to maintain coagulation times within reference ranges.
4. **Monitor and maintain serum glucose** within the normal range with insulin therapy or dextrose supplementation, as needed.
5. **Monitor and supplement electrolytes**, as needed.
6. **Ensure a mean arterial pressure** of at least 65 to 70 mm Hg (not > 130 mm Hg).
7. **Maintain heart rate** between 70 and 120 beats/min (may be breed dependent); administer antiarrhythmic agents, as needed.
8. **Monitor for increased respiratory rate and effort** as an early indicator for volume overload/pulmonary edema/acute lung injury.
9. **Monitor and ensure urine output** of at least 1 to 2 mL/kg/H.
10. **Use supplemental oxygen**, as needed, to maintain a pulse oximeter reading > 93% or PaO₂ > 80 mm Hg. To prevent oxygen toxicity, do not use inspired oxygen concentrations of > 60% for > 24 hours.

- Packed cell volume (PCV) below 25% to 30%.
- **Fresh frozen plasma therapy** may benefit patients with:
  - Evidence of bleeding
  - Prolonged clotting times.
  
Other important parameters that help determine a patient’s transfusion needs are increasing lactate level, changes in respiratory rate, and increasing heart rate; all of these are possible indicators of poor oxygen delivery to the tissues.

Suggested doses for transfusion therapy are:

- Packed RBCs: 10 to 15 mL/kg
- Fresh whole blood: 20 to 25 mL/kg
- Fresh frozen plasma: 15 mL/kg.

Therapy should be guided by the individual patient’s response and improvement of tissue perfusion parameters.

**Albumin Therapy**

Albumin is critical for the transport of drugs, chemicals, toxins, bilirubin and enzymes, and for wound healing.

Animals with SIRS/sepsis and severe hypoalbuminemia (ie, albumin level < 2 g/dL) may benefit from concentrated albumin (human or canine)
therapy. Studies in dogs showed that administration of human albumin increased circulating albumin concentrations, total solids, and colloid osmotic pressure. However, sensitization, acute and delayed reactions, and potentially lethal complications from administration of human albumin to dogs have been reported. Therefore, this treatment should be reserved for patients that are:

- Severely hypoalbuminemic
- At high risk for complications secondary to hypoalbuminemia (i.e., severely ill perioperative patients)
- Likely to benefit from hyperoncotic infusion, such as hypoalbuminemic patients with concurrent hypovolemia and hypotension.

When administering 25% human albumin (250 mg/mL), use the following approach:

1. Calculate the albumin deficit (in g) as:
   \[
   \text{Albumin Deficit} = 10 \times (\text{Serum Albumin Goal} [\text{g/dL}] - \text{Patient's Serum Albumin} [\text{g/dL}]) \times \text{Body Weight} (\text{kg}) \times 0.3
   \]
   or approximately 2 to 3 g/kg

2. Administer the first part of the calculated dose at up to 2 mL/kg over 1 to 2 H

3. Monitor closely for a reaction; then reduce the rate to 0.3 mL/kg/H as a CRI for the remaining dose.

Canine albumin—which is sold as a lyophilized product that has had intermittent availability in recent years—may offer a safer alternative, but further research will prove useful.

### VASOPRESSOR & INOTROPE THERAPY

Patients with SIRS/sepsis can develop hypotension—as a result of excessive vasodilation—despite adequate intravascular volume replacement. This vascular relaxation may necessitate use of adjunct vasoactive agents.

**Treatment for persistently hypotensive patients includes:**

- Maximizing cardiac function with fluid therapy and inotropic drugs and/or
- Modifying vascular tone with vasopressor agents, including catecholamines (i.e., epinephrine, norepinephrine, phenylephrine, dopamine), and vasopressin.

See **When to Use a Vasopressor Drug.**

Most vasopressor drugs are given as a CRI. Initially, the lowest recommended dose is typically used, with upward titration every 15 to 30 minutes based on the patient’s cardiovascular response. Table 1 provides dosages of commonly administered vasopressors.

The general aim of treatment—an attempt to support vital organ perfusion—is a mean arterial pressure of 65 to 70 mm Hg or Doppler blood pressure of > 100 mm Hg.

#### Dopamine

Dopamine has dopaminergic, beta-adrenergic, and alpha-adrenergic effects at varying doses. In a given patient, the actual dose response is unpredictable, but the range typically varies between 5 to 12 mcg/kg/min in hypotensive patients.

#### Norepinephrine

Norepinephrine has preferentially alpha-adrenergic effects, acting as a pressor in animals with normal or increased cardiac output states. Recent human studies have shown that, in septic patients, more renal protective effects and successful outcomes

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**TABLE 1. Receptor Activity, Cardiopressor Effects, & Dosages of Commonly Administered Vasopressors**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RECEPTOR ACTIVITY</th>
<th>EFFECT ON</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta-1 Beta-2 Alpha-1 &amp; Alpha-2</td>
<td>Contractility</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>+++ +++ 0</td>
<td>↑ ↑ ↑ ↑</td>
<td>↑ ↑ ↑</td>
</tr>
<tr>
<td>Dopexamine</td>
<td>0 ++ 0</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>++ + +</td>
<td>↑ ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Dopamine</td>
<td>++ + ++</td>
<td>↑ ↑</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>+ + + +</td>
<td>↑ ↑</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++ +++ +++</td>
<td>↑ ↑ ↑ ↑ ↑</td>
<td>↑ ↑ ↑ ↑</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+ 0 +++</td>
<td>↑</td>
<td>Variable</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>0 0 +++</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0 0 0</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>Angiotensin</td>
<td>0 0 0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a. Activity ranges from **no activity** (0) to **maximal activity** (+++)

b. Effects estimated for higher dose ranges; possible cardiopressor effects include a **mild** (1 arrow), **moderate** (2 arrows), or **marked** (3 arrows) decrease or increase.

are seen when norepinephrine is used as the first-line pressor of choice rather than dopamine. This is most likely because norepinephrine is associated with fewer tachyarrhythmias and a more predictable dose-response curve. In addition, in some patients, dopamine can adversely affect renal blood flow at relatively low doses.

**Epinephrine**

Epinephrine is a potent pressor with mixed alpha- and beta-agonist activity. Compared to other vasopressor drugs, it may have increased proarrhythmogenic effects and a greater tendency to impair splanchnic blood flow. Epinephrine is rarely used as a first-line vasopressor agent due to its high rate of adverse effects, but it may be indicated in critically ill animals.

**Phenylephrine**

Phenylephrine acts as a pure alpha-agonist drug, resulting in profound vasoconstriction. It is typically used in patients unresponsive to other sympathomimetics, but may be considered a sole first-line agent in vasodilated, hypotensive animals. Due to its lack of beta-agonist activity, it is the least arrhythmogenic of the sympathomimetic pressors and may be desirable in patients already displaying tachyarrhythmias. However, adequate cardiac contractility should be confirmed before administering phenylephrine as a sole vasoactive agent because of risks for increased afterload due to this drug’s strong alpha effects.

**Dobutamine**

Dobutamine is a pure beta-agonist that results in increased cardiac output and oxygen delivery and mild peripheral vasodilation. It is useful in patients with decreased systolic function, but may worsen tachyarrhythmias and increase cardiac oxygen consumption.

**Vasopressin**

Vasopressin is a nonadrenergic vasoconstrictor agent with both direct and indirect effects on the vascular smooth muscle via V1 receptors. During the early stages of shock, endogenous vasopressin is released to help stabilize arterial pressure and organ perfusion, but this results in depleted hypothalamic stores during prolonged states of shock. Use of low-dose vasopressin in the later stages of catecholamine-refractory vasodilatory shock may be beneficial. Vasopressin is also more effective in severely acidicemic patients because, in states of low pH, the catecholamine response is blunted.

**ANTIBIOTIC THERAPY**

In recent human guidelines for treatment of sepsis, one of the only treatments that significantly decreased the risk for death was initiation of appropriate antimicrobials as soon as possible. The risk for death secondary to sepsis increased by 7.6% every hour that appropriate antimicrobial use was delayed. In septic dogs, early empiric antimicrobial therapy has proven beneficial. When an early antibiotic protocol was used to treat intra-abdominal sepsis, survival increased from 60% to 70%

Before antimicrobial administration, obtain samples from any suspected sources of sepsis for culture and susceptibility testing, if possible. Common fluid samples submitted for culture include urine, respiratory secretions (endotracheal or transtracheal wash), pleural or peritoneal fluid, wound exudates, and blood (if endocarditis highly suspected). Once samples have been obtained for culture, or if high suspicion for a septic process exists but samples cannot be obtained immediately, initiate broad-spectrum therapy.

**TABLE 2. Empiric Broad-Spectrum Antimicrobial Options for Dogs & Cats with SIRS/Sepsis**

<table>
<thead>
<tr>
<th>ANTIBIOTIC COMBINATIONS</th>
<th>DOSAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic Combinations</strong></td>
<td></td>
</tr>
<tr>
<td>Ampicillin and Enrofloxacin</td>
<td>22 mg/kg IV Q 6–8 H and 15 mg/kg IV Q 24 H (dogs); 5 mg/kg IV Q 24 H (cats)</td>
</tr>
<tr>
<td>Ampicillin and Amikacin</td>
<td>22 mg/kg IV Q 6–8 H and 15 mg/kg IV Q 24 H</td>
</tr>
<tr>
<td>Clindamycin and Cefotaxime</td>
<td>10 mg/kg IV Q 8–12 H and 40 mg/kg IV Q 8 H</td>
</tr>
<tr>
<td>Clindamycin and Enrofloxacin</td>
<td>10 mg/kg IV Q 8–12 H and 15 mg/kg IV Q 24 H (dogs); 5 mg/kg IV Q 24 H (cats)</td>
</tr>
<tr>
<td><strong>Single Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Ticarcillin/clavulanic acid</td>
<td>50 mg/kg IV Q 6 H</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>15–30 mg/kg IV Q 4–6 H</td>
</tr>
<tr>
<td>Imipenem</td>
<td>5–10 mg/kg IV Q 6–8 H</td>
</tr>
</tbody>
</table>
spectrum antimicrobial therapy as soon as possible (Table 2, page 39).

- Empirical antimicrobial choices should be effective against gram-positive, gram-negative, and anaerobic bacteria.
- If the patient has recently received antibiotic therapy, a higher-tier antimicrobial combination may be indicated to combat potential inherent antimicrobial resistance.

**GASTROINTESTINAL THERAPY**

Gastrointestinal (GI) bleeding and dysfunction secondary to SIRS/sepsis is common:

- Decreased perfusion to the GI mucosa may lead to excessive gastric acid secretion, impaired protective mucus secretion, and subsequent ulceration.
- GI transit time may be significantly decreased by cardiovascular instability, the SIRS/sepsis inflammatory cascade, and opioids used for analgesia.

Strategies to minimize and treat GI upset include use of antiemetics, antacids, promotility agents, and early enteral nutrition (Table 3).

**CARE AFTER STABILIZATION**

**Enteral Feeding**

Once a patient has been stabilized, nutritional needs should be addressed. If tolerated by the patient, enteral feeding is preferred to maintain GI villi health, decrease bacterial translocation, and encourage gastric motility. See Options for Enteral Feeding.

**TABLE 3. Gastrointestinal Drugs for Dogs & Cats with SIRS/Sepsis**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DRUG</th>
<th>MODE OF ACTION</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antacids</strong></td>
<td>Omeprazole</td>
<td>Proton pump inhibitor</td>
<td>0.7–1 mg/kg PO Q 24 H</td>
</tr>
<tr>
<td></td>
<td>Pantoprazole</td>
<td>Proton pump inhibitor</td>
<td>0.7–1 mg/kg IV Q 24 H</td>
</tr>
<tr>
<td></td>
<td>Famotidine</td>
<td>Histamine-2 receptor antagonist</td>
<td>0.5–1 mg/kg IV or PO Q 12–24 H</td>
</tr>
<tr>
<td><strong>Antiemetics</strong></td>
<td>Ondansetron</td>
<td>Serotonin-3 receptor antagonist 1</td>
<td>0.2–0.8 mg/kg IV Q 8 H</td>
</tr>
<tr>
<td></td>
<td>Dolasetron</td>
<td>Serotonin-3 receptor antagonist</td>
<td>0.6 mg/kg IV Q 12–24 H</td>
</tr>
<tr>
<td></td>
<td>Maropitant</td>
<td>NK-1 receptor antagonist</td>
<td>1 mg/kg IV or SC Q 24 H</td>
</tr>
<tr>
<td><strong>Promotility Agents</strong></td>
<td>Metoclopramide*</td>
<td>5-HT3 antagonist 5-HT4 agonist Dopamine-2 receptor antagonist Muscarinic effects</td>
<td>1–2 mg/kg/day IV CRI</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>5-HT3 agonist Motilin agonist</td>
<td>0.5–1 mg/kg PO or IV Q 8 H</td>
</tr>
<tr>
<td></td>
<td>Ranitidine</td>
<td>Acetylcholinesterase inhibitor</td>
<td>1–2 mg/kg PO or IV Q 12 H</td>
</tr>
</tbody>
</table>

* Also an antiemetic; recent evidence suggests that higher doses (> 3x) may be needed for promotility effects.

**FIGURE 1.** A critically ill postoperative patient receiving total parenteral nutrition, multiple vasopressor agents, oxygen therapy with nasal cannula, and intensive fluid therapy.
**Assistance** for feeding methods that can be used alone or in combination.

**Parenteral Nutrition**

Pursue parenteral nutrition if enteral feeding results in vomiting, nausea, or abdominal pain, and does not appear to be well tolerated.

Parenteral nutrition is typically administered through a centrally placed IV catheter due to its high osmolality, which may cause thrombophlebitis if given peripherally (Figure 1). However, isotonic parenteral nutrition solutions can be delivered through a peripheral catheter if central venous access is not possible.

Patients should be monitored every 12 to 24 hours for:
- Electrolyte derangements (phosphorus, magnesium, potassium, and sodium fluctuations)
- Hyperglycemia
- Lipemic serum.

Electrolytes should be supplemented as indicated, and hyperglycemia should be avoided because, in humans, it has been associated with a higher risk for infection and morbidity.23

**In-Hospital Monitoring**

 Patients with SIRS/sepsis can be very dynamic and require frequent adjustment and changes in treatment; thus, close monitoring of patient parameters is important (Table 4, page 42). Intensively manage these animals in a hospital with 24-hour care. Figure 2 demonstrates a critically ill patient receiving intensive monitoring, including continuous electrocardiography and direct measurement of arterial blood pressure.

**PROGNOSIS**

Prognosis for patients with SIRS/sepsis depends on the type of underlying disease, ability to correct the underlying disease process, and patient’s response to aggressive treatment and supportive care.

Due to the typical prolonged length of hospitalization, intensive monitoring, and necessity for 24-hour care, these patients require a substantial financial commitment from their owners, and regardless of cause, SIRS/sepsis has a high mortality rate in both humans and animals. The most common causes of a declining condition, even with

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**FIGURE 2.** A critically ill patient receiving total parenteral nutrition through a jugular catheter, multiple fluids and drug infusions, oxygen therapy with a mask, and close monitoring via continuous electrocardiography and direct arterial blood pressure measurement.
Examination

Important Patient Parameters to Table 4.

Analysis

Body weight Other

Tinton Falls, New Jersey. at Red Bank Veterinary Hospital in her small animal rotating internship university of Pennsylvania and completed She received her VMD from University McGowan, VMD, is a sec- 4.0 Tinton Falls, New Jersey.

Physical Examination

Capillary refill time Mucous membrane color Pulse rate and quality Respiratory rate and effort Rectal and extremity temperature Thoracic auscultation

Blood Analysis

Body weight Blood pressure Electrocardiography Pulse oximetry Urine output

Other

Blood gas: pH, PCO₂, HCO₃⁻, lactate, PO₂ Blood glucose Chemistry values: creatinine, bilirubin, albumin Coagulation parameters: prothrombin time, activated partial thromboplastin time, D-dimer Complete blood count: white blood cell and platelet counts Electrolytes: sodium, potassium, chloride, magnesium, phosphate PCV/total solids

Chemistry values: creatinine, bilirubin, albumin Coagulation parameters: prothrombin time, activated partial thromboplastin time, D-dimer Complete blood count: white blood cell and platelet counts Electrolytes: sodium, potassium, chloride, magnesium, phosphate PCV/total solids

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Aggressive treatment, include cardiovascular collapse, persistent coagulation abnormalities, multiorgan dysfunction syndrome, and acute lung injury. A patient’s chance of survival depends on:

- Early recognition of SIRS/ sepsis process
- Aggressive early fluid resuscitation
- Early appropriate antimicrobial use
- Identification and treatment of underlying disease process
- Close monitoring and treatment of anemia and coagulation disorders.

CRI = constant rate infusion; GI = gastrointestinal; HTS = hypertonic saline; PCV = packed cell volume; RBC = red blood cell, SIRS = systemic inflammatory response syndrome

References


3. Rizoli SB, Rhind SG, Shek PN, et al. The immunomodulatory

2. Cotton BA, Guy JS, Morris JA, et al. The cellular, metabolic and

References


