SYSTEMIC INFLAMMATORY RESPONSE SYNDROME, SEPSIS, AND MULTIPLE ORGAN DYSFUNCTION

Colleen A. Brady, DVM, and Cynthia M. Otto, DVM, PhD

The onset of inflammation triggers a complex set of interactions within a highly sophisticated immune system to minimize injury and preserve function. Injury or pathogenic invaders are promptly dealt with by a tightly regulated local inflammatory defense that includes the cellular response to injury, neurohumoral defenses, and the anti-inflammatory cascade, which modulates the degree of inflammation.

A controlled inflammatory response can become quickly dysregulated by ongoing injury, the addition of new physiologic insults (e.g., hypoxia, hypoperfusion, infection, surgery), or a compromised immune system (e.g., immunosuppressive therapy, primary immune-mediated disease). This compounding factor leading to the progression from a local to a systemic inflammatory response is the basis for the "second-hit" theory.28

An unchecked inflammatory response can progress to organ dysfunction, organ failure, and death. Once multiple organ dysfunction has developed, mortality exceeds 50%.12 Despite recent developments in the understanding of the pathophysiologic findings of the systemic inflammatory response syndrome (SIRS), sepsis, and multiple organ dysfunction syndrome (MODS), treatment remains largely supportive.55 Numerous clinical trials targeting different stages of the inflammatory cascade, the patient’s immune response, and specific pathogens have

From the Section of Critical Care, Department of Clinical Studies, Veterinary Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
not demonstrated any consistent benefit. In light of the high mortality associated with MODS, aggressive clinical efforts should be directed at preventing these sequelae.

The purpose of this article is to review the understanding of sepsis and multiple organ dysfunction and to illustrate our current concepts through a clinical application. To further this goal, several terms need to be defined, because they are frequently used in the veterinary and human clinical literature.\textsuperscript{1} It is important to recognize that much of our understanding of SIRS, sepsis, and MODS is extrapolated from the human literature and the research laboratory. Although much of the available information is valuable and applicable, a true understanding of these syndromes in companion animals requires controlled veterinary studies.

1. Bacteremia: The presence of live bacteria in the bloodstream
2. SIRS: Clinical manifestation of the systemic response to injury or microbial invasion. Physiologic derangements indicative of SIRS are listed in Table 1. It is important to note that SIRS can occur with injury or infection. Identification of SIRS is useful for recognizing patients at risk of progression to severe sepsis and MODS; however, the lack of specificity in this criterion is a serious limitation.
3. Sepsis: The inflammatory response to infection with gram-negative or gram-positive bacteria or viral, protozoal, or fungal organisms
4. Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Clinical manifestations include lactic acidosis, oliguria, and altered mentation.
5. Septic shock: Sepsis with hypotension despite fluid resuscitation. (Specific endpoints for fluid resuscitation and a definition of hypotension are not available in the veterinary clinical literature.)
6. MODS: The derangements of cardiovascular, pulmonary, renal, neurologic, coagulation, gastrointestinal (GI), and hepatic function in response to SIRS or sepsis

\textbf{PATHOPHYSIOLOGIC FINDINGS}

Gram-negative infections are the best described cause of sepsis; however, gram-positive, fungal, viral, and protozoal micro-organisms also can initiate the SIRS/sepsis cascade. Noninfectious causes of SIRS include pancreatitis, heatstroke, snake envenomation, tissue trauma (e.g., crush injury, major surgery, burns), and neoplasia.\textsuperscript{11}

Regardless of the inciting cause, the inflammatory response is mediated by cytokines initially released from macrophages in response to tissue injury or microbial invasion. Activation of macrophages is the essential initial step in the SIRS/sepsis cascade.\textsuperscript{14} A complex series of interactions between macrophages, other leukocytes, and endothelial cells results in cell activation and release of additional cytokines, eicosa-
Table 1. CRITERIA FOR SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>Dogs</th>
<th>Cats*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>&gt;120 bpm</td>
<td>&lt;140 bpm or &gt;225 bpm</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>&gt;40 bpm or PaCO₂ &lt;30 mm Hg</td>
<td>&gt;40 bpm</td>
</tr>
<tr>
<td>Temperature</td>
<td>&lt;100.4°F or &gt;104.0°F</td>
<td>&lt;100.0°F or &gt;104.0°F</td>
</tr>
<tr>
<td>Leukogram</td>
<td>&gt;18,000 white blood cells/μL or &lt;5000/μL</td>
<td>&gt;19,000 white blood cells/μL or &lt;5,000/μL</td>
</tr>
</tbody>
</table>

Note. The term sepsis implies the presence of systemic inflammatory response syndrome (SIRS) secondary to an infection. Traditionally, two or more criteria are needed for the diagnosis of SIRS.

*The cat may show bradycardia rather than tachycardia in critical illness.

bpm = beats per minute.


noids, and free radicals. A controlled response maintains a balance between proinflammatory mediators and anti-inflammatory mediators. A disproportionate response is the hallmark of SIRS.11,14 An imbalanced immune response may be caused by excess activity on the proinflammatory side, decreased anti-inflammatory mediators (i.e., loss of negative feedback), or immune paralysis (i.e., excessive anti-inflammatory mediators).6 Classic proinflammatory mediators include tumor necrosis factor (TNF) and interleukin (IL)-1. Anti-inflammatory mediators include IL-4 and IL-10.47

In the veterinary clinical literature, gram-negative enteric bacteria are the most commonly described cause of sepsis.2,8,13,18,23 Gram-negative bacterial endotoxin (lipopolysaccharide [LPS]) is the best-characterized trigger of SIRS/sepsis and the most powerful stimulus recognized clinically. LPS binds to LPS-binding protein in the plasma. This complex binds to the CD14 receptor on macrophages.14 The LPS/LPS-binding protein/CD14 complex stimulates the Toll-like receptor 4 on the macrophage membrane, which results in activation of the macrophage. It is this activation that is required for the initiation and perpetuation of the inflammatory response.

Gram-positive sepsis can be mediated by soluble exotoxins called superantigens, which trigger a response similar to LPS but act through the Toll-like receptor 2. Bacterial superantigens directly stimulate T-cell proliferation and activate macrophages through major histocompatibility complex class II receptors without the intermediate step of antigen recognition and presentation.32 The best-known example of gram-positive sepsis is Streptococcus canis infection, which can result in toxic shock syndrome and necrotizing fasciitis in the dog.27,37 It is important to recognize that gram-positive sepsis is often triggered in the absence of exotoxins. Cell wall components (e.g., peptidoglycans, lipoteichoic acid, bacterial DNA) can trigger cytokine release, complement activation, endothelial cell activation, and platelet aggregation. Cell wall compo-
ments are markedly less potent stimuli for TNF release than endotoxin. LPS is 1000 times more potent than peptidoglycan as a stimulus for TNF release; this helps to explain why gram-positive sepsis is much less frequent than gram-negative sepsis.¹⁶

Acute pancreatitis is a well-recognized trigger of SIRS.²⁰ The early systemic manifestations of acute pancreatitis (e.g., tachycardia, fever, tachypnea) are a result of cytokine release by leukocytes invading the injured pancreatic acini. In animal models, IL-1 and TNF are also produced by the pancreatic acinar cells and then later in the liver, lung, and spleen.¹⁵ The pancreatic tissue levels of TNF and IL-1 with acute pancreatitis are high enough to have direct cytotoxic effects in the absence of activated enzymes.⁹,¹⁵ The interplay of inflammatory mediators such as IL-1, TNF, bradykinin, platelet-activating factor, complement, nitric oxide, and free oxygen radicals results in vascular leakage, hypovolemia, acute respiratory distress syndrome, shock, and MODS. The strong correlation between increasing serum concentrations of IL-6 and increased severity of acute pancreatitis has led some physicians to use serum IL-6 concentrations to guide intensity of treatment.²²

A 6-year-old, overweight, female, spayed Black Labrador Retriever is brought to the hospital for a 3-day history of profuse vomiting and hematochexia. The findings of the initial physical examination are listed in Table 2.

An abdominal ultrasound scan suggests severe necrotizing pancreatitis and an abdominal effusion. The abdominal effusion is a modified transudate with degenerate neutrophils and no bacteria present. The working diagnosis is severe necrotizing pancreatitis.

The clinical picture presented here illustrates a classic presentation of the inflammatory response. The presence of tachycardia, tachypnea, and pyrexia fulfills the established criteria for SIRS.¹⁹ The hyperdynamic phase of SIRS is characterized by normal to increased cardiac output and manifests clinically as brick red mucous membranes, rapid capillary refill time, tachycardia, and bounding pulse quality. Cardiac output is maintained by increasing heart rate or stroke volume to maintain perfu-

<table>
<thead>
<tr>
<th>Table 2. FINDINGS OF INITIAL EXAMINATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Examination</strong></td>
</tr>
<tr>
<td>Temperature = 103.6°F</td>
</tr>
<tr>
<td>Heart rate = 160 bpm</td>
</tr>
<tr>
<td>Respiratory rate = 40 bpm</td>
</tr>
<tr>
<td>Normal auscultation</td>
</tr>
<tr>
<td>Dark pink mucous membranes</td>
</tr>
<tr>
<td>CRT &lt;1 second</td>
</tr>
<tr>
<td>Bounding pulse</td>
</tr>
<tr>
<td>Painful distended abdomen</td>
</tr>
<tr>
<td>Melena on rectal examination</td>
</tr>
</tbody>
</table>

bpm = beats per minute; CRT = capillary refill time; PCV = packed cell volume; TS = total solids; BUN = blood urea nitrogen; BE = base excess; MAP = mean arterial pressure.
sion in the face of decreased systemic vascular resistance and decreased preload. The hemodynamic instability of early sepsis or SIRS is characterized by this hyperdynamic state, which involves components of distributive shock and may progress to become compounded by hypovolemic and cardiogenic shock. TNF is a major mediator of this early phase. Many of the clinical signs of SIRS, including pyrexia, peripheral vasodilation, and increased vascular permeability, can be reproduced in the laboratory by administration of TNF.

TNF and other mediators are direct negative inotropes and contribute to the progression of SIRS and development of cardiogenic shock. Local thrombosis and myocardial hypoxia may further exacerbate systolic dysfunction. Ultimately, myocardial depression compromises cardiac output and tissue perfusion, leading to late-stage sepsis. Clinically, lactic acidosis and an elevated base excess (BE) reflect inadequate tissue perfusion.

Hyperglycemia may be seen with early sepsis caused by enhanced glycogenolysis secondary to the actions of the counterregulatory hormones: epinephrine, growth hormone, and cortisol. Increased hepatic gluconeogenesis is common and is not inhibited by hyperglycemia. An abnormally high glucagon-to-insulin ratio occurs, and a shift from oxidation of glucose to preferential metabolism of fatty acids perpetuates the hyperglycemia. Hypoalbuminemia is common and reflects increased vascular permeability as well as decreased hepatic production. Hyperbilirubinemia and mild elevations in liver enzymes are common with sepsis and reported in the veterinary clinical literature. The mechanism of this hyperbilirubinemia is partially through endotoxin-mediated inhibition of the sodium–potassium–adenosine triphosphatase pump, which depresses the movement of conjugated bilirubin to the bile canaliculi. In addition, TNF decreases hepatocyte membrane pumps and transporters for bile acids by 50% to 90% in laboratory models. Initial fluid therapy is directed at restoring perfusion through replacement of volume deficits. Both crystalloids and colloids or a combination of the two may be used. There is no documented benefit to the use of one fluid type over the other. Appropriate responses to fluid therapy include restoration of perfusion as shown by improvements in blood pressure, heart rate, and capillary refill time. Objective measures of restored perfusion include improvements in lactate values and BE.

The dog is treated with a bolus of 20 mL/kg of isotonic crystalloids, and fluids are continued at 6 mL/kg/h. She responds well to initial therapy and is much improved over the next 6 hours. Heart rate is 120 beats per minute, mean arterial pressure is 70 mm Hg, capillary refill time is 1 to 2 seconds, and pulses are less bounding. A database reveals that lactate is 3 mmol/L and BE is −4.

**SHOCK ORGANS**

Recognition of SIRS/sepsis allows for anticipation of several physiologic events. The GI tract is the shock organ in the dog. SIRS is associated
with shunting of blood flow away from the mesentery, resulting in decreased GI integrity. Clinical manifestations include ulceration, melena, and ileus. Compromised GI defenses may allow bacterial translocation. The vulnerability of the GI tract is the basis for gastric tonometric monitoring. Decreases in gastric intramucosal pH reflect decreased perfusion to the stomach and may serve as an early indicator of mucosal ischemia.

The lung seems to be the most vulnerable organ in the cat, as respiratory failure is the most frequent finding in cats with sepsis. Pulmonary edema and pleural effusion often limit the fluid volume that can be administered for resuscitation. Early signs of dyspnea are subtle in the cat. Frequent thoracic auscultation with serial recordings of respiratory rate and effort may help to identify early respiratory compromise.

COAGULATION ABNORMALITIES

The early phase of sepsis is associated with a hypercoagulable state caused by progressive endothelial cell activation and dysfunction. There is upregulation of tissue factor (TF) and adhesion molecule expression and release of platelet-activating factor. TF is a glycoprotein secreted by activated endothelial cells and monocytes into the circulation, and it is normally present in minute quantities. TF is a thrombogenic molecule, and the hypercoagulable state is correlated with increased TF activity. TF is not routinely measured, and no other routine coagulation evaluation is able to predict hypercoagulability; however, decreased antithrombin III (AT3), increased fibrinogen, and abnormal thromboelastography were recently shown in dogs with septicemia secondary to parvovirus enteritis.

In sepsis, the inhibitory coagulant pathways are downregulated, including important anticoagulants: protein C, AT3, and thrombomodulin. Protein C is a vitamin K-dependent protein that is activated by the thrombin-thrombomodulin complex on endothelial cells. Activated protein C inhibits the procoagulant activity of factors V and VIII. Septicemic foals with circulating endotoxin have greatly decreased activity of protein C and AT3. TNF decreases thrombomodulin-mediated activation of protein C.

Endothelial cell activation and platelet sludging cause widespread microvascular injury, resulting in tissue edema, maldistribution of blood flow, and local tissue hypoxia. Deleterious effects of this hypercoagulable state include pulmonary thromboembolism, formation of microthrombi in peripheral vasculature, and progression to disseminated intravascular coagulation (DIC). No proven clinical benefit has been established for the use of anticoagulants (i.e., heparin) in early sepsis. Newer studies examining the effects of selective inhibition of coagulation with protease inhibitors show some promise.

The dog is admitted to the intensive care unit and treated with plasma, fluids, antiemetics, intraperitoneal bupivacaine, intravenous analgesics, and ampicillin. Nevertheless, she continues to vomit overnight; the vomitus has an
increasingly fetid odor. Monitoring overnight includes temperature, pulse quality + rate, respiration (TPR)/auscultation every 4 hours; blood pressure every 4 hours; and packed cell volume (PCV), total solids (TS), glucose, and electrolytes every 6 hours.

**BACTERIAL ISOLATION AND ANTIBIÓTICS**

Several hematologic and biochemical abnormalities are common to all patients with sepsis, and some are specific to the underlying disease. Leukogram changes are variable. A leukocytosis may be present early in sepsis. The presence of band and toxic neutrophils is an indication of increasing severity.

Unlike sepsis, the use of antibiotics in SIRS is controversial. Recognition that SIRS can occur without a microbial cause has led some clinicians to pause before prescribing antibiotics. Clear indications for antibiotics include a leukogram with a left shift or marked toxic change, GI bleeding (e.g., melena, hematemesis), immune suppression, and clinical deterioration of the patient.

Identification of the nidus of infection can be difficult in some patients. Common foci of sepsis in dogs include but are not limited to peritonitis, pyometra, pyelonephritis, pneumonia, and endocarditis. Cats have similar septic foci, including peritonitis, pneumonia, pyothorax, and pyelonephritis (Table 3). Prompt collection of culture specimens

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Common Bacteria and Prevalence</th>
<th>Common Bacteria and Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Enteric ++</td>
<td>Enteric ++</td>
</tr>
<tr>
<td></td>
<td>Pasteurellae +</td>
<td>Pasteurellae +</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Anaerobes ++</td>
<td>Anaerobes ++</td>
</tr>
<tr>
<td>Pyothorax</td>
<td>Staphylococci ++</td>
<td>Staphylococci ++</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Enteric ++</td>
<td>Enteric ++</td>
</tr>
<tr>
<td></td>
<td>Anaerobes ++</td>
<td>Anaerobes ++</td>
</tr>
<tr>
<td>Septic peritonitis</td>
<td>Staphylococci ++</td>
<td>Staphylococci ++</td>
</tr>
<tr>
<td>Renal</td>
<td>Enteric ++</td>
<td>Enteric ++</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Staphylococci ++</td>
<td>Staphylococci ++</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Enteric ++</td>
<td>Enteric ++</td>
</tr>
<tr>
<td></td>
<td>Anaerobes +</td>
<td>Anaerobes +</td>
</tr>
<tr>
<td>Prostatic abscess</td>
<td>Staphylococci ++</td>
<td>Staphylococci ++</td>
</tr>
<tr>
<td>Pyometra</td>
<td>Streptococci +</td>
<td>Streptococci +</td>
</tr>
</tbody>
</table>

Microbial sensitivity may differ between hospitals.
Data from references 2, 8, 13, 17, 18, and 23.
(e.g., blood, urine, abscesses, bronchoalveolar fluid) is recommended. It is well documented that clinical outcome is improved when antibiotic therapy is based on culture results. Obtaining culture specimens is not always safe, however, especially in patients with severe pulmonary compromise or coagulopathies. Although a positive blood culture confirms septicemia, negative blood cultures are common and do not rule out sepsis.

The early use of broad-spectrum antibiotics is essential for early stabilization of the septic patient. The goal of early intervention is to arrest the progression of sepsis to severe sepsis, septic shock, and multiple organ failure. Septic patients may have a greater volume of distribution than normal, and plasma antibiotic concentration should be monitored when available. Recommended intravenous regimens for broad-spectrum antibiotics in the septic patient include the following:

- Ampicillin (22 mg/kg every 8 hours) and amikacin (15 mg/kg every 24 hours) or gentamicin (6 mg/kg every 24 hours)
- Cefazolin (22 mg/kg every 8 hours) and amikacin (15 mg/kg every 24 hours) or gentamicin (6 mg/kg every 24 hours)
- Cefoxitin (30 mg/kg once, then 15 mg/kg every 4 hours)
- Ampicillin (22 mg/kg every 8 hours) and ceftazidime (22 mg/kg every 8 hours)
- Ampicillin (22 mg/kg every 8 hours) and enrofloxacin (10 mg/kg every 24 hours in dogs, 5 mg/kg every 24 hours in cats)
- Clindamycin (10 mg/kg every 12 hours) and enrofloxacin (10 mg/kg every 24 hours in dogs, 5 mg/kg every 24 hours in cats)

For resistant organisms, the following regimens are recommended:
- Ticarcillin/clavulanic acid (50 mg/kg every 6 hours) and enrofloxacin (10 mg/kg every 24 hours in dogs, 5 mg/kg every 24 hours in cats)
- Imipenem (3–10 mg/kg every 6–8 hours)

The findings of evaluation of the dog 8 hours later are listed in Table 4.

Based on the evaluation, we are concerned that the patient is in late-stage septic shock (the hypodynamic or “cold” form). Hypothermia, tachycardia, peripheral vasoconstriction, tachypnea, and hypoglycemia are all indications of advanced sepsis and overwhelming infection.

HEMODYNAMIC RESUSCITATION

Addressing the hemodynamic instability of this patient begins with an accurate evaluation of the volume status. Blood volume is commonly assessed indirectly from measurements of arterial pressure, heart rate, urine output, and hematocrit. Placement of a central line allows central venous pressure (CVP) monitoring, which provides a more accurate assessment of blood volume than the indirect measures. Traditionally, adequate blood volume is reflected by a CVP of 8 to 10 mm Hg, although
Table 4. FINDINGS OF EXAMINATION AT 8 HOURS

<table>
<thead>
<tr>
<th>Physical Examination</th>
<th>Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature = 98.4°F</td>
<td>PCV = 38%</td>
</tr>
<tr>
<td>Heart rate = 180 bpm</td>
<td>TS = 4.2 g/dL</td>
</tr>
<tr>
<td>Respiratory rate = 60 bpm (with panting)</td>
<td>Glucose = 40 mg/dL</td>
</tr>
<tr>
<td>Crackles on right side on auscultation</td>
<td>BUN = 12 mg/dL</td>
</tr>
<tr>
<td>Pale pink mucous membranes</td>
<td>pH = 7.21</td>
</tr>
<tr>
<td>CRT = 3 seconds</td>
<td>Base excess = −16</td>
</tr>
<tr>
<td>Pulse quality = weak</td>
<td>Lactate = 10 mmol/L</td>
</tr>
<tr>
<td>Painful distended abdomen</td>
<td>Icteric serum</td>
</tr>
<tr>
<td>Recumbent</td>
<td>MAP = 35 mm Hg</td>
</tr>
<tr>
<td>Rectal examination reveals melena</td>
<td>PT/PTT are prolonged (×3)</td>
</tr>
<tr>
<td></td>
<td>Platelets = 65,000 per microliter</td>
</tr>
</tbody>
</table>

bpm = beats per minute; PCV = packed cell volume; TS = total solids; BUN = blood urea nitrogen; CRT = capillary refill time; MAP = mean arterial pressure; PT/PTT = prothrombin time/partial thromboplastin time.

trends may be more important than absolute numbers.\textsuperscript{21} The CVP should never be used as the sole determinant of volume status, however. CVP values and changes in the CVP after therapy depend on venous wall compliance, which accommodates to wide variations in blood volume. Recognition of the limitations with this tool can facilitate appropriate interpretation of the information generated.\textsuperscript{33} The CVP is increased by blood volume, impaired cardiac function, increased intrathoracic or increased intra-abdominal pressure, vasopressors, and fluid therapy. Decreased CVP is present with reduced intrathoracic pressures, vasodilators, hypovolemia, and sudden fluid losses.\textsuperscript{40}

A fluid challenge can be helpful in determining volume status. For example, a dog with an initial CVP of 0 mm Hg would be given 10 to 20 mL of crystalloids over 10 to 20 minutes. The CVP should immediately rise after the bolus. If the CVP stays elevated (4–5 mm Hg) after 20 minutes, the fluid challenge was adequate. If the CVP drops back to baseline, more fluids are needed. If the CVP remains high, consider heart failure or hypervolemia. An arterial catheter can be placed in the dorsal pedal artery for continuous direct-pressure monitoring and arterial gas analysis.\textsuperscript{21} A urinary catheter is necessary for careful monitoring of urine output and fluid balance.

The initial CVP is 4 mm Hg. The initial systolic pressure is 65 mm Hg, diastolic pressure is 23 mm Hg, and mean arterial pressure is 38 mm Hg. The patient is administered a bolus of 30 mL/kg of crystalloid, 10 mL/kg of colloid, and 0.5 g/kg of 50% dextrose diluted in an equivalent volume of crystalloid. The dog seems more alert after the bolus. The CVP rises to 10 mm Hg. The systolic pressure increases to 72 mm Hg, the diastolic pressure is 30 mm Hg, and the mean arterial pressure is 42 mm Hg.

If appropriate volume resuscitation does not correct hypotension, therapy to address myocardial depression and decreased vascular resistance may be indicated. Beta-adrenergic stimulation often corrects myo-
cardial depression.\textsuperscript{38} Dobutamine and dopamine are the first line of therapy, and epinephrine is reserved as a second-line therapy (Table 5). Although dobutamine and dopamine can be used in dogs and cats, the authors tend to first use dopamine in cats and dobutamine in dogs.

Systemic vascular resistance can be improved through the use of alpha-adrenergic agents. Generalized vasoconstriction helps to normalize peripheral resistance by moving blood from large-capacitance vessels to the central circulation.\textsuperscript{37} Dopamine in low doses is often the first choice, because the concurrent stimulation of dopaminergic receptors may preserve blood flow to the kidneys in dogs. Note that recent research has demonstrated that the feline kidney lacks dopamine receptors.\textsuperscript{53} Clinical experience suggests that dopamine is an effective agent at restoring blood pressure in the cat. Norepinephrine and high-dose epinephrine have marked vasoconstrictive effects. Phenylephrine primarily has alpha effects and is also an effective vasoconstrictor. Caution should be used when prescribing vasopressors, because use of vasoconstricting agents may compound already compromised visceral perfusion and may increase cardiac workload.\textsuperscript{47} In some cases, inotropes may be necessary before or concurrent with vasopressors.

The goal of maintaining blood pressure is to maintain oxygen delivery to the tissues. The major systemic determinant of cardiac output is regional vascular resistance. Local control of tissue perfusion is at the level of the arterioles, capillaries, and precapillary venules. Sepsis disrupts local microvascular control, causing unregulated opening of capillary beds, decreased peripheral resistance, maldistribution of cardiac output, and overperfusion of some organs at the expense of others.\textsuperscript{45} Functional shunting of blood at the periphery occurs. It is important to remember that the exogenous administration of vasopressors does not allow redistribution of cardiac output to the tissues with the greatest oxygen needs and may actually compromise perfusion of some tissues.

Prolonged use of all catecholamines results in decreased sensitivity to their effects, because receptors are downregulated in the target tissues.

\begin{table}
\centering
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Drug} & \textbf{Receptor} & \textbf{Clinical Effect} & \textbf{Dose Range} \\
\hline
Dobutamine & $\beta_1$: ++ + & Inotropic & 5-20 $\mu$g/kg/min \\
 & $\beta_2$: + & Mild chronotrope, mild vasodilation & \\
Dopamine & Da: ++ + & Inotropic & 5-20 $\mu$g/kg/min \\
 & $\beta$: ++ + & Chronotropic & \\
 & $\alpha$: + (higher doses) & Vasoconstriction, diuresis (canine) & 1-5 $\mu$g/kg/min \\
Epinephrine & $\beta$: ++ + & Inotropic & 0.005-0.1 $\mu$g/kg/min \\
 & $\alpha$: ++ + & Chronotropic & (double dose in cats) \\
Norepinephrine & $\beta$: + & Vasoconstriction & 0.05-1.0 $\mu$g/kg/min \\
 & $\alpha$: ++ + & Mild inotropic & \\
Phenylephrine & $\alpha$: ++ + & Vasoconstriction & 0.05-0.2 $\mu$g/kg/min \\
\hline
\end{tabular}
\caption{Circulatory Support and Catecholamine Use in Sepsis}
\end{table}
Clinical research is being conducted in people to determine the role of adrenal exhaustion and catecholamine dependency in sepsis. The use of vasopressin as a vasopressor in refractory septic shock is undergoing clinical trials in human medicine and may prove to be a valuable adjunctive therapy.24

Clinical signs of late-stage sepsis are more commonly recognized than signs of hyperdynamic sepsis in cats. Relative bradycardia (<140 beats per minute) in a hypotensive cat is an indication of inadequate cardiovascular compensation. Some cats with hypotension refractory to fluid resuscitation and catecholamine support may show improvement with low doses of anticholinergic drugs (0.01 mg/kg of atropine or 0.005 mg/kg of glycopyrrolate administered intravenously or intramuscularly). Doppler measurement of blood pressure in a cat is fraught with error, especially near the low range. Doppler measurements should always be evaluated within the context of a complete clinical evaluation; pharmacologic intervention should not be solely based on the Doppler-derived estimate.

A dobutamine constant-rate infusion (CRI) is started at 5 μg/kg/min, and a dopamine CRI is started simultaneously at 3 μg/kg/min. The mean arterial pressure increases to 48 mm Hg, and diastolic pressure increases to 40 mm Hg. There is no change in heart rate. Urine output is 0.8 mL/kg/h. The dobutamine CRI is increased to 10 μg/kg/min, and the mean arterial pressure increases to 60 mm Hg. Urine output increases to 3 mL/kg/h.

PCV and TS should be checked frequently during fluid resuscitation. Anemia and hypoproteinemia may limit volume loading, because excessive hemodilution (PCV <20%, TS <3) can be harmful. Remember to give the fluids a chance to equilibrate. Aggressive fluid therapy in a patient with decreased oncotic pressure and increased vascular permeability can cause volume overload. This commonly manifests as pleural effusion or pulmonary edema in the cat and severe bowel edema in the dog. Generalized edema in the dog seems to be a negative prognostic indicator. One of the earliest signs of edema in the dog is swelling at the hocks and gastrocnemius tendons.

Dextrose should be supplemented as needed to maintain normal serum glucose concentrations. Hypoglycemia can contribute to poor vascular tone and impaired mentation. The reticuloendothelial system is also depressed by hypoglycemia; euglycemia is essential for normal phagocytic function.10

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC) is frequently seen in the septic/SIRS population. Fibrin and microthrombi deposition in microvascular beds contributes to ongoing tissue damage, poor perfusion and dysregulation of oxygen delivery.46 High levels of plasminogen activator inhibitor limit degradation of fibrin. The treatment of DIC is
controversial. Currently, therapy is still directed at correcting the inciting cause; however, newer therapies target specific sites in the coagulation cascade. Use of AT3 or protein C concentrates is undergoing human clinical trials with mixed results. In veterinary medicine, nonspecific replacement of AT3 and coagulation factors is often attempted with fresh-frozen plasma transfusions.

The search for new septic foci in the deteriorating patient is essential. Only reversal of the inciting cause can ultimately halt the downward spiral. Careful attention should be paid to the pulmonary, renal, and abdominal cavities as sites of common secondary infection. Catheter sites should be unwrapped and examined carefully.

Further diagnostics performed on this patient included an arterial blood gas, repeat thoracic radiographs, abdominal ultrasound, a complete blood cell count and chemistry profile, urinalysis, and urine culture. An alveolar pattern in the right middle and right cranial lung lobes is evident on thoracic radiographs. Abdominal ultrasound examination confirms pancreatitis but does not reveal evidence of a pancreatic abscess. Abdominal effusion shows no intracellular bacteria. Arterial blood gas reveals hypoxemia (partial pressure of arterial oxygen \( [PaO_2] = 72 \) mm Hg) and a widened alveolar-arterial gradient (48 [normal < 15]). The complete blood cell count reveals a nonregenerative anemia and leukopenia with a left shift (3400 white blood cells per microliter with 10% bands). Abnormalities on the chemistry panel include azotemia, hypoalbuminemia, elevated serum alkaline phosphatase, serum alanine transaminase, and decreased bicarbonate. Urine sediment shows white blood cells with intracellular and extracellular rods. Working diagnoses include necrotizing pancreatitis, aspiration pneumonia, and bacterial cystitis versus pyelonephritis.

**MULTIPLE ORGAN DYSFUNCTION**

MODS is a frustrating complication of the sepsis/SIRS complex and is responsible for 50% to 80% of all deaths in human surgical intensive care units.\(^{12}\) Independent of the triggering event, MODS usually progresses on a similar path in all patients. Signs of pulmonary and GI compromise are often the earliest indicators and manifest clinically as hypoxia, melena, and ileus. Prolonged clotting times and thrombocytopenia are indications of failure in the coagulation system. Hepatic and renal insufficiency manifests as hyperbilirubinemia, azotemia, and oliguria. Overt cardiac failure is usually a late manifestation, although arrhythmias may occur early. Neurologic abnormalities such as depression and coma can occur at any time.

Despite extensive research, there are few available data to help identify patients at the greatest risk for developing MODS.\(^{29,30}\) Several theories regarding causative factors for the development of MODS are being explored.\(^{44}\) One hypothesis suggests that inadequate resuscitation with prolonged tissue hypoxia causes irreversible cell damage in end organs. Hypoxia limits adenosine triphosphate availability to cells and alters gene expression and free radical production. Cells are further
compromised through reperfusion injury when ischemia is corrected. Intuitively, the duration of shock is correlated with mortality. Organ insult from microthrombi secondary to DIC may also play a role in the initiation and progression of MODS. A cycle is created in which MODS exacerbates tissue hypoxia, which perpetuates end organ dysfunction.

Thirty percent of human patients who die with bacteremia from multiple organ failure have no known site of infection. This has led to the hypothesis of bacterial translocation from the ischemic GI tract in patients with sepsis or SIRS. In addition to bacterial invasion, mesenteric ischemia leads to cytokine release from the gut-associated lymphoid tissue and macrophages residing in the lamina propria. Along with release of inflammatory mediators from the mesenteric lymph, bacteremia can result in end organ damage.

The two-hit theory of SIRS suggests that MODS occurs after multiple physiologic insults. For example, a trauma patient may be able to tolerate a severe orthopedic injury but the secondary pneumonia may prove fatal. The repeated stimulation of the immune system results in massive derangement of homeostatic mechanisms.

PATIENT MONITORING AND THERAPEUTIC INTERVENTION

Vigilant patient monitoring and aggressive supportive care are essential. Careful attention to body weight changes, urine sediment analysis, pain, and mentation allows early detection of dysfunction. Frequent urine sediment evaluation may detect tubular casts, which may precede oliguria and changes in blood urea nitrogen or creatinine as an indicator of early renal injury.

The patient is treated with oxygen supplementation. Antibiotic coverage is expanded to ampicillin and enrofloxacin. Dobutamine and dopamine infusions are continued to maintain a mean arterial pressure of 60 to 70 mm Hg and a urine output of at least 1 mL/kg/h. A balanced electrolyte solution with 2.5% dextrose supplementation (4 mL/kg/h) and hetastarch (1 mL/kg/h) is given to maintain a CVP of 8 to 10. Subjective monitoring includes respiratory rate and effort, pulse quality, and mucous membrane and capillary refill time every 2 hours. Objective monitoring includes continuous electrocardiographic, CVP, and arterial pressure tracings. Temperature and urine output are checked every 4 hours. Electrolytes, PCV, TS, and glucose are checked every 4 to 6 hours. The patient is weighed, and catheter sites are unwrapped and checked every 8 to 12 hours.

CONCLUSIONS

At our current level of understanding of SIRS, sepsis, and MODS, clinical intervention is still largely supportive. Growing familiarity with
the pathophysiologic findings of uncontrolled inflammation and the role of immune paralysis increases the potential for future pre-emptive therapeutics and recognition of early signs of dysfunction. Current work unraveling the relation between the coagulation system and the inflammatory system should provide new insights and possible therapeutic regimens. The advent of clinical tools that objectively measure hypercoagulability may allow more specific uses and titration of anticoagulant therapy. SIRS and MODS continue to be the most challenging of clinical syndromes.

References

39. Shirey T: The use of lactate to identify the severity of trauma and to guide therapy. Trauma Care 10:26-28, 2000

Address reprint requests to
Colleen A. Brady, DVM
Section of Critical Care
Department of Clinical Studies
University of Pennsylvania
3900 Delancey Street
Philadelphia, PA 19104–6010

e-mail: cbrady@vet.upenn.edu