CHAPTER 91
SEPSIS AND SEPTIC SHOCK

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KEY POINTS

- Sepsis is a clinical syndrome of systemic inflammation in response to infection. Much of the morbidity and mortality associated with sepsis is a result of the host's inflammatory response.
- Alterations in the regulation of vasomotor tone, increased vascular permeability, dysfunctional microcirculation, and coagulation abnormalities are hallmarks of sepsis.
- Microcirculatory abnormalities are often present in the face of normal macrohemodynamics.
- Treatment should be directed at targeted resuscitation, early administration of antimicrobials if bacterial sepsis is suspected, and controlling the source of infection.
- Untreated sepsis can progress to septic shock, which is characterized by hypotension, vascular leak, and microvascular dysfunction. This macrocirculatory and microcirculatory impairment leads to tissue and global oxygen debt, organ failure, and possibly death.

Sepsis, severe sepsis, and septic shock are common causes of morbidity and mortality: The incidence of severe sepsis in humans in the United States is high, killing one in four patients or approximately 215,000 people each year.[1,2] The incidence of sepsis in veterinary medicine is unknown, but the mortality rates appear to be similar, ranging from 20% to 68%.[3-8] The incidence of sepsis is increasing in human health care, likely because of advanced and invasive treatments, widespread use of antimicrobials, increased incidence of resistant infections, and an increasing number of elderly, debilitated, and immunocompromised patients.[9] Recognition, early and aggressive intervention, and intensive supportive care are key to the treatment of sepsis and septic shock.

DEFINITIONS AND CLINICAL MANIFESTATIONS

In 2001 the International Sepsis Definitions Conference produced consensus guidelines for definitions and terminology for syndromes

BOX 91-1 *Definitions*[10,90]

Bacteremia: The presence of live bacterial organisms in the bloodstream.
Sepsis: The clinical syndrome caused by infection and the host's systemic inflammatory response to it; may be of bacterial (gram positive or gram negative), viral, protozoal, or fungal origin.
Severe sepsis: Sepsis complicated by dysfunction of one or more organs.
Septic shock: Acute circulatory failure and persistent arterial hypotension (despite volume resuscitation) associated with sepsis. In people, hypotension is defined by a systolic arterial pressure less than 90 mm Hg, a mean arterial pressure less than 60, or a reduction in systolic pressure of greater than 40 mm Hg from baseline despite adequate volume resuscitation, in the absence of other causes of hypotension.[10]
Systemic inflammatory response syndrome (SIRS): The clinical signs of systemic inflammation in response to infectious or noninfectious insults (e.g., trauma, pancreatitis, burns, snakebites, neoplasia, and heat stroke).
Multiple organ dysfunction syndrome (MODS): Physiologic derangements of the endothelial, cardiopulmonary, renal, nervous, endocrine, and gastrointestinal (GI) systems associated with the progression of uncontrolled systemic inflammation and disseminated intravascular coagulation (DIC).

Table 91-1[5] Systemic Inflammatory Response Syndrome Criteria for Dogs and Cats

Species	Dogs	Cats
Temperature (Celsius/Fahrenheit)	<37.2/99, >39.2/102.5	<37.8/100.4, >40/104
Heart rate (beats/min)	>140	<140, >225
Respiratory rate (breaths/min)	>30	>40
WBC × 10^3/μl	<6, >19	<5, >19

WBC, White blood cells.

Table 91-2 Diagnostic Criteria for Sepsis in People (Defined as Known or Suspected Infection and Some of the Following)[10]

	Human Parameters
General Variables	
Fever	Core temperature >38.3°C
Hypothermia	Core temperature <36°C
Heart rate	>90/min or >2 SD above the normal value for age
Tachypnea	
Altered mental status	
Significant edema or positive fluid balance	>20 ml/kg over 24 hrs
Hyperglycemia	Plasma glucose >120 mg/dl in the absence of diabetes
Inflammatory Variables	
Leukocytosis	WBC count >12,000/μl
Leukopenia	WBC count <4000/μl
Normal WBC count with >10% immature forms	Normal WBC count with >10% immature forms
Plasma C-reactive protein	>2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value	>2 SD above the normal value
Tissue Perfusion Variables	
Hyperlactatemia	(>1 mmol/L)
Decreased capillary refill or mottling	
Other Variables	
$ScvO_2$	>70%
Cardiac index	>3.5 L/min

SD, Standard deviation; *WBC,* white blood cells.

Table 91-3 Diagnostic Criteria for Severe Sepsis in People (Defined as Sepsis with Organ Dysfunction)[10]

Organ Dysfunction Variables:	
Arterial hypoxemia	PaO_2/FiO_2 <300
Acute oliguria	Urine output <0.5 ml/kg/hr or 45 mmol/L for at least 2 hours
Creatinine	>2 mg/dl
Coagulation abnormalities	INR >1.5 or aPTT >60 seconds
Thrombocytopenia	Platelet count <100,000/μl
Hyperbilirubinemia	Plasma total bilirubin >2 mg/dl or 35 mmol/L

aPTT, Activated partial thromboplastin time; *INR,* international normalized ratio.

associated with microbial infection and the subsequent host response called systemic inflammatory response syndrome, or SIRS (Box 91-1 and Table 91-1; see Chapter 6).[5,10] SIRS has been previously described in veterinary patients.[5] Studies in both human and veterinary medicine are seeking to identify reliable and specific biomarkers of inflammation that can be used to assess the host inflammatory response to infection. Currently it is more feasible to use deviations in heart rate, respiratory rate, body temperature, and white blood cell count as markers of systemic inflammation. These clinical parameters are most valuable for screening sick patients for eligibility to participate in clinical studies of sepsis. The SIRS criteria lack specificity (many nonseptic patients can fit the criteria) and rarely dictate interventions but can help increase the index of suspicion for sepsis. In human medicine, *sepsis* is defined as a documented or suspected infection with one or more general or inflammatory variables that suggest the presence of SIRS (Table 91-2).[10] *Severe sepsis* is defined as a documented or suspected infection and signs of organ dysfunction such as those listed in Table 91-3.[10] Multiple organ dysfunction syndrome (MODS) involves the physiologic derangements of the endothelial, cardiopulmonary, renal, nervous, endocrine, microcirculatory, and gastrointestinal systems associated with progression of uncontrolled systemic inflammation and disseminated intravascular coagulation (DIC). *Septic shock* is defined as acute circulatory failure and persistent arterial hypotension despite volume resuscitation. Acute circulatory failure (in people) is defined as a systolic blood pressure of less than 90 mm Hg, mean arterial pressure of less than 60 mm Hg, or a reduction in systolic blood pressure greater than 40 mm Hg from baseline despite adequate volume.[10] In veterinary patients there are no studies to define critical blood pressures, but it is reasonable to consider that similar blood pressure values are appropriate.[11]

Sepsis is a clinical syndrome characterized by a systemic inflammatory response to a bacterial, viral, protozoal, or fungal infection. Bacteremia, defined by the presence of live organisms in the bloodstream, may be variably present in septic patients. The syndrome of sepsis includes the continuum of severity from uncomplicated (SIRS with an infection) to severe (where organ failure becomes a component) to septic shock (the development of hypotension despite volume resuscitation). The prognosis for survival decreases with

progression along this continuum and the associated progressive systemic inflammation, organ dysfunction, and ultimately cardiovascular collapse. Dysregulation of vasomotor tone, increased vascular permeability, dysfunctional microcirculation, and coagulation abnormalities are hallmarks of sepsis. The clinical manifestations and course of disease in patients with sepsis ultimately depend on the location of infection; virulence of the organism; size of inoculums; host nutritional status, comorbidities, age, immune response, and organ function; and genetic host response, including coding for cytokine genes, immune effector molecules, and receptors. After the 2001 International Sepsis Definitions Conference, a concept called *PIRO* was adopted to stage sepsis and to describe clinical manifestations of the infection and host response to it.[10] In this model, PIRO is an acronym for *p*redisposition, *i*nsult or *i*nfection, *r*esponse, and *o*rgan dysfunction. This conceptual and clinical framework attempts to incorporate patient factors with the microbial insult in order to stage the disease process and identify factors that may contribute to morbidity and mortality. The PIRO approach may employ advanced diagnostic techniques not yet available in veterinary medicine, but hopefully it can serve as a guideline until similar methods are available and validated.

PATHOGENESIS OF THE SEPTIC SYSTEMIC INFLAMMATORY RESPONSE

Microbial Factors

Sources for gram-negative sepsis commonly include the gastrointestinal (GI) and genitourinary systems. The gram-negative bacterial cell wall contains a potent molecule, lipopolysaccharide (LPS). This pathogen-associated molecular pattern (PAMP) is recognized as one of the most potent stimuli of the host immune response. Host recognition and reaction involves binding of LPS to lipopolysaccharide binding protein (LBP), followed by the LPS-LBP complex binding to membrane-bound CD14 on macrophages.[12,13] This binding activates the macrophage and initiates signaling transduction via the Toll-like receptors to the nucleus to start transcription of inflammatory cytokines,[14] most notably tumor necrosis factor-α (TNF-α), interleukin (IL) 1, IL-6, IL-8, and interferon γ. In addition to proinflammatory mediators, the response also generates production of counterinflammatory mediators (IL-4, IL-10, IL-13, transforming growth factor β, and glucocorticoids), also referred to as the compensatory antiinflammatory response syndrome, or CARS.[13]

Common sources for gram-positive sepsis include skin, injured soft tissue, and intravenous catheters.[15] Activation of the inflammatory cascade by gram-positive bacteria occurs in response to cell wall components (lipoteichoic acid, peptidoglycan, peptidoglycan stem peptides) or bacterial DNA or via elaboration of soluble bacterial exotoxins. Gram-positive bacterial exotoxins can act as "superantigens" and induce widespread activation of T cells, leading to uncontrolled release of inflammatory cytokines such as interferon γ and TNF-α.[13] In both gram-negative and gram-positive sepsis, interaction with these PAMPS largely drives the host response and clinical manifestations of sepsis.

Host Response to Bacterial Infection

Activation of macrophages initiates the sepsis-induced systemic inflammatory response, and TNF-α production is a key factor in the early phase of sepsis.[2] LPS is the most potent stimulus for the release of TNF-α, which acts as an early central regulator of interactions among cytokines. Macrophage-derived cytokines, such as TNF-α, activate other inflammatory cells (i.e., neutrophils, monocytes), and chemokines serve to attract other cells to the affected area. Neutrophil responses to cytokine signaling can result in extensive host tissue damage secondary to the release of products such as reactive oxygen species, proteases, lysozymes, lactoferrin, cathepsins, and defensins. Neutrophils produce relatively small amounts of TNF-α, IL-1, and platelet-activating factor.

A controlled inflammatory response is beneficial to the host. Such a response is localized and represents a balance between activation of the inflammatory cascade and host CARS. An excessive inflammatory response results from disproportionate activation of the proinflammatory mediators or lack of regulatory counterparts. On the other extreme, "immune paralysis" results from excessive antiinflammatory activity. Additionally there may be regional and temporal differences in proinflammatory versus antiinflammatory activity.[16]

LOSS OF HOMEOSTATIC MECHANISMS IN SEPSIS

Many of the pathophysiologic derangements and subsequent clinical signs in septic patients are related to derangements of normal homeostatic mechanisms responsible for regulating vasomotor tone, inflammation, coagulation, endothelial permeability, and microvascular perfusion.

Loss of vasomotor tone

In patients with severe sepsis and septic shock, loss of the normal homeostatic balance between endogenous vasoconstrictors and vasodilators occurs, resulting in dysregulation of vasomotor tone. Overproduction of nitric oxide (NO) during sepsis is a major contributing factor.[17] NO is a powerful vascular smooth muscle relaxant that contributes to the vasodilatory state of patients with septic shock, leading to clinical signs such as hyperemic mucous membranes, short capillary refill time, and tachycardia in dogs and in people.[5,17-20] Cats do not typically display the hyperemic, hyperdynamic state.[20-22] In response to stimulation with endotoxin, TNF-α, IL-1, or platelet activating factor (PAF), inducible nitric oxide synthase (iNOS) accumulates and generates high levels of nitric oxide (NO), thereby contributing to signs of vasodilatory shock.[17,23] In one prospective, observational study in dogs, the NO breakdown products nitrate/nitrite in plasma were was significantly greater in septic dogs or in dogs with SIRS compared with healthy controls.[24]

Dysregulation of inflammation and coagulation

Bacterial infection and host inflammatory cytokines upregulate tissue factor (TF) levels; TF then combines with factor VIIa to initiate the coagulation cascade.[25] The TF-fVIIa complex and its downstream products (i.e., thrombin) can also trigger the elaboration of inflammatory cytokines and platelet activation.[25] Normally, initiation of the coagulant pathway causes a counterregulatory activation of fibrinolytic and anticoagulant pathways to maintain hemostasis without excessive thrombosis. In septic patients, however, natural anticoagulant and fibrinolytic processes (as well as other complex processes) are inhibited via downregulation of antithrombin, tissue factor pathway inhibitor, and tissue plasminogen activator (tPA) and increased plasminogen activator inhibitor (PAI-1).[25] The protein C/S pathway is also inhibited, leading to a reduction of the normal activated protein C anticoagulant and antiinflammatory effects. Platelets also play a major role in this procoagulant state. Platelets exacerbate expression of procoagulant products such as TF, factor Va, and VIIIa; express the fibrinogen receptor; recruit additional platelets; and serve as part of the support structure of clots.[26] The hemostatic balance in septic patients, therefore, favors the procoagulant and antifibrinolytic state initially. Progression over time to a hypocoagulable state depends on host protein synthesis, effectiveness of natural coagulation inhibitors, virulence of the invading organism, and resolution of the inflammatory source.

Hemostatic dysfunction has been reported in septic dogs.[26,27] One study showed that septic dogs had significantly lower protein C levels and antithrombin (AT) activities and higher prothrombin time, partial thromboplastin time, D-dimer, and fibrin(ogen) degradation products than did controls.[4] In a study of dogs with septic peritonitis, coagulation abnormalities, lower AT activity, lower protein C, higher fibrinogen, and less hypercoagulable thromboelastograms were associated with poor outcomes.[28] Dogs with naturally occurring parvoviral enteritis had decreased AT activity and increased maximum amplitude on the thromboelastogram, consistent with hypercoagulability (see Chapter 104).[29] Commonly available laboratory testing may elucidate these hematologic and hemostatic changes (see Table 91-2).[18,26,30]

Endothelial, microcirculatory, and mitochondrial abnormalities

Alterations in the endothelium, increased vascular permeability, and microcirculatory derangements can be caused by many different and complicated mechanisms, including endothelial dysfunction,[31] alterations and damage to the endothelial glycocalyx layer,[32] rheologic changes to red blood cells,[33] leukocyte activation, microthrombosis, and loss of vascular smooth muscle autoregulation.[34] The overall regulation of vascular permeability is complicated (see Chapter 11). The decreased functional capillary density, increased diffusional distance for oxygen, and heterogenous microvascular blood flow all lead to alterations in tissue oxygen extraction and tissue hypoxia.[35-37] Importantly, serious microcirculatory disturbances can occur despite normal macrohemodynamic variables (e.g., blood pressure); this disconnect between systemic hemodynamics and microcirculatory perfusion, also known as cryptic shock, is characteristic of both septic human and canine patients.[35,36]

One prospective observational study in critically ill dogs evaluated vascular endothelial growth factor (VEGF) levels and edema formation in critically ill dogs. VEGF is a hypoxia-responsive angiogenic factor that is also associated with increasing vascular permeability. Although VEGF levels were not correlated to presence of edema on physical examination, dogs that had markedly elevated VEGF levels were less likely to survive.[37] Increased vascular permeability causes efflux of water, proteins and solutes into the interstitial space, thereby causing an increased distance from the red blood cells within the capillaries to the target cell mitochondria, and consequently impairment of oxygen transport and delivery to the mitochondria.[35] One can think of the endothelium itself as an "organ," subject to dysfunction and failure in sepsis, just as the heart, kidneys and brain (and others) can become dysfunctional. There are likely regional and temporal differences in microcirculatory function and dysfunction. Areas that are very dysfunctional contribute to arteriovenous shunting as a result of functional and mechanical obstruction; the associated tissue suffers from a hypoxic insult. The dysfunctional endothelium has been proposed as the "motor" of MODS. New technology such as sidestream darkfield imaging enables visualization and assessment of microcirculatory derangements during sepsis and in response to therapy.

Even if the microcirculation is functional, mitochondrial changes still occur secondary to sepsis.[35] Mitochondria themselves can become dysfunctional in septic patients (termed *cytopathic hypoxia*), which contributes further to heterogenous hypoxic tissue beds.[33,38] In addition to their critical role in oxidative phosphorylation, mitochondria are also involved in apoptotic pathways and cell death.

EPIDEMIOLOGY

Septic Foci, Diseases, and Pathogens Associated with Sepsis

The available epidemiologic information describing the septic foci and common pathogens in small animals can be found in Table 91-4. Although there are numerous possible septic sources (see Table 91-4 and Chapters 23, 97 to 102, 117, 122, and 126), septic peritonitis is a common cause of sepsis, particularly in dogs. Leakage of contents from the GI tract occurs secondary to GI neoplasia, ingestion of foreign bodies (and subsequent perforation), dehiscence of biopsy sites, enterotomies or resected intestine,

Table 91-4 Septic Foci in Cats and Dogs and Pathogens Involved[4,19,21,22,40-45,89-92]

Site	Disease Examples	Dogs (%)	Cats (%)	Pathogens
Peritoneal cavity	GI perforation	35%-36%[2,4,8]	47%[10]	Coagulase-negative *Staphylococcus* spp, *Enterococcus* spp, B-hemolytic *Streptococcus* spp, *Escherichia coli, Klebsiella* spp, *Enterobacter* spp, *Pasteurella* spp, *Corynebacterium* spp[4,40,42,43]
Pulmonary parenchymal, pleural	Pneumonia	20%[4,41]	24% (pyothorax) + 14% (pneumonia)[21]	B-hemolytic *Streptococcus* spp, *E. coli, Bordetella bronchiseptica, Staphylococcus* spp, *E. coli, Klebsiella* spp, *Pseudomonas* spp, *Enterococcus faecalis, Acinetobacter* spp, *Pasteurella* spp[4,44]
Gastrointestinal	Enteritis, bacterial translocation	4%	5%[21]	*E. coli*[21]
Reproductive	Pyometra Prostatitis	25%[4,6]		Group G *Streptococcus* spp, *Enterococcus* spp, B-hemolytic *Streptococcus* spp, *E. coli, Klebsiella* spp[4]
Urinary tract	Pyelonephritis Bacterial cystitis	4%-10%[4]	8%,[22] 7%[21]	B-hemolytic *Streptococcus* spp, *E. coli, Acinetobacter* spp, *Enterococcus* spp[4,22]
Soft tissue, bone	Trauma, osteomyelitis, bite wounds	29%	16%,[22] 3% (osteomyelitis) + 3% (bite wounds[21]; 3%-50%[6,21,22]	*E. coli, Enterobacter* spp[4]
Cardiovascular	Endocarditis		14%[21]	*Staphylococcus lugdunensis, Bartonella* spp, *S. aureus, E. faecalis, Granulicatella* spp, *Streptococcus* spp, *Brucella* spp[45]

nonsteroidal antiinflammatory drug (NSAID)–associated ulcers, perforation of megacolon, and severe colitis. Other reported causes of septic peritonitis include contamination from the urinary bladder, gallbladder, or uterine rupture; GI disease such as salmonellosis or parvoviral enteritis; and hepatic, pancreatic, splenic, and mesenteric lymph node abscess formation.[6,22,40] Aside from septic peritonitis, other less common causes of sepsis include pyelonephritis, pneumonia, septic arthritis, deep pyoderma, bacterial endocarditis, tick-borne diseases, vasculitis, septic meningitis, pyothorax, trauma, bite wounds, osteomyelitis, septic prostatitis, and immune suppression.*

Gram-negative enteric bacteria are the most commonly implicated organisms in sepsis in dogs and cats; however, mixed infections and gram-positive infections are also described.[4,22,40,42-45] Culture of infected tissue should be obtained whenever possible (i.e., safe for the patient) because early and appropriate antimicrobial selection is essential for preventing bacterial replication and reducing the host inflammatory response to infection. Knowledge of common isolates and the hospital antibiogram may help guide empiric antimicrobial selection (see Chapter 175).

RESUSCITATION AND TREATMENT OF SEPSIS, SEVERE SEPSIS, AND SEPTIC SHOCK

Introduction to the Bundle Concept

Major improvements in outcome in septic human patients have been accomplished through use of sepsis treatment "bundles." A *bundle of care* refers to a group of therapies that, when instituted together, result in better outcomes than if each individual component were to be implemented alone.[46] For sepsis, evidence-based guidelines for sepsis management are published in the Surviving Sepsis campaign international guidelines. Hospitals[47] that have implemented the guidelines report decreased mortality rates.[48-50] Bundle recommendations and the current guidelines were born out of earlier landmark studies in early goal-directed resuscitation.[51] Although there is still controversy regarding the best individual bundle components, numerous studies have since shown that implementation of a sepsis bundle reduces mortality.[52] Enthusiasm remains for the bundle approach (even in veterinary medicine), and it stands to reason that the same approach may improve outcomes in veterinary patients.†

Bundle Element: Lactate

Lactate production is a result of anaerobic metabolism, most commonly as a result of hypoperfusion. High initial lactate levels are associated with poorer outcomes, particularly if the hyperlactatemia persists and if accompanied by hypotension.[55-62] However, lactate clearance as it relates to traditional (e.g., blood pressure) and more recent (e.g., $ScvO_2$) parameters remain unclear. Lactate kinetics in the individual patient probably depends on the phase of sepsis; lactate together with $ScvO_2$ may provide complementary information about the efficacy of resuscitation (see Chapter 183).[58,63] The Surviving Sepsis campaign guidelines recommend measuring lactate within the first 6 hours of admission and promptly initiating fluid resuscitation for patients with lactate concentrations 4 mmol/L or greater.[38] The available veterinary literature supports this recommendation (see Chapter 56).[36,53,55]

Bundle Element: Samples for Culture (Blood, Tissue, or Fluid Cultures)

In human health care, obtaining blood cultures in patients with sepsis or suspected sepsis is very much the standard of care and blood cultures are positive in 30% to 50% of patients with severe sepsis or septic shock.[1,48] In veterinary medicine, blood cultures may be less routinely performed. In one study, however, 49% of critically ill dogs and cats had positive blood cultures.[64] Another study reported that 43% of dogs with gastric dilation and volvulus developed positive blood cultures. The importance of obtaining samples for culture to aid in selection (and deescalation) of antimicrobials cannot be overemphasized; however, obtaining the samples should not cause a delay in initiating resuscitation nor put the patient at risk.

Bundle Element: Early Source Control and Early Antibiotic Administration *(see Chapters 175 to 182)*

Of paramount importance in treating the septic patient is the identification and removal of the septic focus ("source control") and early administration of antimicrobials. In human patients with septic shock, elapsed time from shock recognition and qualification for early goal-directed therapy to appropriate antimicrobial therapy is a primary determinant of mortality; there is no reason to think that the same is not true in veterinary patients.[65-67] Early antimicrobial therapy is now conceptually "bundled" with more traditional aspects of sepsis resuscitation such as hemodynamic stabilization.[68] Empiric selection of appropriate antimicrobials can be challenging and should consider the location of the infection (and the ability of the antibiotic to penetrate the site), the suspected bacterial flora, community versus nosocomial source, duration of hospitalization, and previous exposure to antimicrobials (see Chapter 175). Bactericidal rather than bacteriostatic antimicrobials are preferred. In both veterinary and human studies, administration of inappropriate antimicrobials is associated with increased mortality.[6,67] In patients who have been hospitalized for some time, the chances of infection with multidrug-resistant bacteria increase, so careful consideration of hospital antibiograms should be employed when choosing empiric antimicrobials therapy.[69] In some patients, sample collection may be impossible because of cardiopulmonary instability or coagulopathy; however, the inability to gather samples for culture and susceptibility testing should never cause a delay in the administration of antimicrobials to patients with sepsis, severe sepsis, or septic shock. Septic patients require a broad-spectrum bactericidal antimicrobial regimen that is administered via the intravenous route (see Chapters 175 and 182). Following are some examples of four-quadrant therapy (i.e., therapies that are effective against gram-positive and gram-negative aerobes and anaerobes). All dosages are listed for the *intravenous* route, except when indicated otherwise:

- Ampicillin (22 mg/kg q8h) and enrofloxacin (10 to 20 mg/kg q24h; 5 mg/kg q24h in cats)
- Ampicillin (22 mg/kg q8h) and amikacin (15 mg/kg q24h [dog], 10 mg/kg q24h [cat])
- Ampicillin (22 mg/kg q8h) and gentamicin (10 mg/kg q24h [dog], 6 mg/kg q24h [cat])
- Cefazolin (22 mg/kg q8h) and amikacin (15 mg/kg q24h [dog], 10 mg/kg q24h [cat])
- Cefazolin (22 mg/kg q8h) and gentamicin (10 mg/kg q24h [dog], 6 mg/kg q24h [cat])
- Ampicillin (22 mg/kg q8h) and cefoxitin (15 to 30 mg/kg q4-6h)
- Ampicillin (22 mg/kg q8h) and cefotaxime (25 to 50 mg/kg q4-6h)
- Ampicillin (22 mg/kg q8h) and ceftazidime (30 to 50 mg/kg q6-8h)
- Clindamycin (8 to 10 mg/kg q8-12h) and enrofloxacin (5 to 20 mg/kg q24h; 5 mg/kg q24h in cats)
- Clindamycin (8 to 10 mg/kg q8-12h) and amikacin (15 mg/kg q24h [dog], 10 mg/kg q24h [cat])
- Clindamycin (8 to 10 mg/kg q8-12h) and gentamicin (10 mg/kg q24h [dog], 6 mg/kg q24h [cat])

*References 4, 6, 21, 22, 29, 41.
†References 18, 36, 48, 50, 53, 54.

Table 91-5 **Circulatory Support in Severe Sepsis and Septic Shock**[20]

Fluid Therapy	Indications	Dose	Comments
Isotonic crystalloids	Intravascular volume replacement Interstitial fluid deficits Maintenance	*Dog:* Up to 60 to 90 ml/kg* *Cat:* Up to 40 to 60 ml/kg*	May precipitate interstitial edema in patients with capillary leak or a low colloid osmotic pressure
Synthetic colloids (e.g., hydroxyethyl starch)	Volume replacement Colloid osmotic support	*Dog:* 5 to 20 ml/kg* *Cat:* 5 to 10 ml/kg*	Dose-related coagulopathies and acute kidney injury (humans) have been documented An arbitrary recommendation is ≤20 ml/kg q24h
Human albumin solution (HSA)	Colloid osmotic pressure support Volume replacement Albumin supplementation	2 ml/kg/hr of 25% HSA for 1 to 2 hours followed by 0.1 to 0.2 ml/kg/hr × 10 hours Or, calculate albumin deficit: Alb deficit (in grams) = 10 × (desired Alb – patient Alb) × wt (kg) × 0.3 and replace over 4 to 6 hours	Doses extrapolated from human literature Monitor closely for reactions
Fresh frozen plasma	Coagulopathies Factor deficiencies Supplemental volume and colloid osmotic support	10 to 15 ml/kg as needed	Not effective at increasing albumin concentration
Packed red blood cells	Anemia	10 to 15 ml/kg will raise PCV by ~10%	—
Fresh whole blood	Anemia Thrombocytopenia Coagulopathies and factor deficiencies Volume replacement	20 ml/kg will raise PCV by ~10%	—

Alb, Albumin; *HSA,* human albumin serum; *PCV,* packed cell volume.
*Listed intravenous fluid doses are "shock doses." Generally, a fraction of the listed dose is given (e.g., one fourth to one half) and response is assessed; the dose is repeated as necessary or until fluid tolerance is reached. Cats seem to have a poor pulmonary tolerance to volume resuscitation; therefore smaller doses may be tried first.

- Ticarcillin and clavulanic acid (50 mg/kg q6h) and enrofloxacin (10 to 20 mg/kg q24h; 5 mg/kg q24h in cats)
- Imipenem (5 to 10 mg/kg q6-8h)
- Meropenem (24 mg/kg q24h or 12 mg/kg SC q8-12h)
- Chloramphenicol (25 to 50 mg/kg q8h; 12.5 to 20 mg/kg q12h in cats)

Bundle Element: Treat Hypotension with Fluids and Possibly Vasopressors

Assessment of volume status and responsiveness

Because septic shock patients are, by definition, in circulatory collapse despite volume resuscitation, cardiovascular support is of key importance. Fluid therapy is essential to maintain adequate tissue oxygen delivery and to prevent the development of MODS and death (see Chapter 60). Assessment of volume status and the potential for volume responsiveness can be difficult. Traditionally, static measures to indirectly measure preload, such as pulmonary artery occlusion pressure (PAOP) and central venous pressure (CVP), have been used. However, they can be cumbersome (PAOP) and not predictive of volume responsiveness (CVP).[70] Dynamic measures of fluid responsiveness may include echocardiographic evaluation of cardiac function and arterial waveform variation in ventilated patients. More simple yet still dynamic measures may include administering serial small fluid boluses or (in people) passive leg elevation and evaluation of the hemodynamic response.[52,71] Accurate monitoring of body weight and urine output via an indwelling urinary catheter is also helpful in assessing total fluid balance as well as monitoring for oligoanuric renal failure. It should be noted, however, that urinary output is a result of the balance between preglomerular and postglomerular resistance. Thus a marked increase in postglomerular resistance can induce an increase in urinary output in the presence of renal hypoperfusion.

Fluid choice

The first line of resuscitation in septic patients is fluid therapy. Isotonic crystalloids, hypertonic crystalloid solutions, synthetic colloids, and blood component therapy may be used for fluid therapy in the septic patient (Table 91-5). The choice of fluids depends on the overall clinical and clinicopathologic picture (see Chapters 58 and 60). Recent studies in human septic patients have called into question the safety of synthetic colloids, specifically hydroxyethyl starches, which now have a black box warning for this population of human patients.[72,73] Synthetic colloids have been a staple of fluid resuscitation in veterinary medicine; however, human studies have shown that resuscitation with these fluids in people is associated with an increased incidence of acute kidney injury and need for renal replacement therapy and, in the case of the Perner et al study, an increased risk of death at day 90. The results of other studies regarding the safety of synthetic colloids were mixed, and no safety studies to date are available in veterinary patients.[74-76] The current recommendation in human critical care is to avoid synthetic colloids in septic patients, especially when other fluid therapy options such as albumin, plasma, or crystalloids are available, or until more rigorous data on the safety of synthetic colloids are published.[52]

Patients with severe sepsis and septic shock are very often hypoalbuminemic.[77,78] Unfortunately, large volumes of fresh frozen plasma are required for albumin replacement (i.e., 22 ml/kg of plasma to raise the albumin concentration by 0.5 g/dl).[78] Fresh frozen plasma is therefore generally only used to prevent a further decline in albumin in severely hypoalbuminemic patients and for correction of

Table 91-6 Commonly Used Constant Rate Infusion Vasopressor Therapy

Vasopressor	Dose rate
Norepinephrine	0.1-2 mcg/kg/min IV
Vasopressin	0.5-5 mU/kg/min IV
Dopamine	5-15 mcg/kg/min IV

coagulopathies and factor deficiencies. Human serum albumin (5% or 25%) is still in the early stages of clinical use in veterinary medicine and research is ongoing. The 25% human serum albumin solution is hyperoncotic (colloid osmotic pressure = 100 mm Hg) and should be used judiciously in patients with limited fluid tolerance (see Chapter 58 for further details). Although it does seem effective in raising albumin concentration, questions regarding its safety exist.[79-81] Coagulopathies, anemia, and thrombocytopenia may prompt the use of blood component therapy (e.g., fresh frozen plasma, packed red blood cells, fresh whole blood, respectively).

Hypotension despite volume resuscitation (septic shock)

Hypotension that persists after restoration of intravascular volume is an indication for vasopressors or inotropic agents to support flow to tissues (see Chapters 8, 157, and 158). The decision to use a vasopressor or cardiotonic drug depends on the clinical presentation and objective information obtained from the septic patient (e.g., assessment of cardiac contractility). Vasopressors such as norepinephrine, vasopressin, dopamine, and phenylephrine are most commonly used in patients with peripheral vasodilation (Table 91-6). Norepinephrine is preferred to dopamine in septic human patients, and vasopressin is also considered a reasonable first-line vasopressor.[52,82,83] Studies in septic veterinary patients are ongoing. Although vasopressors may maintain arterial blood pressure, they can also result in excessive vasoconstriction, particularly to the splanchnic and renal circulation, thereby causing GI and renal ischemia. Particularly in the dog, splanchnic vasoconstriction may exacerbate the septic state by promoting loss of gut barrier function and bacterial translocation of bacteria to the bloodstream.

Positive inotropic agents such as dobutamine are generally used in patients with evidence of impaired myocardial contractility (decreased fractional shortening on M-mode echocardiography, decreased cardiac output per invasive or noninvasive measurements). They might also be combined with more selective vasoconstrictors such as vasopressin or phenylephrine.

Bundle Element: Target Central Venous Pressure and Central Venous Pressure and $ScvO_2$

Venous oxygen saturation is a measure of the saturation of hemoglobin with oxygen in the venous blood; it is reflective of the difference between oxygen delivery (DO_2) and oxygen consumption (VO_2). Venous oximetry is monitored intermittently via blood sampling or co-oximetry, or continuously using fiberoptics (spectrophotometry).[84] Mixed venous oxygen saturation (SvO_2) refers to venous blood in the pulmonary artery. Mixed venous blood is pooled blood from the entire body, including blood from the caudal half of the body (i.e., the abdomen and lower extremities) and the coronary circulation. SvO_2 can be viewed as the result of the overall difference in oxygen delivery (DO_2) and oxygen consumption (VO_2) and therefore is a marker of global oxygen debt. Central venous oxygen saturation ($ScvO_2$) generally refers to the saturation of blood in the cranial vena cava, reflective of oxygen delivery and utilization in the head and upper body. In health, $ScvO_2$ is slightly lower than SvO_2 by about 2% to 3%, in part because of the high metabolic rate of the brain and cranial half of the body and also because of the contribution of vascular circuits that use blood for nonoxidative phosphorylation needs in the caudal half of the body (e.g., the renal blood flow).[84] In shock states the relationship between central and mixed saturation can reverse; $ScvO_2$ can be much higher than SvO_2; this likely is due to redistribution of blood flow from the splanchnic circulation to the coronary and cerebral vascular beds.[85-87] Consensus and the international guidelines state that measuring $ScvO_2$ in lieu of SvO_2 (because it technically easier) can be used successfully during sepsis resuscitation.[48]

In health much more oxygen is delivered than is extracted; however, when delivery decreases to a critical threshold, extraction decreases in concert and the patient experiences oxygen debt and lactic acidosis. Monitoring venous oxygen saturation and using it as a therapeutic target is a recommendation in the Surviving Sepsis guidelines.[48] The few veterinary studies that have evaluated $ScvO_2$ as a therapeutic goal suggest its potential value in resuscitating septic and critically ill veterinary patients.[53,88] In both studies, $ScvO_2$ was associated with prognosis.[53,88] These veterinary studies mirror a large body of work in human medicine that resulted in a recommendation in the Surviving Sepsis campaign to resuscitate to an $ScvO_2$ of 70% or greater or an SvO_2 65% or greater.[48]

CONCLUSION

Sepsis is an important and very common problem in both veterinary and human health care. Hallmark pathophysiologic changes include widespread endothelial disruption, microcirculatory failure, progressive inflammation or immune paralysis, and activation of the coagulation cascade. Throughout the progression from sepsis to septic shock, there is extensive interplay between the coagulation and immune systems. Ultimately, circulatory collapse (both macro- and micro-) leads to hypoperfusion, tissue ischemia, organ failure, and death. Treatment of septic patients critically depends on early recognition, early antimicrobial therapy, and aggressive hemodynamic support. Bundled care appears to be very effective in human septic patients, and studies in veterinary medicine are starting to suggest the same.

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