Sepsis and Systemic Inflammatory Response Syndrome

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As in every specialty there are specific syndromes which are within the realm of the highly trained specialists. Inflammatory bowel disease, polyradiculoneuritis, and eosinophilic granuloma complex represent syndromes that internist, neurologist, and dermatologists treat and consider unique to their specialty. In critical care medicine we have the same types, although they tend to have high mortality rates. Systemic Inflammatory Response Syndrome (SIRS), Sepsis, Multiple Organ Dysfunction Syndrome (MODS) and Multi-organ failure (MOF), and Disseminated Intravascular Coagulation (DIC), are critical care syndromes which typically cause the high rates of morbidity/mortality in these highly debilitated patients. The frustrating element of these syndromes is that various disease processes (pancreatitis, GI disease, etc) can cause them and thus they must be anticipated and watched for in any of the critically ill we treat in our ICU's.

SIRS

SIRS represents a syndrome of widespread systemic inflammation which can be incited by an infectious or sterile source. SIRS in the face of bacteremia is typically termed sepsis. Patients can be mildly affected or severely affected by SIRS. If an infectious cause is the culprit gram-positive and negative bacteria can both produce endotoxins (lipopolysaccharide, or LPS for example) that activate monocytes and macrophages. This is a normal response from the immune system in the face of an infection. These white blood cells (WBC's) release inflammatory mediators that are responsible for the characteristic localized signs of infection: redness, swelling, heat, and pain. The inflammatory mediators, termed cytokines, include tumor necrosis factor- α(TNF-α), IL-1 and IL-6. There is also an anti-inflammatory reaction that serves to balance this influx of inflammatory cytokines; IL-10, IL-13 are prototypical anti-inflammatory cytokines.

As the inflammatory process continues, inflammatory responses move from the local level to the systemic level. As inflammation has many positive characteristics and serves to protect and alert the body to infection/trauma, free-flowing cytokines can wreak havoc with bodily systems if left to their own devices. It appears that these cytokines can cause three major negative effects to the body's natural processes:

1. Vasodilation
2. Endothelial barrier damage
3. Activation of coagulation pathways

Vasodilation, resulting from a loss in vascular tone, reduces cardiac output, perfusion to tissues, and ability to maintain vascular volume. Nitric oxide, a potent vasodilator, is often produced in inflammatory states (leading to redness- increased blood flow to areas to deliver macrophages). Systemic release of nitric oxide leads to systemic vasodilation, as opposed to beneficial localized vasodilation of a small capillary bed. An additional theory of vasodilation in SIRS is vasopressin deficiency. Lack of vasopressin reduces systemic vascular resistance as vasopressin binds to V1 receptors in vascular smooth muscle to induce vasoconstriction during low volume states.

Endothelial barrier damage

Activation of the coagulation pathways can lead to coagulation factor exhaustion and a hypercoagulable state. Cytokines induce tissue factor (TF) production and thus activate the tissue factor pathway in vivo. As TF is produced, micro-clots are formed and may deposit in the microvasculature. These micro-clots cause cell death, and tissue hypoxia leading to organ failure. As widespread coagulation ensues, systemic anti-coagulant systems are consumed and exhausted, which shifts the patient into coagulation over-drive.

SIRS Criteria

Published criteria for SIRS in small animals tend to be somewhat general and non-specific. This means that many patients may or may not ACTUALLY have SIRS but fit these criteria. Several bio-markers have been researched in humans but authoritative studies are lacking in veterinary medicine. Hence the following criteria:

	DOGS	CATS
Temperature	<100.6 F or >102.6 F	<100 F or > 104 F
HR	>120 beats/minute	<140 or >225 beats/minute
Respiratory rate	> 20 breaths/minute	>40 breaths/minute
WBC count or percentage of bands	<6,000, >16,000, >3% bands	<5,000 or >19,000

Hopper, Silverstein. Small Animal Critical Care Medicine. pg. 48

Patients with SIRS may also manifest the following clinical signs

- Tacky, injected mucous membranes
- Bounding peripheral pulses
- Vomiting/diarrhea
- Neutrophilic leukocytosis with toxic changes. Left shift may be present
- Hypoglycemia
- Hyperbilirubinemia
- Cholestasis

Treatment of SIRS

There is no specific treatment of a patient experiencing systemic over-inflammation. Treatment is aimed at supportive care and should follow a systematic approach. Important patient concerns include:

- Supporting appropriate fluid balance
- Suspecting GI bacterial translocation if gut integrity compromised
- Treating and reversing hypoglycemia
- If septic: providing source control, appropriate Anti-microbial selection, culture/sensitivity
- Oxygenation support
- Nutritional support
- Stress ulcer prophylaxis
- Preparing for and treating refractory hypotension

Sepsis

Sepsis is essentially SIRS + infection. Sepsis represents the hyper-inflammatory state that arises when a bacteria, virus, protozoa, or fungus infection incites the inflammatory cascade to begin. Sepsis may cause or be caused by bacteremia, or the presence of a bacterial infection in the bloodstream. Severe sepsis is defined as sepsis and organ dysfunction. Septic shock is defined as sepsis with refractory hypotension, despite volume resuscitation. These categories are important as a patient can be septic and have systemic inflammation, and not necessarily be hypotensive, or have organ dysfunction or failure.

As with SIRS there are criteria to diagnose/suspect sepsis in a patient. Many are similar to SIRS with the addendum that infection is proven or highly suspected. In addition to those listed above the following should increase suspicion for sepsis:

- Hyperglycemia
- Altered mental status
- Edema
- Hypotension
- Organ dysfunction (lungs, kidney, liver)
- Oliguria/anuria
- Hyper/hypocoagulability
- Hyperlactatemia

Staging of sepsis

An international sepsis staging schema exists to categorize the severity of a patient's septic response. Some patients may be pre-disposed to septic inflammation, but do not yield severe systemic manifestations, while other patients may have multiple concomitant co-morbidities all rooted in the septic syndrome.

PIRO

- **P-** Predisposition
  - Signalment, underlying disease process
- **I-**Insult/infection
  - What is the underlying infection? Organism?
- **R-** Response
  - SIRS? Hypotension? Shock?
- **O-** Organ dysfunction
  - Signs of organ dysfunction: Oliguria, azotemia, pulmonary edema, increased liver enzymes/cholestasis, etc.

Identifying the septic focus

Source control, referring to finding the septic source and eliminating it, can be achieved by searching for and identifying the septic focus. We often go on a "hunt" for sepsis in patients we suspect it in but cannot initially prove it (no outward abscess as culprit). Septic foci can be present in essentially every organ system, but septic peritonitis is a common cause of sepsis. Other foci for sepsis, other than the abdomen, can be the respiratory tract, thorax (pyothorax), GI system, cardiac (endocarditis), urinary tract (urosepsis), pancreas, and integument (abscess, bite wounds). These systems should be ruled in or out when doing a sepsis "hunt."

Bacterial sepsis

Bacterial sepsis is most commonly identified and responsible for systemic dysfunction. Gram-negative bacteria produce lipopolysaccharide, an endotoxin, which stimulates the systemic response. Gram-positive bacteria produce various toxins including: lipoteichoic acid, and peptidoglycan. Common species of bacteria implicated in sepsis include: E. Coli, Enterococcus sp, α/β-hemolytic Streptococcus, Pseudomonas, and Clostridium.

Sepsis "hunt"

Some recommendations to investigate sepsis in a patient who has developed a clinicopathologic suspicion for sepsis:

- Evaluate invasive devices: unwrap and inspect catheters and tubes
- Perform abdominal/thoracic ultrasonography
- Blood culture collection
- Urine culture submission
- Consider joint taps, CNS tap, abdominal tap

Treatment of sepsis

In patients that have a highly suspicious septic focus early anti-microbial therapy is warranted. Antibiotics administered within 1 hour of presentation reduced morbidity and mortality. If possible cultures should be obtained to ensure adequate and targeted anti-microbial therapy. Patients should have all critical care parameters monitored and special attention paid to fluid balance, vascular volume/blood pressure, and blood glucose levels, as these tend to fluctuate most often. Specific treatments include:

- Supplementation with 50% dextrose as needed
- Insulin therapy to control hyperglycemia
- Vasopressor therapy to assist with vascular tone as needed
- Consider ACTH stim and/or low-dose steroids if hypotension is refractory to vasopressors
- Consider Vasopressin CRI for vasopressor therapy

Multi-organ dysfunction syndrome/multi-organ failure

MODS or MOF can occur secondary to septic insults or hyper-inflammatory states. Many factors influence organ dysfunction including:

- Hypoperfusion from aberrant fluid balance/cardiac output/vascular tone
- Vasodilation amongst organ specific tissue beds
- Decreased oxygen delivery to organs
- Micro-thrombi causing ischemia
- Direct damage caused by infectious agents

Systems approach to treating MOF

- Acute renal failure/oliguria
- Acute liver failure
- Acute mentation change
- ARDS

References available upon request.