2016 DEFINITIONS OF SEPSIS AND SEPTIC SHOCK; WHAT'S NEW AND HOW THEY APPLY TO VETERINARY MEDICINE

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Introduction

Sepsis is a major cause or morbidity and mortality in both human and veterinary medicine. Although the true incidence of sepsis in human medicine is unknown, conservative estimates indicate that sepsis is a leading cause of mortality and critical illness worldwide. Similarly, although the epidemiology of sepsis is poorly described in dogs and cats, it is likely to be a major cause of mortality in hospitalized dogs and cats.

Since sepsis is a syndrome rather than one specific disease, having appropriate definitions that are universally adopted is important to understand the epidemiology of the syndrome and for clinical trial entry. Additionally, I would argue that appropriate categorization of a patient as having sepsis should alert the care team of the potential for organ dysfunctions and an unfavorable outcome, and hence allow appropriate allocation of resources to that patient's care.

Historical definitions

1991-1992 ACCP/SCCM consensus definitions (Sepsis-1)

The first consensus definition of the sepsis syndrome in human medicine was developed in 1991-1992.[1] The goal was to provide a broad series of definitions in order to improve "our collective ability to diagnose, monitor, and treat sepsis." **Sepsis** was defined broadly as the systemic inflammatory response to infection, and a series of standardized clinical criteria for its diagnosis were identified. The authors accepted that a clinically useful set of criteria for the diagnosis of sepsis and related conditions would necessarily be somewhat arbitrary since there is no gold standard against which they can be calibrated. Nonetheless they believed that diagnostic criteria can be considered to be successful if they are a useful decision making aid for clinicians at the bedside; and thus criteria for **the systemic inflammatory response syndrome (SIRS)** were developed. By the 1991 ACCP/SCCM definitions, in order to be considered to have SIRS a patient must have 2 or more of the following:

- Temperature < 38°C (fever) or < 36°C (hypothermia)
- Heart rate > 90 beats/min (tachycardia)
- Respiratory rate > 20/min (tachypnea) or $PaCO_2$ < 32mmHg (4.3kPa) (hyperventilation)
- WBCC > 12,000/mm^3 (leukocytosis) or < 4,000/mm^3 (leukopenia) or > 10% immature bands (significant left shift).

The SIRS criteria were proposed to provide a reference for the complex findings that result from systemic activation of the innate immune response, regardless of cause (ie. infectious or non-infectious). Indeed we recognize that binding of pathogen associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs) to pattern recognition receptors (PRRs) of the innate immune system, results in the upregulation of a variety of inflammatory mediators that are endogenous pyrogens (inducing fever), stimulate bone marrow release of leukocytes, activate coagulation, may result in cardiovascular instability causing tachycardia, and have a variety of other systemic effects.

A patient would then be described as having **sepsis** if they fulfilled SIRS criteria and had a strongly suspected or confirmed infection. Recognized methods for confirming infection included culture, cytology, and histopathology. **Infection** was defined as a pathologic process caused by invasion of a normally sterile tissue, fluid, or body cavity by pathogenic or potentially pathogenic microorganisms. The authors did however recognize that this definition is not perfect; for example*, Clostridium difficile* colitis (a sepsis syndrome) results from overgrowth of an organism that can be present in health, in a non-sterile location (ie. colon), that is not due to the bacteria itself, but rather its exotoxin.

These criteria became known as the AACP/SSCM criteria since they were developed at the consensus conference convened by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM). Concurrently, **severe sepsis** was defined as sepsis complicated by organ dysfunction, while **septic shock** was defined as sepsis induced hypotension persisting despite adequate fluid resuscitation.

2001-2003 SSCM/ESICM/ACCP/ATS/SIS consensus definitions (Sepsis-2)

A decade after the original definitions, another consensus conference of experts, opinion leaders, and society representatives (n=29) was convened to review the definitions for sepsis and related conditions. This conference was sponsored by SCCM, the European Society for Intensive Care Medicine (ESICM), ACCP, the American Thoracic Society (ATS), and Surgical Infection Society (SIS).[2] Those involved in this second consensus conference recognized some of the strengths of the original definitions; they had been widely used, and often served as the foundation for inclusion into clinical trials. Nonetheless they documented an impetus from experts in the field to modify the criteria to reflect the current understanding of the pathophysiology of sepsis based on new experimental and clinical trial data. There was also evidence from physician surveys that many clinicians felt that the 1992 consensus definition did not provide a clear definition of sepsis (ie. a gap in clinician understanding). As such, the goals of the 2001 consensus conference were to:

- Identify the strengths and weaknesses of the existing definitions of sepsis and related conditions
- Identify ways to improve the existing definitions; and
- Identify methodologies for increasing the accuracy, reliability, and/or clinical utility of the diagnosis of sepsis.

One of the main limitations of the existing SIRS criteria that the participants cited, were that they were too nonspecific to be of utility in diagnosing the cause of the syndrome or identifying a distinct pattern of host response. As part of this second consensus conference the authors goals for any potential revision of the sepsis criteria were that they:

- Are broadly useful to both clinicians caring for patients and researchers designing observational studies and clinical trials to improve the understanding and treatment of sepsis
    - Although clinical utility was thought to be more important, hence the need for "some" criteria to be met in the table below
- Are sensitive enough to identify most patients with the syndrome, while minimally sacrificing inevitable specificity
- Should not be so cumbersome that clinicians will resist a commitment to memory or application
- Only included assays that were either widely available at the time or were likely to be in the near future; and
- Were applicable to adult, pediatric, and neonatal patients.

Since one of the main limitations of existing SIRS criteria were their lack of specificity the authors of the 2001 definitions included a significantly expanded list of possible signs of systemic inflammation in response to sepsis, to further aid diagnosis. They suggested that these are physical and laboratory findings that prompt an experienced clinician to conclude that an infected patient "looks septic". Particularly findings of early organ dysfunction; once again however they caution that these findings are not specific for sepsis. The authors also suggested that in the future, biochemical markers may replace clinical criteria (eg. IL-6, procalcitonin [PCT]); although there was no large-scale prospective evidence at the time to support this suggestion.

The expanded diagnostic criteria for sepsis proposed in 2001 are listed in the table below.

Table 1. Diagnostic criteria for sepsis proposed in 2001

Infection	**Documented, or suspected, and some of the following**
General variables	Fever (core temperature > 38.3C)
	Hypothermia (core temperature < 36C)
	Heart rate > 90/min or > 2SD above the normal value for age
	Tachypnea
	Altered mental status
	Significant edema or positive fluid balance (>20mL/kg over 24 hours)
	Hyperglycemia (Plasma glucose > 120mg/dL or 7.7mmol/L) in the absence of diabetes
Inflammatory variables	Leukocytosis (WBC count > 12,000/uL)
	Leukopenia (WBCC < 4,000/uL)
	Normal WBCC with > 10% immature forms
	Plasma C-reactive protein (CRP) > 2SD above the normal value
	Plasma procalcitonin (PCT) > 2 SD above the normal value

Hemodynamic variables	Arterial hypotension (SBP < 90mmHg, MAP < 70, or SBP decrease > 40mmHg in adults or < 2 SD below normal for age)
	$ScvO_2$ > 70% (adults only)
	Cardiac index > 3.5L/min
Organ dysfunction variables	Arterial hypoxemia (P/F < 300)
	Acute oliguria (UOP < 0.5mL/kg/hr)
	Creatinine increase > 0.5mg/dL
	Coagulation abnormalities (INR > 1.5 or aPTT > 60 seconds)
	Ileus (absent bowel sounds)
	Thrombocytopenia (Plt count < 100,000/uL)
	Hyperbilirubinemia (Tbili > 4mg/dL or 70mmol/L)
Tissue perfusion variables	Hyperlactatemia (> 1mmol/L)
	Decrease CRT or mottling

Although the clinical criteria for sepsis were thoroughly refined in 2001 to expand the list of diagnostic criteria, the definitions of sepsis, severe sepsis, and septic shock did not fundamentally change. The authors stated that they would ideally like to base the definition of sepsis on biomarkers, but that this was premature at the time. The other main change was the introduction of the PIRO staging scheme.

The authors of the 2001 consensus identified that the definitions of sepsis, severe sepsis, and septic shock do not allow for precise characterization and staging of patients with these conditions. They recognized that a clinically useful staging system stratifies patients by both their baseline risk of an adverse outcome and their potential to respond to therapy. The PIRO scheme was developed to address this need, and was based on the TNM (tumor/node/metastases) staging system from oncology. The PIRO system was designed to stratify patients on the basis of their **P**redisposing condition, the nature and extent of the **I**nsult (infection), the nature and magnitude of the host **R**esponse, and the degree of concomitant **O**rgan dysfunction.

Each domain of the PIRO staging scheme is discussed below:

Predisposition:

- Premorbid illness /factors that are known to influence morbidity and mortality of sepsis
- For example, the consequences of an infection depend heavily on genetic predisposition (eg. genetic polymorphisms in components of the inflammatory response such as TIR, tumor necrosis factor [TNF], interleukin[IL]-1, CD14)
- Other factors to consider here include age, sex, race, concomitant disease, immunosuppression etc.
- The key is to improve our understanding of specific interactions between pathogens and host

Insult / infection:

- It is common sense that specific therapies directed against an inciting insult (in the case of sepsis, the infection), require demonstration and characterization of that insult
    - We specifically want to characterize the site, type and extent of the infection
    - Additionally, the site, type and extent of infection affect prognosis
- Classically this is performed with first identifying the site of the infection, C&S testing, and determining whether or not it is amenable to source control
- The authors also proposed that other parameters might be helpful in the future such as assays for microbial products (lipopolysaccharide [LPS], mannans, bacterial DNA), and gene transcript profiles

Response:

- It is known that both mortality risk and potential to respond to therapy vary with non-specific measures of disease severity (eg. the presence or absence of shock)
- Additionally, mediator-directed therapy is predicated on the presence and adverse activity of that mediator
- Features of the host response that might be relevant to characterize the host response include SIRS, other signs of sepsis, shock, CRP concentrations etc.
- In the future, other nonspecific markers of activated inflammation (eg. PCT, IL-6) or impaired host responsiveness (HLA-DR) may prove helpful to characterize the host response
- Some specific host mediators (and markers of disease) that may be measured as the target of therapy include protein C, TNF, and platelet activating factor (PAF)

Organ Dysfunction:

- Undoubtedly the presence and severity of organ dysfunction is important in determining the prognosis of sepsis; the authors liken ODs in sepsis to metastases in cancer
- Additionally, the presence and type of ODs may aid in therapeutic stratification
- Organ dysfunction can be classified simply as a number of failing organs, or a composite score (eg. Sequential organ failure assessment [SOFA] score) that quantitatively describes the degree of OD developing over the course of critical illness.

The authors of the 2001 consensus proposed the PIRO scheme as a template for future investigation and a work in progress, rather than a model to be definitively adopted.

New definitions – Sepsis-3

A few years in the making, the Sepsis-3 definitions were published in early 2016. Three manuscripts and an editorial on the topic were published in a Special Communication Section of the Journal of the American Medical Association.[3-6] These manuscripts reported the Third International Consensus Definitions of Sepsis and Septic Shock.

The rationale for the third consensus definitions, was that considerable advances in our understanding of sepsis have been made since the last revision in 2001. Specifically, the authors point to advances in pathobiology (changes in organ function, morphology cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis. These changes they proposed, suggested the need for re-examination of the consensus definitions. As such the objective of the third consensus conference was to evaluate and, as needed, update the definitions of sepsis and septic shock.

Similarly to the second consensus definitions, a task force (n=19) of clinical specialists (in critical care, infectious disease, surgery and pulmonology) and experts in sepsis pathobiology, clinical trials, and epidemiology was convened by SCCM and ESICM. This process started in January 2014 and involved meetings, a Delphi process, analysis of electronic health record databases, and voting to create the sepsis-3 definitions and clinical criteria. Subsequently, these were circulated to international professional societies for peer review and endorsement (n=31).

As previously, the consensus group began by identifying limitations in previous definitions. These were considered to include:

- An excessive focus on inflammation
- The misleading model that sepsis follows a continuum from sepsis, through severe sepsis, to septic shock
- Inadequate sensitivity and specificity of the SIRS criteria; and
- That multiple definitions are currently in use for sepsis, septic shock, and organ dysfunctions which lead to discrepancies in reported incidence and observed mortality.

The consensus group started out by defining some key concepts of sepsis:

- Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly
    - The recognition of sepsis mandates urgent attention
- Sepsis is a syndrome shaped by pathogen factors and host factors with characteristics that evolve over time
    - Host factors include age, sex, race and other genetic determinants, comorbidities, and environment
    - What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of ODs
- Sepsis-induced organ dysfunction may be occult
    - The presence of ODs should be considered in any patient presenting with infection
    - Conversely, unrecognized infection may be the cause of new-onset organ dysfunction
        - Any unexplained OD should raise the possibility of underlying infection
- The clinical and biological phenotype of sepsis can be modified by pre-existing acute illness, long-standing comorbidities, medication, and interventions
- Specific infections may result in local ODs without generating a dysregulated systemic host response.

New terms and definitions provided by Sepsis-3 are as follows:

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection
    - Under this terminology "severe sepsis" becomes superfluous
- Organ dysfunction can be identified as any acute change in total SOFA score ≥ 2 points consequent to the infection:
    - The baseline SFA score can be assumed to be 0 in patients not known to have pre-existing organ dysfunction
    - A SOFA score ≥ 2 reflects an overall mortality risk of ~ 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if already not being instituted
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified with the bedside qSOFA
    - Alteration in mental status
    - SBP ≤ 100mmHg; or
    - Respiratory rate ≥ 22 breaths/min
- Septic shock is a subset of sepsis in which underlying circulatory and cellular / metabolic abnormalities are profound enough to substantially increase mortality
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mmHg and having a serum lactate level > 2 mmol/L (18mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%

The authors of the new consensus definitions spend some time talking about potential controversies and potential limitations of their definitions within the manuscripts. Additionally, numerous other authors and organizations have documented their concerns with the new definitions. As such this will continue to be an evolution. The authors are hopeful that prospective validation of the new definitions, both within and outside the US, will occur to assess the robustness of the new definitions.

So how do these new definitions apply to veterinary medicine?

Although sepsis is a common syndrome identified in our ER and ICU patients in small animal veterinary medicine, we are quite a bit behind our colleagues in human medicine in understanding the epidemiology and pathobiology of sepsis in our patients.

The current definitions for SIRS and sepsis used in veterinary medicine are derived from those originally published in human medicine.[1] SIRS is a clinical diagnosis, made on the basis of abnormalities in vital signs and white blood cell count. While specific criteria are published,[7-11] there is no consensus in veterinary medicine; what denotes SIRS varies between species and publications (Table 2).

Table 2. Criteria for the systemic inflammatory response syndrome (SIRS) used in dogs and cats by various authors

Criteria	Dogs (2/4 criteria)			Cats (3/4 criteria)	
	Hauptman et al. 1997(7)	**deLaforcade et al. 2003(8)**	**Okano et al. 2002(9)**	**Brady et al. 2000(10)**	**DeClue et al. 2011(11)**
Temperature (°F / °C) • Fever • Hypothermia	>102.2°F (>39°C) <100.4°F (<38°C)	>103°F (>39.4°C) <100°F (<37.8°C)	>103.5°F (>39.7°C) <100°F (<37.8°C)	>103.5°F (>39.7°C) <100°F (<37.8°C)	≥103.5°F (>39.7°C) ≤100°F (<37.8°C)
Heart rate (beats/min) • Tachycardia	>120	>140	>160	> 225 < 140	≥ 225 ≤ 140

• Bradycardia					
Respiratory rate (breaths/min) • Tachypnea	>20	>20	>40	> 40	≥ 40
White blood cell count (cells/uL) • Leukocytosis • Leukopenia • Band neutrophilia (% bands)	>16,000 <6,000 >3%	>16,000 <6,000 >3%	>12,000 <4,000 >10%	> 19,500 < 5,000 > 5%	≥ 19,500 ≤ 5,000 ≥ 5%

Essentially SIRS is considered present if the animal fulfills 2 or 3 out of 4 of the following SIRS criteria: 1) Abnormal temperature, 2) Abnormal heart rate, 3) Tachypnea; and/or 4) A change in the leukon. Sick cats with SIRS and sepsis seem to be more likely to be hypothermic and bradycardic than dogs. Since the primary aim of having SIRS criteria from a clinician's perspective is to flag patients that are systemically unwell and require their attention, the exact cut-off points for these parameters are less important than the overall assessment of the patient in light of their signalment, history, and physical examination findings.

As used currently in veterinary medicine, sepsis refers to the systemic inflammatory response to infection. Diagnosis of sepsis requires identification (or a high index of suspicion) of infection and fulfillment of SIRS criteria.

Similarly, we have previously used the term severe sepsis refers to the presence of sepsis with one or more organ dysfunctions. While there is not a consensus definition for what denotes organ dysfunctions in veterinary medicine, various parameters have been suggested by different authors, but the lack of consensus is problematic.

Septic shock is said to occur in patients with sepsis and persistent arterial hypotension that is non-responsive to intravascular volume expansion; by definition patients with septic shock are vasopressor dependent. Multiple organ dysfunction syndrome is said to be present in patients with SIRS or sepsis when two or more organ dysfunctions are evident.

So, thinking about which of the new definitions in human medicine might apply to our patients and practice?

- It seems reasonable that we could define sepsis is as life-threatening organ dysfunction caused by a dysregulated host response to infection
- It seems reasonable that we could remove the terminology "severe sepsis"
- Organ dysfunction needs to be better defined in our patients, and this should be based on clinical evidence
- Having a lay definition would also be extremely useful in veterinary medicine. The same definition as used in human medicine is appropriate ie. In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs
- It seems reasonable that we could define septic shock as sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mmHg and having a serum lactate level > 2 mmol/L (18mg/dL) despite adequate volume resuscitation. In fact, many of us likely already operate with a definition very similar to this.

It is my hope that we are able to arrange a consensus group in veterinary medicine that can perform a similar process to complete systematic reviews, undergo a Delphi process, meet, vote, create definitions and have these undergo peer review. The recognition that our first iteration does not have to be perfect is an important one, and should prevent concern that we don't have enough evidence to start this process now. Additionally, prospective entry of septic cases into a multi-institutional database will also be very beneficial for clinical validation of future iterations of veterinary sepsis definitions.

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