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Received: 23 October 2023 | Revised: 22 December 2023 | Accepted: 3 January 2024

DOI: 10.1111/vec.13359

Journal of Veterinary Emergency and Critical Care

WILEY

SPECIAL ARTICLE

Defining sepsis in small animals

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Robert Goggs presented some of the material contained within this review at the 2021 European Veterinary Emergency and Critical Care Online Congress.

Funding information
American College of Veterinary Emergency and Critical Care

Abstract

Objective: To discuss the definitions of sepsis in human and veterinary medicine.

Design: International, multicenter position statement on the need for consensus definitions of sepsis in veterinary medicine.

Setting: Veterinary private practice and university teaching hospitals.

Animals: Dogs and cats.

Interventions: None.

Measurements and Main Results: Sepsis is a life-threatening condition associated with the body's response to an infection. In human medicine, sepsis has been defined by consensus on 3 occasions, most recently in 2016. In veterinary medicine, there is

Abbreviations: DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; PIRO, predisposition, infection, response, organ dysfunction; PRR, pattern recognition receptor; qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

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little uniformity in how sepsis is defined and no consensus on how to identify it clinically. Most publications rely on modified criteria derived from the 1991 and 2001 human consensus definitions. There is a divergence between the human and veterinary descriptions of sepsis and no consensus on how to diagnose the syndrome. This impedes research, hampers the translation of pathophysiology insights to the clinic, and limits our abilities to optimize patient care. It may be time to formally define sepsis in veterinary medicine to help the field move forward. In this narrative review, we present a synopsis of prior attempts to define sepsis in human and veterinary medicine, discuss developments in our understanding, and highlight some criticisms and shortcomings of existing schemes.

Conclusions: This review is intended to serve as the foundation of current efforts to establish a consensus definition for sepsis in small animals and ultimately generate evidence-based criteria for its recognition in veterinary clinical practice.

KEYWORDS
canine, feline, immune response, infection, systemic inflammatory response syndrome

1 | INTRODUCTION

The word "sepsis" and the disorder caused by severe infection have ancient origins,[1] but our understanding of the syndrome has greatly evolved over the last 120 years.[2] Minor infections that incite a localized host immune response and elicit circumscribed tissue reaction are commonplace and do not constitute sepsis. By contrast, sepsis represents a life-threatening host response to an infection that is overwhelming in its severity or widespread in its extent.[3,4] Sepsis is a major public health concern and the leading cause of death in human noncardiac ICUs.[5] It is estimated that in 2017, almost 49 million adults developed sepsis worldwide resulting in 11 million sepsis-related deaths, accounting for nearly 20% of global mortality.[6] In the United States alone, the Centers for Disease Control and Prevention estimate that over 1.7 million adults develop sepsis annually, resulting in roughly 350,000 fatalities.[7] While mortality rates have improved in high-income countries, the global burden of sepsis remains substantial, particularly in low- and middle-income countries, with noticeable heterogeneity in worldwide survival rates.[8,9]

In veterinary medicine, there are no accurate estimates of the incidence of sepsis, but mortality rates of between 20% and 68% are frequently reported.[10–14] Mortality rates are higher in patients with greater degrees of physiologic parameter disturbance[15] and in those with organ dysfunction.[16,17] In people, early diagnosis and subsequent prompt therapeutic intervention are crucial in the management of sepsis.[18–20] Delays in recognition and initiation of definitive care worsen outcomes.[21,22] Equivalent evidence is lacking but delayed diagnosis likely contributes to worsened outcomes in animals also. Consequently, the definition of sepsis and its implications for patient care are of great importance.[23–25] The distinction between a definition and the criteria that facilitate clinical recognition is critical and not simply a question of syntax. A sepsis definition should describe what sepsis "is."[4] In contrast, the syndrome cannot presently be diagnosed using any standardized, validated test and hence sepsis definitions cannot readily be applied to the clinical setting. Consequently, there is a need to establish objective parameters that can be measured in individual animals, and which relate to the pathophysiology and sequelae of the sepsis. To enable early recognition, these parameters should be easy and inexpensive to measure in diverse settings, without requiring costly equipment or specialized laboratories.[26,27] Rapid identification of sepsis is complicated by the clinical heterogeneity of the syndrome. The PIRO concept (predisposition, infection, response, organ dysfunction) introduced by the human 2001 definition process proposed considering factors that influence this heterogeneity to stage sepsis akin to cancer staging.[28] Surprisingly, despite offering insights into sepsis, the PIRO approach has not been widely adopted.[29,30]

A major challenge facing any attempt to define sepsis is reconciling the distinct needs of clinicians and researchers. In the emergency room and ICU, clinicians require a sensitive definition of sepsis with clinical correlates that facilitate early, accurate diagnoses to ensure all patients with sepsis are identified. An increased false positive rate (overdiagnosis) is preferable to overlooking patients with a potentially life-threatening condition. In contrast, researchers evaluating novel therapies require a more specific sepsis definition to avoid inadvertently dismissing promising therapies as ineffective by testing them in individuals with no likelihood of response. Clinical research can accommodate a higher false negative rate that minimizes enrollment of patients without definitive sepsis. Higher specificity, perhaps achieved by including biomarkers, might enhance study comparability between distinct locations, improve assessment of illness severity, and enable patient stratification during analysis.[31] Consequently, clinicians might find it easier to allocate resources and prognosticate. Potential drawbacks of more stringent criteria include false negatives, delays in diagnosis, and

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TABLE 1 Concepts and terminology from the 1991 human consensus conference.

Term or concept	Definition
Infection	Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms
Bacteremia	The presence of viable bacteria in the blood
Sepsis-induced hypotension	A systolic arterial pressure (SAP) <90 mm Hg or a reduction of ≥40 mm Hg from baseline in the absence of other causes for hypotension
Multiple Organ Dysfunction Syndrome (MODS)	Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention
Systemic Inflammatory Response Syndrome (SIRS)	The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by 2 or more of the following: - Hyperthermia (>38°C, >100.4°F) or hypothermia (<36°C, <96.8°F) - Tachycardia (>90/min) - Tachypnea (>20/min) or hyperventilation ($PaCO_2$ < 32 mm Hg) - Leukocytosis (>12 × 10^9/L, >12,000/μL) or leukopenia (<4 × 10^9/L, <4000/μL) or left shift (>10%)
Sepsis	The systemic response to infection manifested by SIRS resulting from infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion includes, but is not limited to, lactic acidosis, oliguria, and acute alteration in mental status.
Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation with hypoperfusion including, but not limited to, lactic acidosis, oliguria, and acute alteration in mental status

increased costs, which may impede access to care or hinder dissemination of research findings. Below, we present the historical context of prior attempts to define and codify sepsis to serve as the foundation of our efforts to establish a consensus definition for sepsis and evidence-based criteria for its recognition in veterinary clinical practice.

2 | SEPSIS-1 (AMERICAN COLLEGE OF CHEST PHYSICIANS/SOCIETY OF CRITICAL CARE MEDICINE CONSENSUS 1991)

Before 1991, it was well-established that sepsis was a common cause of morbidity and mortality and that its incidence was increasing in parallel with changing patient demographics, developments in therapeutic strategies, and the use of new procedures. It was also recognized that the multitude of terms associated with the syndrome affecting these patients was impeding the interpretation and application of clinical trial data. To address these issues, the 1991 consensus conference defined various terms and concepts relevant to sepsis, many of which remain in use (Table 1).[32] Three levels of sepsis severity (sepsis, severe sepsis, and septic shock) were defined, and these terms remained in use until 2016.[4] Central to the 1991 definitions was the concept of the systemic inflammatory response syndrome (SIRS) wherein sepsis was the presence of SIRS due to an infection (Figure 1).[33] This definition derived from the then-prevailing premise that sepsis resulted from a hyperinflammatory response to infection. Inflammation is an important component of the immune response to injury or infection that is usually localized, constrained, controlled, and protective. In contrast, when an inflammatory response to a profound or sustained insult is no longer localized, but generalized, it is termed systemic inflammation or SIRS.[33] Crucially, the identification of SIRS is highly context dependent. For instance, an exercising dog with physiologic increases in heart rate, respiratory rate, and body temperature meets the established criteria for SIRS, which is nonsensical.[12] Assessments for SIRS criteria are valid only in visibly unwell patients, where clinical signs cannot be adequately explained by pain, anxiety, and medication use, and when the physiologic parameters are altered at rest. Only patients with compatible history, clinical signs, and physical examination findings where there is genuine concern for sepsis should be assessed. The SIRS criteria cease to be informative when applied without this context specificity.

Unfortunately for clinicians, SIRS due to tissue injury resulting from trauma, pancreatitis, thrombosis, or ischemia, and chemical peritonitis from bile or urine leakage, is clinically indistinguishable from SIRS provoked by an infection caused by bacteria, viruses, or fungi.[33] Development of SIRS results from similar biochemical responses to distinct stimuli due to the limited response repertoire of the innate immune system. Pathogens and tissue injury elicit similar responses because they activate the same pattern recognition receptors (PRRs) via pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), respectively.[34] The chemical mediators (eg, cytokines and chemokines) released in response to PRR activation generate the host response we recognize clinically as SIRS.[35] Microbial molecules including bacterial cell wall components, exotoxins, bacterial and viral DNA, and RNA function as PAMPs, while host molecules such as extracellular histones, neutrophil elastase, heat shock proteins, DNA and RNA, and high mobility group box-1, are DAMPs. Stimulation of membrane-bound PRRs such as Toll-like receptors by either PAMPs or DAMPs activates common intracellular signaling pathways resulting in the clinical manifestations we recognize

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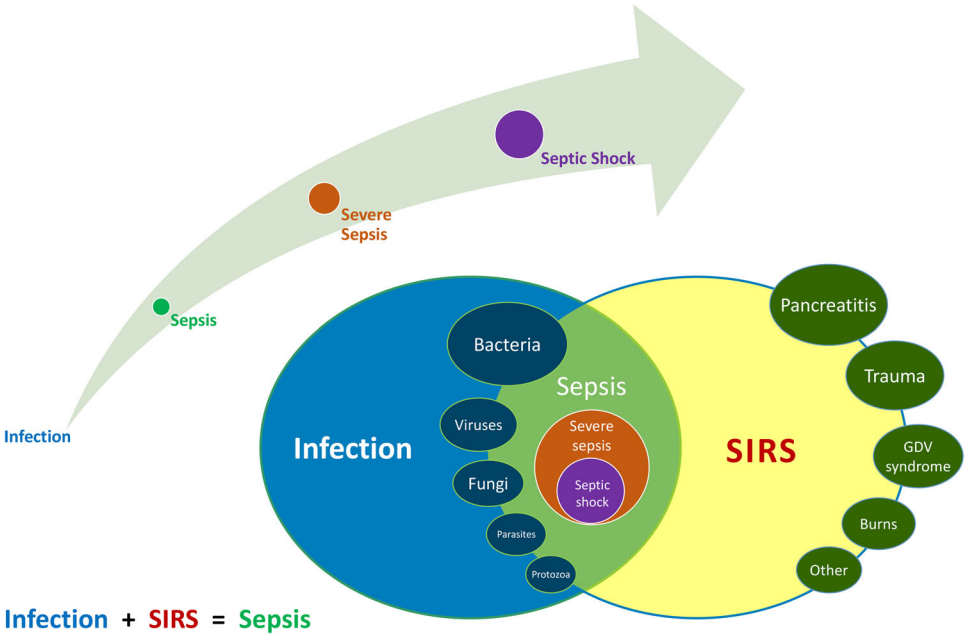


FIGURE 1 A schematic representation of sepsis as defined by the 1991 Consensus Conference. Per the 1991 (Sepsis-1) consensus definitions, sepsis is the result of the systemic inflammatory response to infection. The systemic inflammatory response syndrome (SIRS) can result from both infectious or noninfectious insults (eg, pancreatitis, trauma, or, in veterinary patients, syndromes such as gastric dilation volvulus). The combination of infection (bacterial, viral, or fungal) with systemic inflammation is termed sepsis. Severe sepsis is characterized by the development of organ dysfunction, while septic shock represents a subset of these patients in which cardiovascular compromise has occurred. In this scheme, there is a progression in severity from infection to sepsis, from sepsis to severe sepsis, and from severe sepsis to septic shock. Modified from Delano and Ward (2016)[131] after Bone et al (1992).[32]

as SIRS. The lack of response specificity poses diagnostic challenges for clinicians attempting to differentiate noninfectious causes of SIRS from sepsis (eg, acute pancreatitis from septic peritonitis).

Despite subsequent criticisms, the 1991 sepsis consensus conference represents a milestone in our understanding and recognition of sepsis. The definitions it established have had a lasting impact on clinical practice and research in both human and veterinary medicine as evidenced by the >8200 citations of the 1992 publication to date. In particular, the 1991 consensus definitions enabled a structured approach to diagnosis, a framework for the evaluation of novel therapies, and the foundation for future guidelines. After the 1991 consensus conference, an epidemiologic survey across 8 academic medical centers defined sepsis as hyper- or hypothermia, tachypnea or the need for mechanical ventilation, tachycardia, and clinical evidence of infection or a positive blood culture.[36] The study also used clinical criteria to define severe sepsis and septic shock based on evidence of organ dysfunction or hypotension despite a fluid challenge. The Rivers trial of early goal-directed therapy in sepsis[37] combined the 1991 consensus definitions and criteria from the Sands study to define the patient population for their trial. The Rivers study enrolled patients with 2/4 SIRS criteria and hypotension (systolic blood pressure <90 mm Hg) despite a fluid challenge or a plasma lactate concentration >4 mmol/L. The subsequent influence of the Rivers trial on clinical practice helped to embed these cutoffs in the literature.

3 | SEPSIS-2 (INTERNATIONAL SEPSIS CONSENSUS DEFINITIONS 2001; SOCIETY OF CRITICAL CARE MEDICINE, EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE, AMERICAN COLLEGE OF CHEST PHYSICIANS, AMERICAN THORACIC SOCIETY, SURGICAL INFECTION SOCIETY)

The use of SIRS to define sepsis per the 1991 consensus conference was not universally accepted.[38] In particular, the SIRS criteria were felt to be overly sensitive, nonspecific, and poorly reflective of illness severity.[39] A second sepsis definitions conference was held in 2001, but concluded that there was insufficient evidence to warrant a change to the definition.[32] The diagnostic criteria upon which suspicion of sepsis could be based were expanded to better reflect clinical responses to infection (Table 2),[28] but it was recognized that these were inherently arbitrary in the absence of a gold standard against which to calibrate them. Additionally, the 2001 definitions allowed for the use of various organ dysfunction definitions and scores. Use of the multiple organ dysfunction score[40] or the sequential organ failure assessment (SOFA) score[41] was suggested for adults, while 4 different systems were permitted for use in pediatrics.[42–45] While this approach offered flexibility in patient assessment and organ dysfunction scoring, it simultaneously reduced the ability of clinicians and investigators to compare studies or trials employing distinct criteria and hence limited research

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TABLE 2 Diagnostic criteria for sepsis proposed in 2001 including human cutoff values.

Infection	Documented, or suspected, and some of the following
General variables	Fever (core temperature >38.3°C, >100.9°F)
	Hypothermia (core temperature <36°C, <96.8°F)
	Heart rate >90/min or >2 standard deviations (SD) above the normal value for age
	Tachypnea
	Altered mental status
	Significant edema or positive fluid balance (>20 mL/kg over 24 h)
	Hyperglycemia (plasma glucose >7.7 mmol/L, >120 mg/dL) in the absence of diabetes
Inflammatory variables	Leukocytosis (WBC > 12×10^9/L, >12,000/μL)
	Leukopenia (WBC < 4×10^9/L, <4000/μL)
	Normal WBC with >10% immature forms
	Plasma C-reactive protein (CRP) >2 SD above the normal value
	Plasma procalcitonin (PCT) >2 SD above the normal value
Hemodynamic variables	Arterial hypotension (SAP < 90 mm Hg, MAP < 70 mm Hg, or SAP decrease >40 mm Hg in adults or <2 SD below normal for age)
	SvO_2 > 70% (adults only)
	Cardiac index >3.5 L/min
Organ dysfunction variables	Arterial hypoxemia (PaO_2/FiO_2 < 300)
	Acute oliguria (urine output [UOP] < 0.5 mL/kg/h)
	Creatinine increase (>44.2 μmol/L, >0.5 mg/dL)
	Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
	Ileus (absent bowel sounds)
	Thrombocytopenia (platelet count <100×10^9/L, <100,000/μL)
	Hyperbilirubinemia (total bilirubin >70 μmol/L, >4 mg/dL)
Tissue perfusion variables	Hyperlactatemia (>3 mmol/L or >27 mg/dL)
	Decreased capillary refill time or mottling

Abbreviations: aPTT, activated partial thromboplastin time; FiO_2, fraction of inspired oxygen; INR, international normalized ratio; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen in the arterial blood; SvO_2, mixed venous oxygen saturation, SAP, systolic blood pressure.

reproducibility and generalizability. This potentially unintended consequence warrants consideration in any future effort to codify a complex syndrome like sepsis.

4 | PREDISPOSITION, INFECTION, RESPONSE, ORGAN DYSFUNCTION (PIRO)

A key issue for research definition and clinical diagnosis of sepsis is disease heterogeneity. A puppy with parvoviral enteritis is markedly different from an adult dog with septic peritonitis due to an intestinal perforation, which is markedly different again from an elderly dog with sepsis secondary to pyelonephritis. Yet, all these patients could be termed "septic." To address these disparate disease presentations, the human 2001 consensus definitions introduced the PIRO concept (predisposing factors, infection factors, host response, and organ dysfunction) for the staging of sepsis in people (Figure 2).[28,46] The PIRO model was intended as a concept upon which to base future research,[47] but was not validated at the time it was proposed,[48,49] which likely limited its adoption.

4.1 | Predisposing factors

Predisposing factors including age, comorbidities, and concurrent therapies influence host susceptibility to infection and alter the likelihood of sepsis development. Genetic polymorphisms likely play important roles in determining which patients develop sepsis and influence the severity of the resulting syndrome.[50] In people, epidemiological data and candidate gene investigations suggest that genetic risk factors increase susceptibility to, and severity of, sepsis.[51,52] Breed predispositions to parvoviral enteritis and pyometra suggest that genetic factors are relevant to sepsis development in small animals also.[53,54] Veterinary researchers are increasingly applying high-throughput screening technologies to study sepsis,[55–57] but our understanding of these factors in veterinary medicine is rudimentary.[58–61]

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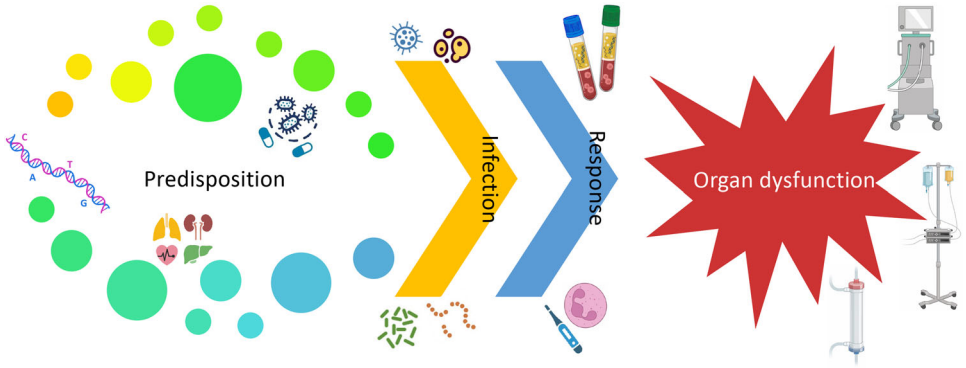


FIGURE 2 The PIRO concept (predisposition, infection, response, organ dysfunction). The 2001 (Sepsis-2) consensus definitions developed the PIRO concept to better understand the heterogeneity of sepsis and provide a means to "stage" the disease. In this scheme, predisposing factors might include genetic susceptibilities, comorbidities, physiologic reserve, or the colonization by microorganisms expressing antimicrobial drug resistance. The nature of the infection would likely vary with each patient in terms of pathogen type, organism species, virulence factor expression, pathogen load, infection location, and the host immunocompetence. The host response to infection can vary between patients and within an individual over time and could be assessed through measurement of biomarkers of the disease or of the host response. The patient's physiologic responses to infection manifest as the clinical signs detectable in the emergency room or ICU. Ultimately, in sepsis, the combination of these predisposing factors, the infection, and the resulting host response give rise to organ dysfunction, necessitating intensification of care through organ system support and correspondingly increasing the risk of mortality.

4.2 | Infection factors

The specific type, source, location, organism, virulence, and resistance profile of the pathogen strongly influence the nature, severity, and prognosis of the resulting sepsis syndrome. Most veterinary sepsis studies to date have focused on bacterial[62–64] or viral infections,[30,65] with fungal forms of sepsis more rarely recognized.[66,67] Few studies differentiate the infecting organism or the location of the infection, which likely impacts the utility of study findings and their applicability to other patient populations. Without better delineation of the type of infection, we may be unable to identify the patients who would benefit the most from a particular intervention. For example, in the PROWESS (Protein C Worldwide Evaluation in Severe Sepsis) trial,[68] patients with urosepsis had significantly lower 28-day mortality compared with patients with a pulmonary source of sepsis. Although only indirectly related to the infection, the timing of sepsis development might also be relevant to outcome. In 1 human study, those who developed septic shock within 24 hours of ICU admission were more severely ill but had better outcomes than those who deteriorated later in their ICU stay.[69]

4.3 | Host response

The host response to infection can vary between patients with the same pathogen, between distinct infections in the same patient, as well as in the same patient over time.[2] The presence of comorbidities, gastrointestinal microbiome composition,[70] genetic and epigenetic variation, and the influence of therapeutic interventions all contribute to this variation. Evaluation of host gene expression (transcriptomics) involves the measurement of messenger RNA in blood or circulating leukocytes.[71] This approach has been widely studied in human sepsis, but there are few publications in veterinary medicine to date.[72–74] The host response can be assessed with biomarkers to gain insights into the disease process, the patient's immune response, and their organ function.[31,75,76] Such assessments may provide a deeper understanding of the host response and enable future treatments to be truly individualized.[77–81]

4.4 | Organ dysfunction

Conceptually in PIRO, organ dysfunction derives from the interplay of predisposing factors, the infection itself, and the resulting host response, and the model suggests that organ dysfunction in sepsis is preventable. Certainly, the severity of organ dysfunction is an important determinant of prognosis in sepsis in both people and small animals.[16,17,40] Composite organ failure assessment scores such as the SOFA[41] or the logistic organ dysfunction score[82] were proposed to aid the quantification of the degree of organ dysfunction while recognizing that measures capable of detecting early cell and tissue damage might be preferable in the future.

5 | PEDIATRIC SEPSIS DEFINITIONS

The 2001 Consensus Conference report included pediatric-specific diagnostic criteria for sepsis, namely, evidence of infection combined with signs and symptoms of inflammation such as hyper- or hypothermia, tachycardia, and evidence of organ dysfunction including altered mental status, hypoxemia, and hyperlactatemia.[28] It was recommended that organ dysfunction in children should be scored using previously reported criteria or established systems such as the Pediatric Logistic Organ Dysfunction (PELOD) score.[45] The 2001 report also noted that owing to their higher basal vascular tone, children

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with sepsis exhibit hypotension only when shock is decompensated and blood pressure criteria should not be used to identify cardiovascular dysfunction. Instead, tachycardia, poor peripheral pulses, altered mentation, delayed capillary refill time, and mottled or cool extremities are preferred indicators of shock in childhood sepsis.

The limited pediatric-specific recommendations within the 2001 Consensus Conference report warranted the generation of guidelines focused on children. A pediatric sepsis consensus conference held in 2002 defined sepsis as systemic inflammation secondary to infection,[83] but despite this definition being contingent on SIRS criteria, specific cutpoints for children were not set. Instead, variations in physiologic parameters that exceeded 2 standard deviations above or were in the lowest 10th percentile of what is considered normal for the age group were preferred to account for the substantial age-related variations between infants, toddlers, school-age children, and adolescents. Additionally, persistent unexplained heart rate alterations were also considered to provide sufficient evidence of cardiovascular instability. Similar peer-group-referenced, population-indexed parameters were also used to define organ dysfunction. For instance, blood pressure in the lowest 5th percentile or exceeding 2 standard deviations below normal for age indicates cardiovascular dysfunction.

Following the 2016 redefinition of sepsis in adults, it was recognized that variables specific to children for sepsis identification and the prediction of patient-centered outcomes had not been systematically reviewed. To address this gap, the Pediatric Sepsis Definition Taskforce posed 2 questions: (i) In children with infections, what factors are associated with the development of sepsis? (ii) In children with sepsis, what factors help predict mortality?[84,85] Answering the first question identified clinical predictors of sepsis, while the second enabled the identification of sepsis severity criteria and codified severe forms of the syndrome including septic shock. The systematic review determined that in children with infections, decreased level of consciousness and higher Pediatric Risk of Mortality (PRISM) scores[86] are associated with sepsis. In children diagnosed with sepsis, comorbidities including cancer; clinicopathologic parameters including plasma lactate, platelet count, fibrinogen, and procalcitonin; and the presence of organ dysfunction are all associated with mortality.[85] This approach to establishing the evidence basis for clinical sepsis diagnosis and prognostication is well suited for application in veterinary medicine.

6 | SEPSIS-3 (SOCIETY OF CRITICAL CARE MEDICINE, EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE 2016)

The SIRS criteria provide rapid, simple, and objective means to identify potential systemic inflammation. Nevertheless, it is widely recognized that in people, the SIRS criteria lack both discriminant and convergent validity resulting in excessive false positives and false negatives.[39,87,88] In 2016, sepsis was redefined using a data-driven approach to enhance the specificity of the associated clinical criteria,[4,89,90] and with a focus on the host response rather than the pathogen trigger. These changes were also intended to lessen the focus on inflammation as

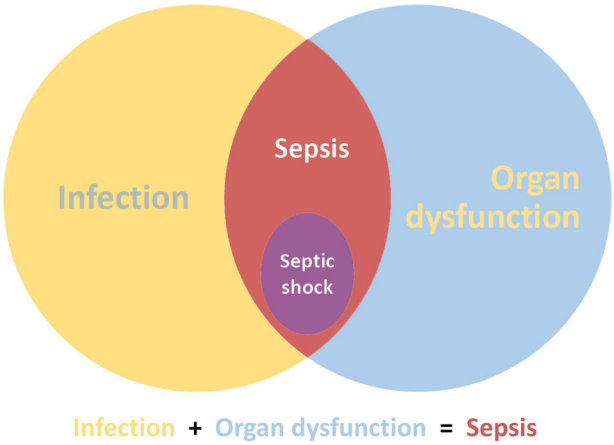


FIGURE 3 A schematic representation of sepsis as defined by the 2016 Sepsis-3 process. In 2016, sepsis in humans was redefined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The term severe sepsis was eliminated, and septic shock was formally defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Clinical criteria derived from the review of large medical record databases were used to "operationalize" the definitions. Recognition of organ dysfunction replaced the identification of the systemic inflammatory response syndrome as the means to identify a dysfunctional host response to infection. Two systems for the identification of organ dysfunction were recommended: (i) the sequential organ failure assessment score (SOFA) primarily for the evaluation of patients in ICUs, and (ii) quick SOFA (qSOFA) consisting of hypotension, altered mentation, and tachypnea for the rapid identification of at-risk patients in non-ICU settings. Modified from Codina and Zeitlinger (2022).[132]

the driving pathological process in sepsis because it is now known that sepsis involves activation of both pro- and anti-inflammatory responses[91] and is accompanied by dysfunction in the cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation systems.[92,93] Per the Sepsis-3 consensus, sepsis is the "*life-threatening organ dysfunction caused by a dysregulated host response to infection*" (Figure 3). The Sepsis-3 definitions removed the term "severe sepsis" to correct the misapprehension that sepsis involves a stepwise progressive deterioration in status and reframe all sepsis as life-threatening. The Sepsis-3 definitions also included a lay description of sepsis: "*sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs,*" which is a potentially valuable means to convey this complex concept to clients.

To identify organ dysfunction, Sepsis-3 definitions recommend a ≥2-point increase in the well-established SOFA score (Table 3),[41,94] for which a veterinary equivalent has been evaluated.[16,95] This represented a substantial shift from the 2001 definitions that were permissive in their use of various published organ function assessment tools. An alternative rapid assessment termed quick sequential organ failure assessment (qSOFA) was also proposed as a means to enable the identification of potential sepsis patients in out-of-hospital, emergency department, or general hospital ward settings.[89,96] To identify organ dysfunction, the qSOFA score requires 2 or more of altered mentation

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TABLE 3 Human sequential organ failure assessment (SOFA) score.

Organ system	Score				
Criterion	**0**	**1**	**2**	**3**	**4**
Respiratory					
Pao_2/Fio_2	>400	<400	<300	<200	<100
Coagulation					
Platelet count, $\times 10^9$/L ($\times 10^3/\mu$L)	>150	<150	<100	<50	<20
Liver					
Bilirubin, μmol/L	20	20–32	33–101	102–204	204
Bilirubin, mg/dL	<1.2	1.2–1.9	2.0–5.9	9.0–11.9	>12
Cardiovascular					
Blood pressure or catecholamine usage (μg/kg/min for at least 1 h)	MAP > 70 mm Hg	MAP < 70 mm Hg	Dopamine <5 or any dobutamine dose	Dopamine 5.1–15 or epinephrine <0.1 or norepinephrine <0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system					
Glasgow coma scale score	15	13–14	10–12	6–9	<6
Kidney					
Creatinine, μmol/L	<110	110–170	171–299	300–440	>440
Creatinine, mg/dL	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Or urine output, mL/h				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen in the arterial blood.

(a diminished Glasgow Coma Scale score), hypotension (systolic blood pressure ≤100 mm Hg), or tachypnea (respiratory rate ≥22/min). It should be noted that qSOFA is a rapid screen for predictors of mortality rather than a means to identify sepsis specifically and has limited prognostic utility in human studies.[97–99] Several studies have evaluated modified qSOFA criteria in dogs with variable results. In a critically ill population of dogs, qSOFA was not predictive of mortality in contrast to plasma lactate concentration, but that population had few dogs with sepsis.[100] When used to assess dogs with surgical sepsis where the overall mortality rates were >30%, qSOFA was associated with duration of hospitalization and mortality.[101,102] In a study of 45 dogs with suspected or confirmed infection admitted to an ICU where the mortality rate was 42%, a composite score of mentation, heart rate, and venous carbon dioxide ($Pvco_2$) was predictive of outcome.[103] These results suggest that incorporating organ dysfunction into severity assessments has merit, recognizing that modifications to parameters or criteria to account for biological variation between species may be required.

The 2016 Sepsis-3 process also redefined septic shock in a data-driven manner that incorporated mortality assessments into the clinical criteria. Within the Sepsis-3 consensus panel, there was unanimous agreement that septic shock should reflect a more severe illness with a much higher likelihood of death than sepsis alone. Retrospective databases were then used to determine clinical parameters that identified the subset of patients with high mortality. In a very large registry dataset collected by the Surviving Sepsis Campaign (n = 28,150),[90] inclusion of lactate in the classification criteria enabled clear mortality stratification, as follows:

Fluid resistant hypotension requiring vasopressors + lactate >4 mmol/L = 49.7%;

Fluid resistant hypotension requiring vasopressors + lactate >2 mmol/L = 42.3%;

Fluid resistant hypotension requiring vasopressors (lactate normal) = 30.1%;

Hyperlactatemia >4 mmol/L = 29.9%;

Hyperlactatemia >2 mmol/L = 25.7%.

These cutoffs were evaluated in 2 separate electronic health record data sets and were reproducible. Thus, septic shock is presently defined as *a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality*. The corresponding clinical criteria are persistent hypotension requiring vasopressors for mean arterial pressure ≥65 mm Hg and a plasma lactate concentration >2 mmol/L after volume resuscitation. With these criteria, the expected mortality for patients in high-income countries with septic shock is >40%, but this figure is unlikely to apply to all middle- and low-income countries.[104–106]

The Sepsis-3 process has various merits, including an updated pathophysiologic basis, standardized organ dysfunction scoring, clarification of terminology, and the use of large datasets to generate evidence-based clinical correlates. However, it should be acknowledged that the updated definitions have not been universally accepted,[107,108] with bodies such as the American College of Chest

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Physicians publishing statements of opposition.[109] Various criticisms have been leveled at the 2016 definitions including concerns about limited sensitivity in non-ICU settings, a lack of specificity for infection in general, and poor performance of the qSOFA score in diseases that directly cause hypotension, tachypnea, or delirium. For instance, community-acquired pneumonia is a common cause of sepsis in people, but qSOFA is inferior to a validated pneumonia-specific score for mortality prediction.[110] Similarly, delayed therapeutic intervention in patients that do not fulfill qSOFA criteria can lead to increased mortality.[96] As such, while Sepsis-3 represents a paradigm shift in our understanding and identification of sepsis, challenges remain in applying the concepts to human health globally or to veterinary patients.

7 | VETERINARY SEPSIS DEFINITIONS

Before 2016, sepsis in veterinary medicine was typically defined per the premise of the 1991/2001 human consensus definitions, that is, "SIRS plus documented or suspected infection."[111] Within the literature, and likely within clinical practice, there are variations in what constitutes documentation and suspicion of infection.[62,112–115] The standard methods described for documenting infection include culture, cytology, and histopathology. For bacterial sepsis, culture and susceptibility testing is ideal to confirm infection, document the organism(s) involved, and identify antimicrobial drug resistance. However, not all organisms can be grown successfully in the laboratory,[116] and culture might not adequately resolve polymicrobial infections. Molecular techniques including 16S rRNA metagenomics can increase sensitivity and identification of multiple bacterial species but as yet are not readily available to veterinary clinicians.[117,118] Nonetheless, molecular techniques designed to detect some pathogens are readily available. Point-of-care tests antigen tests, for canine parvovirus, for example, often have good specificity, but variable sensitivity.[119] In some studies and in clinical practice, identification of intracellular organisms within samples collected from anatomic locations typically considered to be sterile is diagnostic for infection. For example, the identification of bacteria within phagolysosomes of neutrophils in aseptically collected abdominal fluid samples is diagnostic of septic peritonitis. Less commonly cytologic diagnosis of infection involves the identification of intracellular pathogens such as hemotropic pathogens, fungal pathogens, or viral or rickettsial inclusions. However, cytology may have limited sensitivity (ie, high false negative rates) and visual identification of organisms does not necessarily indicate an infection is active (ie, identified organisms may be dead). The terms suspected or highly suspected infection are potentially valuable for patient management since they legitimize intensification of diagnostic assessment or therapeutic intervention where strong clinical suspicion for sepsis exists but where samples cannot readily be obtained or initial testing is pending, negative, or inconclusive. However, from a research perspective, the inclusion of cases with suspected but unconfirmed infection in studies of sepsis might bias results by enrolling animals with less severe disease or by including animals that cannot respond to the treatment under study because they do not have sepsis. As such, variation in the stringency of requirements for documentation or confirmation of infection might lead to, or necessitate, the divergence of sepsis diagnostic criteria for clinical trials compared to clinical practice.

Various sets of SIRS criteria have been reported for both dogs and cats with differing sensitivity and specificity (Table 4).[120–123] Many of these sets of criteria have been repeatedly used, but there is no consensus regarding which set to use. Data from human medicine collected prior to 2016 indicate that the 1991 and 2001 sepsis definitions are highly sensitive, but have poor specificity. A study evaluating the diagnostic accuracy of the 1991 and 2001 definitions found the 1991 sepsis definition to be 95% sensitive and 61% specific, while the 2001 definition was 97% sensitive and 58% specific.[124] Veterinary sepsis definitions derived from these criteria are likely to be similarly affected and legitimate concerns exist regarding construct validity wherein calculations of sensitivity and specificity are predicated on test accuracy that itself may be limited. For instance, in the Hauptman study, the diagnostic criteria for sepsis were evidence of infection and the presence of "systemic illness," a term that was not further described. Questionable construct validity and lack of consistency within the literature create a tension between the demands of patient management and the requirements of clinical trials that cannot adequately be resolved at present. It has been argued that because the primary aim of the SIRS criteria is to identify animals that are systemically unwell and require prompt attention, the exact cutoff points for these parameters are less important than the implication of the derangement, that is, the patient should be thoroughly and urgently assessed. However, a recent study determined that SIRS-positive status was common in small animals presented to the emergency room and primary care, and was only weakly associated with outcome.[125]

Following the publication of Sepsis-3, the human and veterinary definitions are now divergent, further limiting the translation of human sepsis literature to veterinary practice. Moreover, the premise that sepsis is an overexuberant pro-inflammatory response to infection that underpins the use of the SIRS criteria is of questionable validity. Informed by the Sepsis-3 update, the Brazilian Veterinary Emergency and Critical Care Society published consensus definitions for sepsis in 2017,[128] such that there is now geographic variation in the definition of sepsis in veterinary medicine. For all these reasons, it is apparent that a formal redefinition of sepsis in veterinary medicine is warranted to optimally identify sepsis in the clinic and enable future research endeavors.

To these ends, we have established a steering committee comprising 12 enthusiastic, engaged sepsis experts and identified a larger group of participants to help accomplish this task. In the first phase, we will define, by consensus,[83] what we consider sepsis "is," akin to a veterinary dictionary definition.[4] We will independently generate 12 separate definitions before collating and combining these for iterative refinement via an anonymous Delphi survey.[90] Following this, we will perform a systematic review of the veterinary literature to answer 2 Population, Exposure, Comparator, Outcome (PECO) format questions. First, we will seek to identify associations between phenotypic factors in animals with infection and negative outcome measures,

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TABLE 4 Criteria for the systemic inflammatory response syndrome (SIRS) used in dogs and cats.

	Dogs (2/4 criteria)			Cats (3/4 criteria)	
Criteria	Hauptman 1997[12]	de Laforcade 2003[11]	Okano 2002[15]	Brady 2000[126]	DeClue 2011[127]
Temperature	>39°C	>39.4°C	>39.7°C	>39.7°C	≥39.7°C
	>102.2°F	>103°F	>103.5°F	>103.5°F	≥103.5°F
	<38°C	<37.8°C	<37.8°C	<37.8°C	≤37.8°C
	<100.4°F	<100°F	<100°F	<100°F	≤100°F
Heart rate	>120/min	>140/min	>160/min	>225/min	≥225/min
	–	–	–	<140/min	≤140/min
Respiratory rate	>20/min	>20/min	>40/min	>40/min	≥40/min
Leukocyte count	$>16 \times 10^9$/L	$>16 \times 10^9$/L	$>12 \times 10^9$/L	$>19.5 \times 10^9$/L	$>19.5 \times 10^9$/L
	$>16 \times 10^3/\mu$L	$>16 \times 10^3/\mu$L	$>12 \times 10^3/\mu$L	$>19.5 \times 10^3/\mu$L	$>19.5 \times 10^3/\mu$L
	$<6 \times 10^9$/L	$<6 \times 10^9$/L	$<4 \times 10^9$/L	$<5 \times 10^9$/L	$\leq 5 \times 10^9$/L
	$<6 \times 10^3/\mu$L	$<6 \times 10^3/\mu$L	$<4 \times 10^3/\mu$L	$<5 \times 10^3/\mu$L	$\leq 5 \times 10^3/\mu$L
Band neutrophils	>3%	>3%	>10%	>5%	≥5%

to identify predictors of sepsis development. Second, in animals with sepsis (however defined), we will attempt to find associations with mortality, to identify predictors of sepsis severity or septic shock. A similar approach was successfully used to identify clinical criteria for pediatric sepsis.[84,85] We will consider how sepsis should be defined from a scientific perspective to enhance the quality, homogeneity, reproducibility, and generalizability of future research and make recommendations about what data should be collected by future veterinary sepsis studies. The third phase of our work will be to evaluate the diagnostic utility and prognostic value of the clinical criteria established during Phase 2 through retrospective medical record review. Subsequently, we intend to launch a sepsis case registry to prospectively gather multicenter data on small animals with sepsis. We envisage this process will be similar to the Veterinary Committee on Trauma (VetCOT) and Reassessment Campaign on Veterinary CPR (RECOVER) registries for trauma and cardiopulmonary resuscitation.[129,130] Ultimately, we aspire to reach a point where the data collected prospectively can be used to refine or replace the consensus definitions we initially establish.

8 | SUMMARY

The history of efforts to define, codify, and diagnose sepsis in human and veterinary medicine makes clear that it is not straightforward to describe what sepsis is or to determine how best to identify it. Yet, there is an urgent need to reach a consensus on veterinary definitions of sepsis, to harmonize human and veterinary recommendations, and to provide rational, evidence-based guidance for clinicians. We hope that taking a systematic approach will yield useable definitions and practical clinical criteria that enhance clinical recognition and support research initiatives. Taking a global approach to sepsis in veterinary medicine is important from a One Health perspective and will hopefully lead to widely applicable guidelines and improved patient outcomes.

CONFLICT OF INTEREST STATEMENT

Virginia Sinnott-Stutzman is an assistant editor for the Journal but only participated in the review process as an author. The authors declare no other conflicts of interest.

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How to cite this article: Cortellini S, DeClue AE, Giunti M, et al. Defining sepsis in small animals. *J Vet Emerg Crit Care*. 2024;1-13. https://doi.org/10.1111/vec.13359

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