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Sepsis in Dogs and Cats—Consensus Definition and Clinical Criteria

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ABSTRACT

Sepsis is the clinical syndrome that results from the host response to severe or widespread infection and is a frequent cause of death in veterinary critical care settings. Rapid diagnosis aids early treatment initiation, and hence, how sepsis is defined and identified clinically has implications for patient outcomes. Recent changes in the definitions of sepsis in human adult and pediatric patients have reduced the alignment of veterinary sepsis definitions with those in human medicine. We defined sepsis in cats and dogs by consensus and systematically reviewed the veterinary evidence to make recommendations for clinical identification of sepsis in small animals. We define sepsis as the life-threatening syndrome associated with a dysregulated host response to infection, resulting in organ dysfunction. We recommend that, in dogs and cats with infection, identification of organ dysfunction is required for the diagnosis of sepsis. We recommend that a formal illness severity assessment be performed using validated, structured scores and that measurements of the requisite physiological and laboratory parameters be undertaken to enable identification of organ dysfunction or score calculation.

Abbreviations: ALT, alanine aminotransferase; APP, acute phase protein; APPLE, Acute Patient Physiologic and Laboratory Evaluation; AST, aspartate aminotransferase; AT, antithrombin activity; CCL2, chemokine (C–C motif) ligand 2; CPV, canine parvovirus infection; CRP, C-reactive protein; cTnI, cardiac troponin I; CXCL, cysteine-X-cysteine motif ligand; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; NT-pCNP, N-terminal pro-C-type natriuretic peptide; PCT, procalcitonin; PECO, Population Exposure Comparator Outcome; PICO, Population Intervention Comparator Outcome; qSOFA, quick Sequential Organ Failure Assessment; SAA, serum amyloid A; SAPS, Simplified Acute Physiology Score; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; SPI2, survival prediction index-2; TNF, tumor necrosis factor.

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1 | Introduction

In people, sepsis is the clinical syndrome that results from the host response to severe or widespread infection [1, 2] and is the most frequent cause of death in human ICUs [3]. Sepsis resulted in an estimated 11 million human deaths in 2017, equivalent to ~20% of global mortality [4]. Accurate equivalent estimates are not available for dogs and cats, but case fatality rates of up to 68% are reported [5–9], with higher fatality rates in animals with more severe disease [10] or organ dysfunction [11–13]. Rapid diagnosis and early treatment initiation are crucial because worse outcomes are associated with delayed recognition in people [14–18]. Although equivalent data are not available for small animals, it is likely that a similar relationship between delayed intervention and fatality exists, with implications for how sepsis is recognized clinically [19–21].

Disease definitions should be biologically relevant, aid understanding of pathophysiology, and map to readily measurable objective parameters, but codifying sepsis to meet the needs of both clinicians and clinical investigators is challenging. Sensitive criteria that ensure all animals with sepsis are identified might be preferable in the clinic, but the consequent overdiagnosis might result in unnecessary treatment, increased risk of adverse drug effects, diversion of resources away from other patients, or premature euthanasia due to perceived poor prognosis. In contrast, more specific criteria ensure that only animals with sepsis are enrolled in clinical trials, yet this approach could limit generalizability to clinical practice and slow progress because a more stringent definition diminishes the available pool of animals eligible for recruitment.

Since 1991, three sets of sepsis definitions have been proposed for human adults and another three for children. The 1991 and 2001 human adult sepsis definitions established levels of sepsis severity (sepsis, severe sepsis, and septic shock) that remained in use until 2016 [2]. Central to those definitions was the concept of systemic inflammatory response syndrome (SIRS), in which sepsis was defined as the presence of SIRS due to an infection [22, 23]. This has also been the basis for veterinary definitions of sepsis but is highly context dependent, and the premise that sepsis is an overexuberant pro-inflammatory response to infection is of questionable validity. In 2016, sepsis in human adults was redefined to enhance the specificity of the associated clinical criteria [2, 24, 25], with a focus on the host response rather than the pathogen trigger. The 2016 definitions recommended that use of the SIRS criteria be discontinued and made the term "severe sepsis" obsolete by making identification of organ dysfunction central to sepsis recognition. The 2016 definitions use the Sequential Organ Failure Assessment (SOFA) score and an abbreviated version termed qSOFA ("quick" SOFA) for identification of organ dysfunction. Septic shock was defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to cause ~40% mortality in high-income countries.

For human pediatrics, the first consensus definitions for sepsis were based on identification of SIRS using variations in physiologic parameters that substantially deviated from those considered normal for the age group [26]. After the 2016 adult definitions were revised, a Pediatric Sepsis Definition Taskforce was convened and posed two 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? [27, 28]. The first question was used to identify clinical sepsis predictors and the second to identify sepsis severity criteria. This approach forms the basis for our efforts to establish the evidence base for sepsis definitions in dogs and cats. After publication of the pediatric sepsis definitions in 2022, a large database-driven effort redefined sepsis in children in 2024. The resulting Phoenix Sepsis Score was derived from analysis of an international, multicenter database of >3 million care encounters and represents the combination of organ dysfunction criteria most discriminating for sepsis and septic shock in children [29, 30].

Prior to 2016, veterinary definitions of sepsis were aligned with the 1991 and 2001 human consensus definitions of SIRS plus documented or suspected infection [31], albeit with some variation in what constituted infection confirmation [32–36]. Multiple sets of SIRS criteria have been reported for both dogs and cats, but without consensus regarding which to use [37–40]. Data from people indicate that SIRS-based sepsis definitions are sensitive, but nonspecific [41], and SIRS-based veterinary sepsis definitions are likely similarly affected. Indeed, SIRS-positive status is common in small animals in emergency and primary care settings, with poor prognostic value [42]. After publication of Sepsis-3, veterinary definitions were no longer aligned with those in people, limiting the translational utility of human sepsis literature. The publication of consensus definitions by the Brazilian Veterinary Emergency and Critical Care Society [43] also introduced geographic variation in sepsis definitions within small animal medicine.

On this basis, we believed that formally defining sepsis in small animals was warranted to inform clinical care, improve patient outcomes, and facilitate future research [44]. Here, we report the outcomes of our efforts to establish a consensus definition of sepsis and the results of our systematic review of the available veterinary evidence. We present our recommendations for the use of parameters that can be measured or assessed to aid identification of potential small animal sepsis cases in veterinary hospitals. Limitations of the available data, variation among patient populations, hospitals, and settings, and variation among parameters measured in different laboratories preclude us from making detailed recommendations for cutoff values. Pending further research to evaluate and compare specific cutoffs for objective parameters, clinicians will need to continue to interpret identified abnormalities in the context of individual patient assessments. We have also made suggestions, where appropriate, for the data that we believe should be collected by future veterinary sepsis studies. Although informed by a systematic review, our recommendations represent expert opinion and should be refined as more data become available.

2 | Materials and Methods

Development of a consensus definition for sepsis began in June 2023 after informal discussions at the 2023 EVECC Congress in Porto, Portugal. Solicitations for working group participants

were made by email and online videoconferences, and a group of 12 veterinary specialists with applicable expertise and experience assembled. Requisite expertise was established based on a relevant publication track record in the fields of emergency medicine, critical care, infectious disease, and sepsis. The group (chaired by R.G.) included representatives from six countries: the United States ($n = 6$), the United Kingdom ($n = 2$), and Australia, Brazil, Canada, and Italy (each $n = 1$) across university ($n = 7$) and private specialty practice settings ($n = 5$). Throughout the period of guideline development, the group met periodically via online videoconference, with recordings and transcripts shared after each meeting. A position statement from the committee, reviewing the recent history of sepsis definitions and setting out plans for the committee's work, was published in early 2024 [44], with financial support for open access publication provided by the American College of Veterinary Emergency and Critical Care.

Consensus definitions for sepsis and septic shock were developed by a modified Delphi process [45]. Initially, each committee member separately and independently drafted a definition of sepsis. These were collated and circulated for discussion, with keywords highlighted to aid identification of consistent terms or phrases. From the initial set of 12, a distilled list of four possible definitions was constructed, circulated, and discussed. These four definitions were then subjected to three rounds of modified Delphi surveys using an online software platform (Qualtrics XM), resulting in the consensus definition below.

As discussed above, our process was modeled on that of the Pediatric Sepsis Definition Taskforce [27, 28]. Domain descriptions (Data S1) were drafted and revised by the committee in June 2023 and finalized at an initial online videoconference meeting in July 2023. Domain 1 was intended to identify, in dogs and cats with infections, the factors associated with the development of sepsis. Domain 2 was intended to identify, in dogs and cats with sepsis, the factors that predict mortality. Within each domain, a series of questions using a Population, Exposure or Intervention, Comparison, Outcome (PECO/PICO) format was generated as previously reported by other consensus efforts [46–49]. Specifically, for Domain 1, we defined the population of interest as dogs and cats with infections. For Domain 2, we defined the population of interest as dogs and cats with sepsis, however that was determined by the studies reviewed. Typically, sepsis was codified using the prevailing definition at the time the study was conducted, which in most cases was infection concurrent with the SIRS adjudicated using established leukocyte count, heart rate, respiratory, and temperature criteria.

We excluded some specific diseases and certain infectious agents or pathogens from the systematic review (see Data S2), although the rationale for excluding specific infections varied. For instance, rabies was excluded because the disorder is universally fatal and, in many jurisdictions, management of animals with the disorder is subject to legal restrictions. Feline infectious peritonitis was excluded because we considered the pathophysiology sufficiently distinct from most cases of sepsis encountered in clinical practice that the FIP literature might be of limited utility or could distort the final recommendations. Endoparasite infections were excluded because these infections (or infestations) were not deemed plausible causes of sepsis by the committee.

The electronic database search strategies were developed in consultation with two expert librarian information specialists (J.B., E.F.). Trial searches were performed by the committee to inform the scope and limitations of the search, identify the optimal search terms, search locations, and databases, and assess the potential size of the resulting article database. The search was developed iteratively with content experts and information specialists. Databases searched were CAB Abstracts (Ovid), MEDLINE (PubMed), and Web of Science (Core Collection, BIOSIS, and Scielo). The search was limited to sepsis, related conditions, and outcomes in dogs and cats. Filters were used to exclude review articles, guidelines, and articles describing diseases listed in Data S2. Publication years were limited to 1997–2023. No language filters were applied. The complete search strategy can be found in the Supporting Information (Data S3).

An online software platform (Covidence Systematic Review Software, Veritas Health Innovation) was used to facilitate the systematic literature review [50]. In January 2024, 19,030 citations were imported into the Covidence platform from the three database sources (MEDLINE via PubMed $n = 6782$; Web of Science $n = 6267$; and CAB Abstracts $n = 5981$) from the initial search. From these articles, 3356 duplicates were identified automatically and removed, leaving 15,674 articles for screening. In May 2025, the searches were repeated ("bridge search"), and a further 1280 articles were imported into Covidence, of which 311 duplicates were removed, leaving an additional 969 articles for initial screening. A further 58 duplicate articles were identified manually and removed, leaving 16,599 articles in total. From these, 15,444 studies were considered irrelevant, leaving 1155 articles to be assessed for eligibility. After careful evaluation, 803 articles were excluded, leaving 352 articles that formed the basis of the systematic review (Figure 1).

The Covidence software was used to tag articles as relevant to Domain 1, Domain 2, or both; to label articles needing additional scrutiny; to identify duplicates missed by automated processes; and to highlight studies where another opinion was needed to adjudicate suitability for inclusion. The group developed a manuscript screening protocol (Data S4) detailing, a priori, the methods for assessing eligibility for inclusion or exclusion. Two rounds of concordance analysis were performed to determine how consistently independent reviewers agreed in their assessments of article suitability. The results of these analyses were used to refine the manuscript screening protocol. The group reached consensus on how each article should be assessed and developed a process for third-reviewer adjudication in the event of disagreement between primary and secondary article reviewers. For expediency, the group reached consensus to have one person perform data extraction from each full text and have another group member check the extracted data. This corresponds to data extraction method 2 in Covidence. Templates for data extraction and for quality assurance assessment were developed, tested in a pilot study involving 12 articles, and then subsequently revised and finalized prior to being used on the whole database of full-text articles (Data S5 and S6).

Once data extraction and quality assurance scoring were complete, the resulting spreadsheets were downloaded from Covidence (Data S7). Within the spreadsheets, the patient parameters that were measured and compared between groups within each

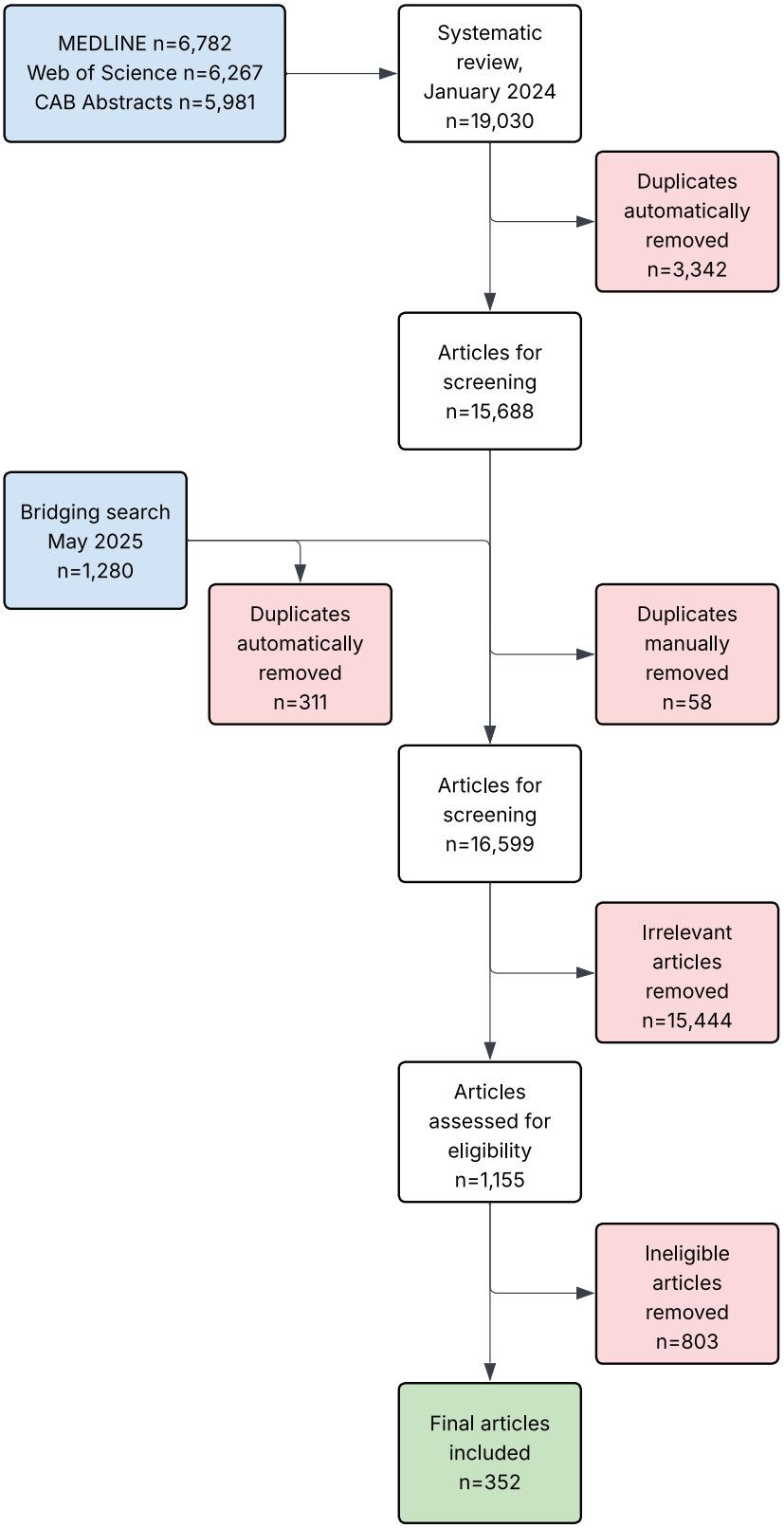

FIGURE 1 | In January 2024, 19,030 citations were imported into the Covidence platform from the three database sources (MEDLINE via PubMed $n = 6782$; Web of Science $n = 6267$; and CAB Abstracts $n = 5981$). From these articles, 3356 duplicates were identified automatically and removed, leaving 15,674 articles for screening. In May 2025, the searches were repeated, and an additional 1280 articles were imported into Covidence, of which 311 duplicates were removed, leaving an additional 969 articles for initial screening. A further 58 duplicate articles were identified manually and removed, leaving 16,599 articles in total for initial screening. From these, 15,444 studies were considered irrelevant, leaving 1155 articles to be assessed for eligibility. After careful evaluation, 803 articles were excluded, leaving 352 articles that formed the basis of the systematic review.

study were categorized using tags. This enabled the division of articles to evidence evaluators for each PICO question. Some variables were relevant and, therefore, considered in multiple PICO questions (e.g., clinicopathologic data, myocardial function parameters). Seven committee members were assigned to Domain 1, four committee members were assigned to Domain 2, and one committee member worked on both Domains. Within Domain 1, the 11 PICO questions were divided among the eight reviewers to achieve approximately equal workloads and to align with member interest and expertise. Domain 1 was subdivided into 1a and 1b. Domain 1a was intended to focus on criteria for clinical settings, whereas Domain 1b focused on criteria for research settings. The same worksheet authors considered both aspects distinctly as they reviewed the literature, and we have made recommendations and suggestions to address these two separate needs. Although Domain 2 was not originally subdivided as was Domain 1 (Data S1), we have also made recommendations and suggestions to address clinical and research settings separately within Domain 2. For Domain 2, the 11 PICO questions were divided among the five reviewers. Exemplar worksheets were generated by two committee members (R.G., C.S.) with prior experience from other consensus efforts and circulated to the group to provide others with guidance on the expected depth, length, format, and scope of evidence evaluation worksheets. These worksheets, once completed, were scrutinized by others within the relevant domain, and then the finalized versions were sent to R.G. for guideline development (Data S8 and S9). The guidelines were drafted using the evidence worksheets, edited to achieve greater homogeneity of structure, depth, and language, and revised to adopt consistent formulations of guideline recommendations. These guidelines were circulated to the group twice for comments, revisions, and suggestions. The finalized versions, including citations, were circulated to the group in January 2026 and revised once. The group met to discuss these final manuscripts prior to submission for publication, and all committee members gave their consent for publication.

Interim updates on the sepsis definition consensus process were presented at the 21st EVECC Congress, Gothenburg, Sweden, in June 2024 and at the 30th IVECC Symposium, St. Louis, MO, in September 2024.

3 | Consensus Definition of Sepsis in Dogs and Cats

Sepsis is a life-threatening syndrome associated with a dysregulated host response to infection, resulting in organ dysfunction.

There are four key elements in this consensus definition. Sepsis represents a severe condition that is associated with morbidity and increased mortality relative to that expected for an uncomplicated infection, even when that infection is itself serious or difficult to treat. This increased mortality derives from the organ dysfunction that is the result of the host response to the infection. Without infection, there cannot be sepsis, but infection alone is insufficient. The clinical syndrome of sepsis is characterized by organ dysfunction that can be local to the site of infection or distant, and that occurs because of an aberrant, dysregulated, or excessive host response. This updated definition puts organ dysfunction at the center of the pathophysiology of sepsis, making it a requirement for identification of the syndrome and key to successful management of the disorder.

4 | Evidence Summaries

Summaries of recommendations are available in the Supporting Information (Data S10).

4.1 | SIRS Criteria

4.1.1 | PICO Question

In dogs and cats with infection (**P**), does assessment of SIRS criteria (temperature, heart rate, respiratory rate, leukocyte count) (**I**), compared to not assessing SIRS criteria (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

4.1.2 | Summary of Evidence

The summary of evidence is as follows:

- Ten studies (six high quality [7, 51–55], three moderate quality [56–58], one low quality [10]) provided evidence that supports the use of SIRS criteria.
- Eighteen studies (eight high quality [59–66], seven moderate quality [67–73], three low quality [33, 74, 75]) were not supportive of the use of SIRS criteria.
- Twenty studies were considered irrelevant to the PICO question [34, 76–94].

4.1.3 | Conclusions

The evidence supporting the use of SIRS criteria for identifying negative outcomes in dogs and cats with infection is limited and conflicting. Timing of SIRS status adjudication was inconsistent, often unreported, and potentially confounded by administered treatments. Typically, studies of dogs reporting SIRS criteria required satisfaction of at least two of four criteria, whereas studies of cats required that two or three of the four criteria be satisfied. Respiratory rate in panting dogs was inconsistently handled, and there was no uniformity in the cutoffs used for each criterion. Few articles considering SIRS in dogs and cats employed methods or reporting styles that enabled the answering of the PICO question, typically because SIRS-positive status was an inclusion criterion, infectious and noninfectious causes of SIRS were compared, or a healthy control population was used. The incidence of SIRS varied significantly across the studies considered and between studies evaluating the same disease and reporting similar mortality rates, which could serve as a proxy for patient severity. Conversely, studies with substantial differences in mortality reported similar SIRS rates, which raises questions about the value of SIRS as a robust prognostic marker. Studies supporting the use of SIRS criteria were often matched by similar studies that were not supportive of the use of SIRS criteria. Although a formal meta-analysis cannot be easily performed, the

overall number of patients evaluated in the nonsupportive studies exceeds that of the patients in the supportive studies.

Only three studies considered SIRS in the context of canine sepsis induced by various infection types. In their retrospective cohort study, Hauptmann and colleagues examined the use of SIRS criteria to identify patients with sepsis, defined as an infection plus systemic illness, among a referral surgical population of dogs, most of which did not have underlying infections. In this population, SIRS criteria were sensitive but not specific for identifying sepsis. The criteria for "systemic illness" were ill-defined, making it difficult to determine if this was an appropriate patient-centered outcome. A similar retrospective cohort study by Okano and colleagues evaluated SIRS criteria in a general referral canine population and found that SIRS status was associated with survival to discharge, with progressively increasing mortality as more SIRS criteria were fulfilled. However, the underlying diseases were not detailed, precluding interpretation of the results in the context of infection. In a single-center prospective observational study, Camargo Jr. and colleagues found an association between SIRS status and survival to discharge, but only when SIRS status was evaluated alongside hypoalbuminemia and hypotension; SIRS status was not independently linked to outcome. Similarly, in canine parvovirus infection (CPV), SIRS status is associated with survival to discharge only when considered in conjunction with mucous membrane color and capillary refill time. In dogs with CPV or pyometra, an SIRS-positive status is associated with worse survival to discharge and longer hospitalization in some, but not all, studies. In dogs with babesiosis, SIRS-positive status is associated with higher serum concentrations of canine pancreatic-specific lipase, indicating a potential connection with organ damage, yet SIRS status was not associated with a clinical pancreatitis diagnosis. No association was found between SIRS status and multiple organ dysfunction or mortality in studies of dogs with babesiosis. In dogs with pyometra, SIRS-positive status was not linked to organ dysfunction incidence, markers of liver injury or kidney dysfunction, or concentrations of lactate or cardiac troponin I (cTnI). In dogs, presence of SIRS status was not associated with outcome in septic peritonitis, pneumonia, or leptospirosis and does not predict the risk of recurrent septic peritonitis in dogs.

Only one study in cats was identified that was partially supportive of the use of SIRS criteria, wherein SIRS-positive status was associated with higher mortality in cats admitted to an emergency service. Notably, the study population encompassed various etiologies, suggesting that not all cats had infection and reducing the relevance of the results to the PICO question. Other studies were not supportive of the use of SIRS criteria to identify negative outcomes in cats. For instance, in critically ill cats with both infectious and noninfectious diseases, the number of SIRS criteria fulfilled did not correlate with survival to discharge. Similarly, SIRS status was not associated with outcome in critically ill cats with infection, with septic peritonitis, or after gastrointestinal surgery.

In summary, for dogs with infection, evidence supporting the use of SIRS criteria to identify negative outcomes is limited and weak. For cats, there is no evidence to support the use of SIRS criteria for identifying negative outcomes. If sepsis is a syndrome associated with life-threatening infection, then using SIRS criteria to identify sepsis in clinical settings cannot be recommended. In clinical settings, individual SIRS variables can still be evaluated to identify patients at risk who should be screened for infection and sepsis, provided the potential influence of context, species, and underlying disease process is accounted for. Moreover, individual SIRS variables are likely to be relevant in the context of organ function assessment and might provide helpful information for patient monitoring and for assessing response to treatment when serially evaluated over time. To facilitate future research, we recommend that SIRS variables and SIRS status still be reported in studies evaluating dogs and cats with infection or sepsis to enable comparisons among studies, future meta-analyses, and scoring system development.

4.1.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with infection, use of the SIRS criteria is not required for the diagnosis of sepsis.
- In dogs and cats with infection,
  - We suggest measurement of heart rate, respiratory rate, and body temperature at presentation and serially during hospitalization in clinical and research settings.
  - We recommend that SIRS criteria be reported in all future studies of dogs and cats with infection.
  - We recommend that raw data or summary statistics for heart rate, respiratory rate, core temperature, leukocyte, and band neutrophil counts be provided in all future studies of dogs and cats with infection.

4.2 | Organ Dysfunction and Illness Severity Scores

4.2.1 | PICO Question

In dogs and cats with infection (**P**), does assessment of organ dysfunction or illness severity (e.g., SOFA, APPLE, SPI2) (**I**), compared to not assessing organ dysfunction or illness severity (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

4.2.2 | Summary of Evidence

The summary of evidence is as follows:

- Twenty-four studies (one high quality [95], 23 moderate quality [11, 12, 54, 67, 69, 96–112]) provided evidence that supports the use of organ dysfunction or illness severity assessments in dogs or cats.
- Ten studies (all moderate quality [72, 73, 113–120]) were not supportive of the use of organ dysfunction or illness severity assessments in dogs or cats.

4.2.3 | Conclusions

Overall, the 24 supportive studies provide a consistent and robust indication of the clinical and prognostic value of assessments of organ dysfunction and illness severity in dogs and cats with infection. Studies using the modified SOFA or validated structured illness severity assessment scores like the Acute Patient Physiologic and Laboratory Evaluation (APPLE) in rapid ($APPLE_{fast}$) or complete ($APPLE_{full}$) forms also showed consistent associations with mortality across a range of infectious conditions, including septic shock, babesiosis, CPV, leptospirosis, and pyometra.

Recent studies demonstrate that both score evolution over time and combinations of scoring with biomarkers can improve prognostication. For instance, presepsin, angiopoietin-2 (Ang-2), and procalcitonin (PCT) might offer utility as complementary tools to illness severity scores, even if they cannot currently be recommended as standalone diagnostic criteria. Some markers, like quick SOFA (qSOFA) alone, were less reliable, showing poor sensitivity in multiple studies. In studies that did not apply formal scoring tools, specific markers of organ dysfunction (e.g., creatinine, bilirubin, respiratory failure, thrombocytopenia) were consistently associated with outcome. Data specific to cats are more limited and less consistent, limiting the ability to draw strong conclusions for this species.

Our consensus definition makes identification of organ dysfunction central to establishing a diagnosis of sepsis. To facilitate that, we have constructed a table of potential indicators of organ dysfunction to enable clinicians and researchers to more readily identify patients with sepsis (Table 1). The parameters in the table were based on a consensus of expert opinion and will need prospective validation. In addition to requiring identification of organ dysfunction for sepsis diagnosis, we recommend incorporating assessments of organ dysfunction or illness severity, especially $APPLE_{fast}$, $APPLE_{full}$, and, where validated, the survival prediction index-2 (SPI2) or Simplified Acute Physiology Score (SAPS) into clinical decision-making and research protocols for both dogs and cats. Illness severity scores help stratify risk, identify severely affected patients earlier, and enable therapeutic approach optimization. We envision that their use complements organ function assessments, improves consistency of care provision, and facilitates comparisons between clinical studies. Although evidence supporting structured illness severity scores in cats is more limited, it is neither practical nor conceptually appropriate to apply different sepsis definitions to dogs and cats. As such, given that our definition of sepsis encompasses organ dysfunction as a core principle, it is essential that the clinical criteria recommended to identify cats with sepsis are aligned with that.

4.2.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with infection, assessments of organ dysfunction are required for the diagnosis of sepsis.
- In dogs and cats with infection,
  - We recommend using a validated, structured illness severity assessment score (e.g., APPLE) to support the diagnosis of sepsis or the assessment of illness severity in clinical and research settings.
  - We suggest using alternative scoring systems (e.g., SPI2, SAPS, SOFA) to support the diagnosis of sepsis, the assessment of illness severity, and the monitoring of patient status over time in clinical and research settings.

4.3 | Additional Physiological or Objective Patient Parameters

At the worksheet stage, two PICO questions were considered individually, and separate guidelines were drafted. During the drafting of this final guidance document, it became necessary to present these together, and the two sets of recommendations have been amalgamated and homogenized in this section. Some variables were relevant and, therefore, considered in both PICO questions (see the Supporting Information for additional information about parameters assessed). Here, the PICO questions, evidence summaries, and discussions are presented sequentially with the combined guidelines duplicated at the end of sections 4.3 and 4.4.

Question 4.3 encompassed physiologic variables that could be objectively measured, such as arterial blood pressure, central venous oxygen saturation, cardiac output, stroke volume variation, or urine output.

4.3.1 | PICO Question

In dogs and cats with infection (**P**), does measurement of objective physiological parameters (**I**), compared to not measuring objective physiological parameters (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

4.3.2 | Summary of Evidence

The summary of evidence is as follows:

- Thirty-seven studies (nine high quality [122–130], 28 moderate quality [36, 53, 55, 57, 63, 76, 82, 89, 108, 116, 120, 131–147]) provided evidence that supports the use of objective physiological parameters in dogs or cats.
- Two studies (both moderate quality [148, 149]) were not supportive of the use of objective physiological parameters in dogs. These nonsupportive studies either did not evaluate relevant physiological markers or lacked structured physiological analysis.

4.3.3 | Conclusions

Most reviewed studies provided evidence supporting the clinical utility of objective physiological parameters for illness sever-

TABLE 1 | Potential markers of organ dysfunction in dogs and cats, categorized by organ system.

Only changes in organ function described below that are NOT likely caused by, or attributable to, the primary disease, known comorbidities, untreated shock, or predictable drug effects should be considered indicators of organ dysfunction.	
Organ system	Suggested clinical or laboratory indicators of dysfunction
Central nervous system[a]	Altered mentation (e.g., obtundation, stupor, coma) or a new deterioration from baseline Modified Glasgow coma scale score ≤14/18 or canine or feline APPLE mentation score ≥1 Encephalopathic signs (e.g., seizures, dysphoria, delirium, new cranial nerve deficits)
Cardiovascular[b]	Clinical signs of abnormal perfusion (e.g., prolonged or rapid capillary refill time, weak peripheral pulses, increased peripheral to core temperature gradient) Hypotension, acute decrease in blood pressure, or new clinical requirement for vasopressor or inotropic drugs Hyperlactatemia (>18.0 mg/dL or >2 mmol/L) Unexplained persistent metabolic acidosis (BD >6 mmol/L) not due to lactate, uremia, or renal tubular acidosis Septic shock [121] Decreased central venous oxygen saturation ($ScvO_2$ <70%) despite adequate fluid resuscitation Sepsis-induced cardiomyopathy (systolic or diastolic dysfunction)
Respiratory	Mild/Moderate, or Severe Acute Respiratory Distress Syndrome (ARDS), per ARDSVet criteria [256]
Renal[c]	Oligo-anuria (<1 mL/kg/h for ≥6 h) [255] Azotemia or acute (<48 h) increase in serum creatinine (≥0.3 mg/dL or ≥26.5 μmol/L) Clinicopathologic evidence of acute kidney injury (e.g., new urinary casts) New requirement for renal replacement therapy (extracorporeal or peritoneal)
Hepatic[d]	Hyperbilirubinemia (>0.5 mg/dL / 8.6 μmol/L) Hyperammonemia Hypocholesterolemia Increased pre- or post-prandial bile acids
Coagulation[e]	Thrombocytopenia (<100×10^3/μL, or <100×10^9/L) or acute decrease in platelet count (>50%) New prolongation of clotting times (>25% of the upper reference interval bound) Hypofibrinogenemia Increased D-dimer concentration Decreased antithrombin activity Decreased protein C activity New thromboembolic or bleeding event
Metabolic or hormonal[f]	Hypoglycemia Critical illness-related corticosteroid insufficiency (CIRCI)
Gastrointestinal[g]	Ileus, feeding intolerance, or marked gastrointestinal dysmotility Persistent vomiting or diarrhea, hematemesis, hematochezia, or melena Intraabdominal hypertension

[a]Central nervous system abnormalities should only be attributed to sepsis if they can be reasonably determined to be unrelated to sedative, analgesic, or anesthetic drug effects, caused by concurrent untreated shock, and in the absence of potentially causative metabolic abnormalities such as hyperammonemia or hypoglycemia.

[b]Cardiovascular system dysfunction should only be adjudicated after adequate fluid resuscitation.

[c]Kidney function should be assessed after adequate fluid resuscitation and in the absence of urinary tract obstruction or post-renal azotemia (e.g., uroperitoneum). Recent ingestion of potential nephrotoxins or administration of potentially nephrotoxic drugs should be considered prior to concluding that new onset kidney injury is due to sepsis.

[d]Assessment of liver function in patients with sepsis should account for pre-existing or concurrent hemolysis, hepatobiliary disease, portovascular anomalies, or pancreatic or proximal gastrointestinal disorders that are alternative causes of prehepatic or posthepatic jaundice, increased bile acids, or decreased blood cholesterol concentrations. Liver parameters can also be assessed in conjunction with coagulation parameters, for example, fibrinogen, clotting times, and blood glucose and urea concentrations, to provide a better assessment of liver function.

[e]Coagulation system evaluation should account for pre-existing congenital factor deficiencies that could confound clotting time assessments, particularly FXII deficiency in cats and prekallikrein deficiency in dogs, which are clinically irrelevant. Likewise, pre-existing immune thrombocytopenia, therapeutic anticoagulation, and recent vitamin K epoxide reductase antagonist toxicity preclude the use of some coagulation system parameters for the assessment of sepsis-associated coagulation dysfunction disorders. While abnormalities of D-dimer concentration and activities of antithrombin and protein C could indicate sepsis-associated coagulopathy, recent cavity hemorrhage, major trauma or surgery, protein-losing disorders, liver disease, or portosystemic shunt can confound assessments based on these parameters.

[f]Blood glucose concentration should not be used as an indicator of sepsis-associated organ dysfunction in patients with known pre-existing disorders, for example, insulinoma that are known to cause hypoglycemia.

[g]Dysfunction of the gastrointestinal disorder is common in critically ill patients of all causes, and similarly, pre-existing gastrointestinal disorders are common in dogs and cats in all types of small animal practice. As such, there might be a greater likelihood of false positive adjudication of organ dysfunction in the gastrointestinal system category than others, and hence scrutiny for potential pre-existing or concurrent gastrointestinal disorders that may be unrelated to sepsis is warranted.

ity assessment and outcome prediction in dogs and cats with infection. Frequently evaluated parameters included:

- Blood lactate concentration (n = 14). Frequently associated with mortality, particularly when persistently increased.
- Arterial blood pressure (n = 11). Hypotension (lower mean or systolic arterial pressure) is repeatedly linked to increased mortality, azotemia, shock progression, and organ dysfunction.
- Serum albumin. Hypoalbuminemia is associated with nonsurvival in studies of surgical sepsis (e.g., peritonitis, pyometra).
- Temperature, heart rate, and respiratory rate. Often correlated with nonsurvival, particularly when two or more parameters are deranged.
- Echocardiographic variables. Diastolic and systolic dysfunction markers are strongly associated with mortality in dogs and cats with sepsis.
- Blood biomarkers. Several have been associated with survival in cats and dogs with sepsis.

Although there was considerable heterogeneity in study design, parameter type, measurement method, and the diseases represented within the reviewed studies (e.g., CPV, babesiosis, pneumonia, surgical peritonitis, and pyometra), physiological derangements, particularly when interpreted serially or in combination, were consistently predictive of outcome. Frequently, serial measurements (e.g., lactate clearance, blood pressure recovery), structured scores (e.g., canine infection mortality score, CIMS), or combinations of scores with laboratory data had superior prognostic accuracy than single variables. The reviewed evidence supports integration of physiological parameters into scoring systems, protocols, and research methodologies to improve prediction, clinical decision-making, and study comparability.

It should be noted, however, that while objective physiological parameters are useful for sepsis diagnosis in infected animals, they are insufficient in isolation. Hypotension, hyperlactatemia, abnormal core temperature, and altered mentation may aid clinical recognition of sepsis but are overly sensitive and too nonspecific to be used alone. Abnormalities in these parameters frequently occur in noninfectious critical illnesses and other systemic disease processes. While several studies confirmed the association between these parameters and sepsis-related organ dysfunction or mortality, few evaluated their utility for the diagnosis of sepsis. Additional research in these areas and on the identification of the optimal combinations of parameters and biomarkers is still needed, combined with broad validation and standardization across diverse clinical settings. In summary, physiological parameters are valuable components of sepsis identification protocols but should be interpreted in combination with clinical context and confirmation of infection to maximize diagnostic accuracy.

4.3.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with infection, measurements of physiological parameters as contributors to assessments of organ dysfunction are required for the diagnosis of sepsis.
- In dogs and cats with infection,
  - We recommend using a validated, structured illness severity assessment score (e.g., APPLE) to support the diagnosis of sepsis or the assessment of illness severity in clinical and research settings.
  - We suggest measurement of heart rate, respiratory rate, body temperature, mentation status, blood pressure, and lactate concentration at presentation and serially during hospitalization.
  - We suggest blood cultures for bacteria or fungi to aid identification of sepsis.
  - We suggest echocardiographic evaluation for myocardial systolic or diastolic dysfunction to aid identification of sepsis.
  - We suggest measurement of biomarkers (e.g., those assessing inflammation, immune status, and organ function) in research settings.

4.4 | Additional Physiological or Objective Patient Parameters

4.4.1 | PICO Question

In dogs and cats with infection (**P**), does measurement of additional objective parameters (**I**), compared to not measuring these additional objective parameters (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

Question 4.4 focused on patient parameters that could be objectively measured but that were not categorized as markers of physiologic function (discussed in Section 4.3). For instance, this question encompassed imaging abnormalities, diagnostic laboratory findings, and proteomic signatures.

4.4.2 | Summary of Evidence

The summary of evidence is as follows:

- Six studies (five high quality [90, 129, 150–152], one moderate quality [141]) provided evidence that supports the use of additional objective parameters in dogs.
- Six studies (four moderate quality [153–156], two low quality [157, 158]) were not supportive of the use of additional objective parameters in dogs.

- One study (moderate quality [159]) provided evidence that supports the use of additional objective parameters in cats.
- Two studies (one moderate quality [160], one low quality [157]) were not supportive of the use of additional objective parameters in cats.

4.4.3 | Conclusions

The reviewed studies involved a heterogeneous group of disease processes and infection types. Similarly, the biomarkers and objective patient parameters studied were also highly variable. Consequently, the evidence base for any individual parameter is limited. The strongest evidence was provided by four studies that evaluated myocardial function parameters. One study used magnetic resonance imaging to assess dogs with pneumonia, and three studies used echocardiographic measures in dogs with CPV. Those studies indicate that evidence of systolic and diastolic dysfunction, such as end-diastolic volume, strain, strain rate, left ventricular ejection fraction, mitral annulus systolic velocity (LVS′), and septal early mitral annulus early diastolic peak velocity (E'), is associated with illness severity and outcome in dogs with sepsis. This suggests that assessments of myocardial function might be a useful means to look for organ dysfunction in dogs with infection that could portend negative outcomes and hence be used to screen dogs for sepsis. When performed by echocardiography, this evaluation is rapid, noninvasive, and point-of-care, and can be serially repeated for trend monitoring.

Two studies (one in cats and one in dogs) suggest that positive blood cultures are prognostic in cats with histoplasmosis and dogs with infectious endocarditis. Obviously, positive blood cultures are a means to identify the underlying cause of infection in animals with sepsis. However, the prognostic utility of these findings suggests that having viable bacterial or fungal organisms in circulation is indicative of more severe disease and hence has utility as a diagnostic and prognostic test in animals with infection.

The final study that was supportive of the use of other objective markers was a proteomics study exploring novel prognostic biomarkers in small numbers of *Babesia*-infected dogs. That paper, while offering potential insights into pathophysiology and identifying possible future biomarkers, should be considered hypothesis-generating for future studies because of the small numbers of dogs involved and the costly, time-consuming, and technically complex liquid chromatography/tandem mass spectrometry methods by which differential expression of these proteins was established.

4.4.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with infection, measurements of physiological parameters as contributors to assessments of organ dysfunction are required for the diagnosis of sepsis.
- In dogs and cats with infection,
  - We recommend using a validated, structured illness severity assessment score (e.g., APPLE) to support the diagnosis of sepsis or the assessment of illness severity in clinical and research settings.
  - We suggest measurement of heart rate, respiratory rate, body temperature, mentation status, blood pressure, and lactate concentration at presentation and serially during hospitalization.
  - We suggest blood cultures for bacteria or fungi to aid identification of sepsis.
  - We suggest echocardiographic evaluation for myocardial systolic or diastolic dysfunction to aid identification of sepsis.
  - We suggest measurement of biomarkers (e.g., those assessing inflammation, immune status, and organ function) in research settings.

4.5 | Acute Phase Proteins (APPs)

4.5.1 | PICO Question

In dogs and cats with infection (P), does measurement of APPs (e.g., C-reactive protein [CRP], serum amyloid A [SAA]) (I), compared to not measuring APPs (C), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (O)?

4.5.2 | Summary of Consensus on Evidence

The consensus on the evidence is summarized as follows:

- Fifteen studies (nine high quality [52, 61, 83, 104, 106, 109, 161–163], five moderate quality [80, 164–167], one low quality [168]) provided evidence that supports the use of APPs in dogs and cats.
- Thirteen studies (six high quality [107, 118, 169–172], seven moderate quality [103, 140, 173–177]) were not supportive of the use of APPs in dogs and cats.
- Fifteen studies were considered irrelevant to the PICO question [78, 87, 89, 101, 115, 137, 178–186].

4.5.3 | Conclusions

The acute phase reaction contributes to innate immune responses to tissue injury or infection. Concentrations of the APPs increase (positive APP) or decrease (negative APP) during the acute phase response, wherein major APPs undergo a 10- to 100-fold increase in concentration, whereas minor APPs increase two- to 10-fold.

4.5.3.1 | Dogs.

4.5.3.1.1 | CRP [Major, Positive APP]. Use of CRP in dogs was supported by 10 studies and not supported by 14. The utility of CRP varied with the cause of sepsis, wherein CRP had greater utility in dogs with CPV or pyometra compared to heterogeneous causes of sepsis. Three studies in dogs with CPV supported the PICO question—two that reported higher CRP in nonsurvivors

than survivors and one in which CRP progressively increased with CPV severity. Numerous studies evaluated CRP in dogs with pyometra. Three studies observed higher CRP concentrations in dogs with sepsis secondary to pyometra (i.e., pyometra with two or more of the four SIRS criteria) compared to dogs with pyometra without sepsis. Four studies did not identify differences in CRP concentrations between dogs with pyometra and sepsis compared to pyometra without sepsis. In dogs with heterogeneous causes of sepsis, only one study supported the use of CRP, whereas five did not, albeit with distinct outcome measures evaluated across the different studies.

4.5.3.1.2 | SAA [Major, Positive APP]. Overall, fewer studies described SAA measurements than CRP, and only one study supports a role for SAA in the diagnosis of sepsis, documenting that SAA but not CRP was higher in dogs with sepsis due to pyometra compared to pyometra without sepsis. However, in that study, SAA was not predictive of hospitalization duration. Six studies of SAA did not support the PICO question. SAA could not differentiate survivors from nonsurvivors with all-cause sepsis, babesiosis, or ehrlichiosis. Similarly, SAA was not associated with the duration of hospitalization for management of pneumonia or after pyometra surgery. In a study including dogs with various causes of sepsis, SAA did not differ between groups with or without septic shock or multiple organ dysfunction.

4.5.3.1.3 | Other APPs. One prospective observational study investigated fibrinogen [minor, positive APP] in 20 dogs with heterogeneous causes of sepsis. Nine dogs died, mostly due to disease severity. Admission fibrinogen concentration was higher in survivors than in nonsurvivors. One prospective study supports the use of alpha-1-acid glycoprotein (AGP) [minor, positive APP] for the diagnosis of sepsis in dogs with pyometra, but the methods were incompletely described. Dogs with sepsis due to pyometra had higher AGP concentrations than dogs with pyometra without sepsis, but no other patient-centered outcomes were assessed. Three studies of dogs with CPV investigated ceruloplasmin [minor, positive]; two were supportive, and one was not supportive. In one supportive study of 25 puppies with CPV infection, ceruloplasmin concentrations at admission were not different between survivors and nonsurvivors, but ceruloplasmin at 72 h was significantly lower in survivors than in nonsurvivors. In the other supportive study, ceruloplasmin concentrations were associated with illness severity and were significantly higher in nonsurvivors than in survivors. Four studies investigated haptoglobin [minor, positive] in dogs with infection; one was supportive, and three were not. In the supportive study, haptoglobin concentrations in dogs with CPV were significantly higher in the moderate severity group compared to the mild severity group, but no difference was observed between the moderate and severely affected groups. One study supports the use of PCT [minor, positive] for the diagnosis of sepsis in dogs, with one study judged to be unsupportive. The supportive single-center study included dogs with heterogeneous causes of sepsis that were categorized by illness severity. Baseline PCT concentrations were significantly higher in dogs with septic shock compared to those without cardiovascular compromise but did not differ between survivors and nonsurvivors. However, when evaluated serially, PCT concentrations decreased in survivors such that PCT "clearance" at 24 h was significantly higher in survivors than in nonsurvivors. The nonsupportive study involved dogs with babesiosis and found no difference between survivors and nonsurvivors, but the sample size was small. Albumin [minor, negative] was measured in numerous studies but was infrequently discussed as an APP. Three studies suggest the utility of albumin as a diagnostic marker for sepsis, while eight found no association between albumin and patient-centered outcome measures.

4.5.3.2 | Cats. In cats, three studies were identified that addressed the PICO question, with conflicting results. Two studies evaluated SAA—one involving kittens with feline panleukopenia supported the PICO question, whereas one study of cats with heterogeneous causes of sepsis did not support the PICO question. In the unsupportive study, SAA was associated with a diagnosis of sepsis versus noninfectious SIRS due to trauma but was less predictive than toxic neutrophils and not associated with survival. In the supportive study, median SAA concentrations were higher in nonsurvivors than survivors, although all measured values clustered at the lower end of the analytical range. One prospective observational cohort study supports the use of PCT as a sepsis biomarker in cats. Serum PCT concentrations were higher in cats with bacterial infection compared to those with viral infection, and in cats with bacterial infection, PCT was higher in nonsurvivors compared to survivors. Concentrations of PCT were not prognostic in cats with viral infection.

4.5.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with infection, measurement of APPs is not required for the diagnosis of sepsis.
- In dogs with infection,
  - We suggest measurement of APPs to aid identification of sepsis and as adjunct markers of illness severity in clinical and research settings.
  - We suggest measurement of CRP as an adjunct marker of illness severity in CPV or pyometra specifically.
- In cats with infection, measurement of APPs is not required for the diagnosis of sepsis.
- In cats with infection,
  - We suggest that measurement of serum PCT concentration might enable differentiation of bacterial and viral infection.
  - We suggest measurement of APPs as adjunct markers of illness severity.

4.6 | Blood Gases, Electrolytes, and Lactate

4.6.1 | PICO Question

In dogs and cats with infection (**P**), does measurement of blood gases, electrolytes, and lactate (**I**), compared to not measuring blood gases, electrolytes, and lactate (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

4.6.2 | Summary of Consensus on Evidence

The consensus on the evidence is summarized as follows:

- Twenty studies (four high quality [82, 151, 171, 187], 11 moderate quality [54, 60, 71, 103, 116, 123, 132, 167, 188–190], five low quality [33, 36, 133, 191, 192]) provided evidence that supports the use of blood gases, electrolytes, and/or lactate in dogs or cats.
- Twenty studies (five high quality [7, 64, 95, 148, 163], 10 moderate quality [56, 57, 68, 70, 115, 127, 130, 141, 144, 193], five low quality [92, 108, 147, 165, 194]) were not supportive of the use of blood gases, electrolytes, and lactate in dogs or cats.
- Thirty-eight studies were considered irrelevant to the PICO question [40, 52, 62, 63, 73, 75, 79, 83, 100, 101, 105, 106, 117, 119, 120, 134, 135, 137, 139, 154, 160, 175, 179, 182, 195–208].

4.6.3 | Conclusions

There was marked heterogeneity in the reviewed studies, including measurement at different points in the disease process, lack of control for comorbidities, no standardization for the level of care, and inclusion of euthanized patients in mortality estimates. Potentially consequently, some of the evidence was conflicting. Although further research is warranted, some evidence supports the measurement of blood gases, electrolytes, and lactate in dogs and cats with suspected sepsis. The changes most frequently associated with disease severity or death in dogs with infection included increased base deficit, lactate, and total or ionized magnesium, and decreased PCO_2 (venous or arterial), bicarbonate, phosphate, sodium, chloride, ionized calcium, strong ion difference, and pH. Only one study supported the use of electrolyte measurements in cats and suggested that hypochloremia was predictive of sepsis in cats with infection. In conclusion, for clinical and research purposes, the use of blood gas, electrolyte, and lactate measurements is suggested for the diagnosis of sepsis in dogs, albeit focused on the parameters for which an association with outcome has been observed. There is insufficient evidence to draw conclusions in cats.

4.6.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with infection, identification of blood gases, electrolytes, and lactate abnormalities is not required for the diagnosis of sepsis.
- In dogs with infection,
  - We suggest measurement of blood gases, electrolytes, and lactate to aid identification of sepsis in clinical settings.
  - We suggest measurement of blood gases, electrolytes, and lactate for incorporation into assessments of organ function or as adjunct markers of illness severity in research settings.
- In cats with infection, identification of blood gases, electrolytes, and lactate abnormalities is not required for the diagnosis of sepsis.
- In cats with infection,
  - There is insufficient evidence to make a recommendation regarding the use of blood gases, electrolytes, and lactate for identifying sepsis or for incorporation into assessments of organ function or as an adjunct marker of illness severity in clinical settings.
  - We suggest measurement of blood gases, electrolytes, and lactate for incorporation into assessments of organ function or as adjunct markers of illness severity in research settings.

4.7 | Complete Blood Counts (CBCs)

4.7.1 | PICO Question

In dogs and cats with infection (**P**), does performing a complete blood count (**I**), compared to not performing a complete blood count (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

4.7.2 | Summary of Evidence

The summary of evidence is as follows:

- Forty-three studies (seven high quality [7, 64, 163, 187, 209–211], 22 moderate quality [56, 60, 71, 75, 76, 80, 97, 103, 115, 123, 135, 142, 151, 158, 167, 171, 172, 174, 202, 205, 212, 213], 14 low quality [33, 36, 65, 92, 131, 133, 165, 192, 214–219]) provided evidence that supports the use of complete blood count variables in dogs or cats.
- Thirty-two studies (one high quality [95], 25 moderate quality [40, 52, 57, 68, 82–84, 105, 117, 119, 127, 130, 132, 141, 144, 154, 160, 175, 188, 190, 198, 207, 220–222], six low quality [6, 102, 108, 181, 223, 224]) were not supportive of the use of complete blood count variables in dogs or cats.
- Thirty studies were considered irrelevant to the PICO question [62, 63, 73, 79, 100, 101, 106, 112, 116, 120, 134, 137, 139, 148, 179, 182, 189, 193, 195–197, 199–201, 203, 204, 206, 208, 225, 226].

4.7.3 | Conclusions

The reviewed studies varied in quality and design. Overall, more studies supported the use of CBC variables to predict the development of sepsis and/or nonsurvival in dogs than studies that did not. However, strong conclusions cannot be drawn because some of the evidence was conflicting and certain diseases (pyometra, CPV, babesiosis) were overrepresented, wherein the associated hematologic changes may not generalize to heterogeneous populations of dogs with sepsis. Furthermore, mortality estimates were typically derived from a combination of euthanasia with natural death, making true survival assessments challenging. The most consistent abnormality associated with the development of sepsis or nonsurvival was an increase in band neutrophils. Other abnormalities frequently associated with sepsis or outcome included neutrophilia, neutropenia, and leukopenia. It should be noted that most studies that identified neutropenia and leukopenia evaluated puppies with CPV.

Seven studies of cats were reviewed, of which three supported the use of CBC variables to identify sepsis. Increased band neutrophils, an increased band neutrophil-to-lymphocyte ratio, and the presence of toxic neutrophil changes were associated with sepsis in these studies. Three studies found no association between CBC variables and nonsurvival in cats with sepsis.

In conclusion, for both clinical and research purposes, CBC variables are recommended for the diagnosis of sepsis and may have some correlation with outcome in dogs. The association of CBC indices and outcome in cats is yet to be determined.

4.7.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with infection, identification of leukocyte count abnormalities is not required for the diagnosis of sepsis.
- In dogs with infection,
  - We recommend performing a CBC to support the diagnosis of sepsis in clinical and research settings.
  - We suggest measurement of total leukocyte, neutrophil, and band neutrophil counts to aid identification of sepsis in clinical and research settings.
- In cats with infection, identification of leukocyte count abnormalities is not required for the diagnosis of sepsis.
- In cats with infection,
  - We suggest performing a CBC to aid identification of sepsis in clinical and research settings.

4.8 | Serum Biochemistry Profile and Urinalysis

4.8.1 | PICO Question

In dogs and cats with infection (**P**), does performing a serum biochemistry profile and urinalysis (**I**), compared to not performing a serum biochemistry profile and urinalysis (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

4.8.2 | Summary of Evidence

The summary of evidence is as follows:

- Thirty-four studies (seven high quality [63, 64, 106, 134, 187, 202, 209], 19 moderate quality [56, 57, 60, 71, 75, 76, 97, 123, 127, 132, 151, 167, 179, 188, 190, 199, 207, 221, 227], eight low quality [33, 36, 107, 131, 133, 192, 217, 218]) provided evidence that supports the use of serum biochemistry profiles and/or urinalysis results in dogs or cats.
- Thirty-five studies (six high quality [7, 52, 82, 95, 148, 201], 16 moderate quality [6, 68, 73, 115, 130, 141, 144, 146, 154, 160, 172, 174, 175, 200, 222, 228], 13 low quality [61, 92, 102, 108, 143, 181, 186, 194, 213, 216, 223, 224, 229]) were not supportive of the use of serum biochemistry profiles or urinalysis in dogs or cats.
- Thirty-six studies were considered irrelevant to the PICO question [40, 62, 79, 80, 83, 100, 101, 103, 105, 116, 117, 119, 120, 135–137, 139, 140, 162, 163, 171, 182, 189, 193, 195–198, 203–206, 208, 219, 225, 230].

4.8.3 | Conclusions

The reviewed studies that support the use of serum biochemistry profiles or urinalysis for the diagnosis of sepsis or prediction of severity identified various chemistry profile parameters, but few studies included urinalysis. Study populations included heterogeneous causes or were focused on specific infectious diseases such as babesiosis or CPV.

In dogs with infection, sepsis diagnosis or severity prediction was supported by lower serum albumin in 13 studies (two on CPV). Higher serum creatinine and other markers of renal dysfunction (urea, phosphate) were predictive in 11 studies (five on babesiosis, one each on leishmaniosis and CPV, and one experimental sepsis model). Increased serum bilirubin was predictive in five studies (three on babesiosis), and lower serum glucose was predictive in six studies (five on babesiosis, one on CPV). Urinary markers and other biochemistry variables, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), lipase, cholesterol, magnesium, and chloride, supported the diagnosis of sepsis but typically in single studies or those focused solely on a specific disease. In cats with infection, a single study supported each of higher serum bilirubin, lower albumin, and increased markers of renal dysfunction to assess illness severity.

The reviewed studies that were not supportive of the use of serum biochemistry profiles or urinalysis included more low-quality studies than the list of supportive studies. In some nonsupportive studies, dogs had heterogeneous causes of sepsis, while others focused on a specific infectious disease such as CPV, leptospirosis, and ehrlichiosis. Serum albumin concentrations were not predictive in eight studies in dogs (including two on CPV). Other serum biochemistry profiles were not predictive of sepsis or sepsis severity in 11 studies in dogs. Urinary markers were not supportive of a diagnosis of sepsis or sepsis severity in two studies, including one focused on CPV. In the six studies on cats, single chemistry parameters (e.g., albumin) or a restricted profile were not supportive of the diagnosis of sepsis or the severity of infection.

The overall body of evidence does not support the use of specific chemistry or urinalysis variables to predict sepsis, its severity, or its outcome in dogs and cats with infection in the clinic. However, albumin and creatinine warrant further use in research to better clarify their potential predictive value in dogs and cats with infection.

4.8.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with infection, identification of serum biochemistry profile or urinalysis abnormalities is not required for the diagnosis of sepsis.
- In dogs with infection,
  - We suggest using serum biochemistry profiles or urinalysis for the assessment of organ function or illness severity in clinical settings.
  - We recommend performing a serum biochemistry profile for the diagnosis of sepsis, the assessment of organ function, and aiding in the assessment of illness severity in research settings.
- In cats with infection, identification of serum biochemistry profile or urinalysis abnormalities is not required for the diagnosis of sepsis.
- In cats with infection,
  - We suggest using serum biochemistry profiles or urinalysis for the assessment of organ function or illness severity in clinical and research settings.

4.9 | Coagulation Parameters

4.9.1 | PICO Question

In dogs and cats with infection (**P**), does measurement of coagulation system variables (**I**), compared to not measuring coagulation system variables (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

4.9.2 | Summary of Evidence

The summary of evidence is as follows:

- Seven studies (five high quality [64, 95, 97, 150, 209], one moderate quality [231], one low quality [220]) provided evidence that supports the use of coagulation system variables in dogs or cats.
- Five studies (one high quality [232], three moderate quality [69, 233, 234], one low quality [186]) were not supportive of the use of coagulation system variables in dogs or cats.
- Four studies were considered irrelevant to the PICO question [6, 79, 215, 235].

4.9.3 | Conclusions

Approximately equal numbers of studies were supportive and not supportive of the use of coagulation variables for predicting the development of sepsis in dogs with infection, although the supportive studies were generally of higher quality. No relevant studies in cats were identified. The four studies involving experimental endotoxemia were considered irrelevant because coagulation parameters were not related to patient-centered outcomes such as mortality. The seven supportive studies included a total of 387 dogs with infection. The five nonsupportive studies included a total of 140 dogs with infection.

Although only seven studies directly supported the use of coagulation variables for predicting sepsis in dogs, all studies observed coagulation system abnormalities in infected dogs. As such, the balance of evidence supports a link between infection and the development of hemostatic dysfunction in dogs, although it is likely that the type and nature of the infection, the site and duration of illness, and the patient's underlying genetics contribute to the coagulation disturbances seen. Two supportive studies involved dogs with heterogeneous infection, while five focused on specific pathogens: *Babesia rossi*, *Babesia canis*, *Leptospira*, *Ehrlichia canis*, and CPV. It remains uncertain whether the coagulation disturbances seen in dogs with babesiosis, leptospirosis, monocytic ehrlichiosis, or CPV are characteristic of sepsis or specific to the pathophysiology of these diseases.

Various assays were employed to study the coagulation system. Some, such as platelet count, are ubiquitously available. Others, such as flow cytometry for identification of platelet–leukocyte aggregates, require specialized instrumentation and expertise. One study employed proteomics techniques with no clinical applicability. Widely available parameters such as platelet count, clotting times, and D-dimers would be most readily incorporated into clinical scoring schemes and might provide early indications of activation of the coagulation system in dogs with severe infection. Additional consideration should be given to the measurement of antithrombin activity (AT) based on its association with outcome in two studies.

Overall, the currently available evidence is insufficient to recommend incorporating specific coagulation system variables into the diagnostic criteria for sepsis, either in clinical or research settings. Stated differently, there is insufficient evidence to suggest that the presence of hemostatic dysfunction is a universal feature of sepsis, and hence, coagulation abnormalities should not be required for sepsis to be diagnosed. Nonetheless, the evidence suggests that coagulation variables are useful adjunct markers of illness severity in dogs with infection and should be considered for inclusion in organ function assessments in dogs and cats with sepsis.

In research settings, evaluating multiple (rather than single) coagulation parameters might provide greater specificity for sepsis identification in dogs and could enhance understanding of the nature and causes of the coagulation disturbances. Assays such as protein C activity, viscoelastic coagulation testing, and platelet function analyses warrant inclusion in studies assessing the coagulation disturbances in dogs with sepsis when available.

4.9.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with infection, identification of coagulation system abnormalities is not required for the diagnosis of sepsis.
- In dogs with infection,
  - We suggest measurement of coagulation system variables such as platelet count, clotting times, D-dimers, and AT for the diagnosis of sepsis in clinical settings.

- We suggest incorporating measurement of coagulation variables into assessments of organ function as adjunct markers of illness severity in clinical and research settings.
- We suggest measurement of multiple coagulation system variables to increase specificity for the diagnosis of sepsis in research settings.

- In cats with infection, identification of coagulation system abnormalities is not required for the diagnosis of sepsis.
- In cats with infection,
  - We suggest incorporating measurement of coagulation variables into assessments of organ function as adjunct markers of illness severity in clinical and research settings.

4.10 | Cytokines

4.10.1 | PICO Question

In dogs and cats with infection (**P**), does measurement of cytokine concentrations (e.g., interleukin [IL]-6, tumor necrosis factor [TNF]-α, chemokine [C–C motif] ligand 2 [CCL2]) (**I**), compared to not measuring cytokine concentrations (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

4.10.2 | Summary of Evidence

The summary of evidence is as follows:

- Fifteen studies (seven high quality [83, 123, 124, 170, 172, 236, 237], seven moderate quality [76, 84, 125, 153, 192, 196, 238], one low quality [218]) provided evidence that supports the use of cytokine concentrations in dogs.
- Five studies (three high quality [34, 52, 239], two moderate quality [113, 197]) were not supportive of the use of cytokine concentrations in dogs.
- Two studies (both high quality) provided evidence supporting the use of cytokine concentrations in cats [60, 79].
- Two studies were considered irrelevant to the PICO question [219, 240].

4.10.3 | Conclusions

Overall, 15 studies in dogs and two in cats provided evidence that supports the use of blood cytokine concentrations for the prediction of sepsis in animals with infection. The sources of sepsis in these studies were diverse and included bacterial, viral, and protozoal causes of naturally occurring sepsis and model systems involving bacterial inoculation and lipopolysaccharide (LPS) challenge. Supportive studies in dogs included dogs with pyometra ($n = 5$), CPV ($n = 4$), bacterial inoculation models ($n = 3$), babesiosis ($n = 2$), miscellaneous sepsis ($n = 1$), and experimental endotoxemia ($n = 1$). The nonsupportive studies involved miscellaneous sepsis ($n = 2$), CPV ($n = 1$), pyometra ($n = 1$), and experimental endotoxemia ($n = 1$). In the two supportive studies of cats, one study involved miscellaneous sepsis causes and one involved experimental endotoxemia.

Cytokines were measured using various techniques, including ELISAs, a bead-based multiplex platform, bioactivity assays, and transcriptomic assessment of differential gene expression. This heterogeneity in infection types and analysis methods is both a strength and a weakness. Noninfectious inflammation is associated with increased cytokine concentrations, and cytokine measurements are not effective for differentiation of sepsis from nonseptic SIRS. However, several studies suggest that cytokine concentrations can help differentiate sepsis from simple infection. These findings suggest that sepsis often involves an exuberant inflammatory response, but this is confounded by the definition of sepsis as the presence of SIRS in combination with an infection. The reliance on SIRS for sepsis identification increases the likelihood of detecting an association between cytokine concentrations and sepsis since both SIRS and cytokines are associated with inflammation. However, cytokine concentrations were associated with outcome in multiple studies and with illness severity scores or organ function markers in others, suggesting that cytokine concentrations would remain of value irrespective of how sepsis was defined. The heterogeneity of disease in the reviewed studies increases the generalizability of cytokine concentration measurements to sepsis generally, but disease heterogeneity simultaneously diminishes the strength of association for any individual cytokine. Most evidence supports the use of TNF-α, IL-6, and cysteine-X-cysteine motif ligand 8 (CXCL8) (IL-8), but KC-Like, IL-10, IL-2, IL-18, and monocyte chemoattractant protein-1 (MCP-1) (CCL2) may also be of value. The diverse assays used preclude recommending any one method be incorporated into recommendations for clinical or research use. Currently, cytokine assays are time-consuming, complicated, and potentially costly laboratory tests unsuitable for routine clinical use. Frequently, they require specialized kits, platforms, or expertise and are suitable only for batch analysis rather than for individual patient samples. This practical limitation precludes recommending them for inclusion as clinical criteria for sepsis. Their value is greater in research settings, but the use of analytically validated methods is essential to ensure accuracy and reliability, and measuring multiple cytokines is prudent.

4.10.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with infection, measurement of cytokine concentrations is not required for the diagnosis of sepsis.
- In dogs and cats with infection,
  - We suggest measurement of cytokine concentrations, particularly TNF-α, IL-6, and CXCL8 (IL-8), to aid the diagnosis of sepsis in research settings.
  - We recommend measurement of multiple cytokines using validated, robust methods of quantitation when cytokine concentrations are measured.

4.11 | Novel Biomarkers

4.11.1 | PICO Question

In dogs and cats with infection (**P**), does measurement of novel biomarkers (e.g., S100A2, NGAL, cfDNA) (**I**), compared to not measuring novel biomarkers (**C**), improve prediction of severity (e.g., development of sepsis or new organ dysfunction) or nonsurvival (**O**)?

4.11.2 | Summary of Evidence

The summary of evidence is as follows:

- Twelve studies (six high quality [162, 208, 241–244], four moderate quality [238, 242, 245, 246], two low quality [168, 247]) provided evidence that supports the use of novel biomarkers in dogs or cats.
- Six studies (three high quality [163, 216, 221], two moderate quality [165, 248], one low quality [249]) were not supportive of the use of novel biomarkers in dogs.
- Twenty-seven studies were considered irrelevant to the PICO question [35, 36, 39, 76, 81, 106, 109, 115, 141, 143, 147, 151, 161, 176, 184, 195, 198, 203, 219, 234, 239, 250–254].

4.11.3 | Conclusions

In dogs, multiple studies evaluated numerous distinct novel biomarkers for the diagnosis of sepsis in dogs, with many studies evaluating multiple biomarkers. Most investigations were small and focused on specific infections (e.g., pyometra) or organisms (e.g., CPV, *Babesia*). Only one study in cats was identified. Some studies in dogs support the use of one marker but not others, and there was incomplete overlap and conflicting evidence among studies. Given the diversity of novel biomarkers, sources, and types of infection, and patient populations involved, directly comparing supportive with nonsupportive studies should be undertaken cautiously. In dogs with infection, 12 studies support the use of at least one novel biomarker, and six studies did not support the use of at least one novel biomarker for predicting the development of sepsis. Study quality varied considerably between studies, but the average quality was similar between supportive and nonsupportive studies.

There is limited evidence in dogs that blood concentrations of the following markers might be beneficial for the diagnosis of sepsis: secretory leukocyte protease inhibitor, prostaglandin F2α metabolite, urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary liver-type fatty acid-binding protein, endothelial cell specific molecule-1, catalase, superoxide dismutase and glutathione peroxidase, malondialdehyde, paraoxonase-1, N-terminal portion of pro C-type natriuretic peptide (NT-pCNP), prostaglandin E_2, lipopolysaccharide, nitric oxide, copper, zinc, copper/zinc ratio, selenium, and cobalamin. For all these biomarkers, additional, more extensive studies in larger, more diverse patient populations are needed before any can be recommended for clinical use. Metabolomics might be a means to identify further novel biomarkers with random forest classification algorithms for lipid-soluble and water-soluble extracts, creatine, glycolate, and fatty acyl chain CH_2CO, showing some initial promise. In cats, copper, copper/zinc ratio, and cobalamin are novel candidate biomarkers, but available data are limited to a single study.

Currently available evidence is insufficient to recommend incorporating specific novel biomarkers into the diagnostic criteria for sepsis, either in clinical or research settings. Available data are inconclusive about the association between every novel biomarker and sepsis, such that we have not recommended requiring their measurement to establish a diagnosis of sepsis. Moreover, routine measurement of most potential novel biomarkers is not feasible, which also limits the application of available research to clinical patients. However, further evaluation of some potential novel biomarkers with promise for the diagnosis of sepsis or illness severity assessment is warranted, including the development of clinically applicable analytical platforms.

For research, novel biomarkers hold great appeal for the diagnosis of sepsis to enable early and accurate recognition of the syndrome and facilitate study enrollment and comparisons of study populations. Currently, however, none of the novel biomarkers studied is supported by sufficient evidence to recommend their generalization to research in sepsis.

4.11.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with infection, measurement of novel biomarkers is not required for the diagnosis of sepsis.
  - We suggest that measurement of novel biomarkers be incorporated into assessments of organ function or used as adjunct markers of illness severity in research settings.

5 | Discussion

This systematic review evaluated over 350 publications in the veterinary literature to identify variables associated with disease severity and negative outcomes in dogs and cats with infection. These data derive from many infection types, patient populations, geographic regions, and practice types, which should improve the general applicability of our recommendations. Some disease processes were excluded a priori, and we recognize this will have impacted the results of our review. We intended to strike a balance between utility, applicability, and expediency, and hence, tradeoffs were required. We extracted an array of data from these publications, but meta-analysis of outcome data or the predictive ability of individual parameters was not performed. The lack of systematically reported and consistent data, combined with the heterogeneity of the available data, limited our ability to perform meaningful statistical analyses. We have reported the data gathered and extracted in the Supporting Information (Data S7) to enable others to further study and scrutinize the information available.

There was sufficient evidentiary support for most of our recommendations. Where the available data were limited, absent, or of poor quality, we chose to provide expert guidance or to defer making recommendations until more information is available. Solid evidence supports the use of organ dysfunction assessments and illness severity scoring for the evaluation of patients with infection to "diagnose" sepsis and identify those patients at highest risk of mortality. This is consistent with our consensus definition that places organ dysfunction at the center of our understanding of what sepsis is. Nonetheless, we recognize that expert-driven consensus definitions are potentially limited by the experiences and biases of the committee members.

Previous sepsis definitions in veterinary medicine were not established by consensus or by a formal process. Rather, they derived from the adoption and adaptation of the 1991 and 2001 human adult sepsis definitions, with the resultant inherent strengths and weaknesses. Those previous veterinary sepsis definitions served the community effectively, but following recent developments in human medicine were decreasingly relevant. Due to the lack of a solid evidence base for continued use of adapted human criteria, we believed it was important to assess the current state of the literature and plot a path forward. This systematic review is hopefully only the first step on that path.

The committee recognizes that the consensus definition of sepsis above is very similar to the Sepsis-3 definition for human adults published in 2016 [2]. This might not be surprising because our collective understanding of sepsis remains strongly influenced by the human medical literature. Yet, for instance, nine of the 12 committee members independently included organ dysfunction in their first draft definition because this is how most view the sepsis syndrome clinically. In the future, we hope that large veterinary databases will allow us to test the associations between organ dysfunction markers and scoring systems, as the Sepsis-3 [24, 25] and Phoenix sepsis processes did [30]. As laid out in our previous position statement, this is the next aspiration for our group [44]. In the interim, we hope that the table of putative organ dysfunction markers included here will help guide veterinary clinicians and clinician scientists to diagnose and study sepsis. Elements of the table derive from other scoring systems [255], such as the ARDSVet criteria [256], which support validity and should improve usability. The existing literature already provides evidentiary support for the connection between organ dysfunction and mortality in dogs and cats with infection [11–13, 110]. Consistent and comprehensive data collection and reporting by future sepsis studies should enhance our ability to test these associations and to determine which organ systems are most closely related to survival. Similarly, there may be elements of the table or existing scores that contribute less to outcome prediction and can be eliminated without detriment, as was the case with the integument component of the animal trauma triage score, for instance [257].

This review has several limitations. Our systematic review was thorough, but the strength and utility of all derived recommendations are limited by the quality of the available evidence. Most included studies were small, often markedly heterogeneous or too homogenous, and rarely prospective or well-controlled. We were pragmatic and generally inclusive in the criteria used to formulate the searches and the subsequent systematic review. As a result, we accepted that animals with infections and animals with sepsis were correctly identified, acceptably defined, and adequately diagnosed by those studies. We recognize that this might not have been universally true. Moreover, previous infection studies used various methods and criteria to establish the presence of infection or the diagnosis of disease, and the sepsis studies typically established the diagnosis using SIRS-based criteria. This creates a potential limitation when those data are used to aid the identification of sepsis defined differently, because the connection may no longer be valid or the association may no longer be robust.

Despite these potential shortcomings, we hope that this systematic review enables clinicians to better identify and manage dogs and cats with sepsis in their practice and hence to improve outcomes. We also aspire to empower researchers to build on the existing evidence base to improve diagnosis, establish better performing scores, and test novel therapeutic strategies using a consistent definition of the syndrome. The next phase of our work must be to evaluate the diagnostic utility and prognostic value of the criteria established here through medical record review and data derived from a prospective multicenter sepsis case registry. We hope that those data will allow us to refine or replace the consensus definitions established here.

Author Contributions

Robert Goggs: conceptualization, funding acquisition, writing original draft, methodology, data curation, project administration, investigation, validation. **Stefano Cortellini:** conceptualization, investigation, writing review editing, methodology, data curation, validation. **Amy E. DeClue:** investigation, writing review editing, methodology, data curation, validation. **Massimo Giunti:** conceptualization, investigation, writing review editing, validation, data curation, methodology. **Kate Hopper:** investigation, writing review editing, methodology, validation, data curation. **Julie M. Menard:** investigation, writing review editing, validation, methodology, data curation. **Rodrigo C. Rabelo:** investigation, writing review editing, methodology, validation, data curation. **Elizabeth A. Rozanski:** data curation, methodology, validation, investigation, writing review editing. **Claire R. Sharp:** writing review editing, investigation, methodology, validation, data curation. **Deborah C. Silverstein:** investigation, writing review editing, methodology, validation, data curation. **Virginia Sinnott-Stutzman:** investigation, writing review editing, methodology, validation, data curation. **Giacomo Stanzani:** conceptualization, investigation, writing review editing, validation, methodology, data curation. **John Bourgeois:** investigation, writing review editing, formal analysis, methodology, validation, data curation. **Erik Fausak:** investigation, writing review editing, formal analysis, methodology, validation, data curation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Offprints

Offprints will not be available from the authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File 1: vec70129-sup-0001-Data S1.pdf **Supporting File 2**: vec70129-sup-0002-Data S2.xlsx **Supporting File 3**: vec70129-sup-0003-Data S3.pdf **Supporting File 4**: vec70129-sup-0004-Data S4.pdf **Supporting File 5**: vec70129-sup-0005-Data S5.pdf **Supporting File 6**: vec70129-sup-0006-Data S6.pdf **Supporting File 7**: vec70129-sup-0007-Data S7.xlsx **Supporting File 8**: vec70129-sup-0008-Data S8.pdf **Supporting File 9**: vec70129-sup-0009-Data S9.pdf **Supporting File 10**: vec70129-sup-0010-Data S10.pdf