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Septic Shock and Prognosis in Dogs and Cats With Sepsis—Consensus Definition and Clinical Criteria

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ABSTRACT

Death from sepsis results from progressive organ dysfunction. Early recognition of increased illness severity or deterioration in clinical status enables timely interventions that can improve outcomes. We aimed to define septic shock by consensus and to use the existing literature to identify associated clinical and clinicopathologic abnormalities that would aid rapid identification of the most severely affected patients. We systematically reviewed the available data on sepsis in dogs and cats to identify factors that were predictive of multiple organ dysfunction or mortality. Septic shock was defined as a subset of sepsis with increased mortality, associated with cardiovascular instability and metabolic abnormalities indicative of impaired tissue perfusion despite adequate fluid resuscitation. Clinically, septic shock can manifest as hyperlactatemia, persistent hypotension, and progressive organ dysfunction. For the assessment of prognosis in dogs, we suggest scoring organ dysfunction and illness severity using validated instruments, and measuring objective physiologic parameters, lactate, and ionized calcium, and performing CBCs and serum biochemistry profiles. Where available, serial measurements of protein C and antithrombin activity, and quantitation of acute phase proteins and cytokine concentrations, should be considered. Fewer data were available for cats, and although many similar conclusions were reached as for dogs, only limited recommendations could be made.

Abbreviations: ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; Apo-A1, apolipoprotein A1; APP, acute phase protein; APPLE, Acute Patient Physiologic and Laboratory Evaluation; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AT, antithrombin activity; CCL2, chemokine (C–C motif) ligand 2; CK, creatine kinase; CPV, canine parvovirus infection; CRP, C-reactive protein; cTnI, cardiac troponin I; CXCL, cysteine-X-cysteine motif ligand; DNI, delta neutrophil index; Flt-3L, FMS-like tyrosine kinase 3 ligand; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MODS, multiple organ dysfunction syndrome; MPV, mean platelet volume; NT-pCNP, N-terminal pro-C-type natriuretic peptide; PDW, platelet distribution width; PECO, Population, Exposure, Comparator, Outcome; PICO, Population, Intervention, Comparator, Outcome; qSOFA, quick Sequential Organ Failure Assessment; SAA, serum amyloid A; SICM, sepsis-induced cardiomyopathy; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; SPI2, survival prediction index-2; SpO_2, blood oxygen saturation determined by pulse oximetry; TNF, tumor necrosis factor.

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1 | Introduction

Understanding, recognizing, and managing organ dysfunction are central to surviving sepsis in human adults [1, 2] and children [3, 4]. Death from sepsis is due to organ dysfunction that results from immune dysregulation, complement activation, inflammation–coagulation crosstalk, endothelial injury, and microvascular flow abnormalities [5]. Sepsis causes severe circulatory system compromise that can manifest as inappropriate vasodilation, venous congestion, maldistributive shock, hypotension, and cardiomyopathy necessitating hemodynamic resuscitation to maintain adequate tissue perfusion [6]. Proposed pathophysiologic mechanisms include inducible nitric oxide synthase expression; relative or absolute deficiencies of cortisol, vasopressin, and angiotensin II; catecholamine insensitivity secondary to acidosis; and ion channel opening leading to vasoplegia [6]. Sepsis-induced cardiomyopathy (SICM) is present in approximately 20% of human sepsis patients [7] and is well documented in dogs [8].

The 1991 American College of Chest Physicians consensus conference defined septic shock as sepsis-induced hypotension despite adequate fluid resuscitation with hypoperfusion, including, but not limited to, lactic acidosis, oliguria, and acute alteration in mental status [9]. The landmark early goal-directed therapy trial built upon this definition, specifying a systolic arterial pressure <90 mm Hg despite a fluid challenge or a lactate concentration >4 mmol/L as clinical correlates and enrollment criteria [10]. The 2001 international consensus conference incorporated this blood pressure cutoff and provided additional diagnostic criteria for identification of septic shock, including cardiac index and mixed venous oxygen saturation [11]. In contrast, the 2001 human consensus definitions noted that in children with sepsis, hypotension manifests only when shock is decompensated due to higher basal vasomotor tone and recommended against the use of blood pressure criteria for identification of cardiovascular dysfunction. Altered mentation, poor peripheral pulses, mottled or cool extremities, slow capillary refill, and tachycardia were suggested as superior indicators of shock in pediatric sepsis.

In 2016, the Sepsis-3 process adopted a data-driven approach that involved using expected mortality rates to establish clinical criteria for the identification of septic shock in human adults [1]. Blood lactate concentration was recommended as a straightforward and widely available means to identify cellular dysfunction and altered metabolism, impaired tissue oxygen delivery, and decreased hepatic clearance. Referencing data from the Surviving Sepsis Campaign, the Sepsis-3 guideline authors also agreed that hyperlactatemia is an important marker of illness severity and increased mortality [1]. Thus, in adults, septic shock is currently 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 a mean arterial pressure ≥65 mm Hg and a blood lactate concentration >2 mmol/L after volume resuscitation [1]. With these criteria, the expected mortality for patients in high-income countries with septic shock is >40% [12].

For human pediatrics, the 2005 consensus definitions of sepsis were based on identification of systemic inflammation using variations in physiologic parameters that substantially deviated from those considered normal for the age group [13]. Clinical criteria for identification of septic shock in children included hypotension, a need for vasopressors, or combinations of clinical indicators of poor perfusion [13]. 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? [14, 15]. The first question was used to identify clinical sepsis predictors and the second to identify sepsis severity criteria. Although the Phoenix pediatric sepsis score is now the recommended approach in children [3, 4], adapting the approach taken by the 2022 Pediatric Taskforce definitions enabled us to assess the evidence base for sepsis definitions in small animals and obviated the need for large databases from which to develop scoring systems.

In an accompanying article [16], we describe our efforts to define sepsis by consensus and make recommendations for clinical recognition of the syndrome. Here, we report on our efforts to define septic shock by consensus and present the results of our systematic review of the literature aimed at identifying prognostic factors for small animals with sepsis. The systematic review informed our recommendations for the assessment of illness severity, identification of organ dysfunction, and clinical recognition of septic shock in dogs and cats. 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 and reported by future veterinary sepsis studies.

2 | Materials and Methods

The process of developing consensus definitions for sepsis and septic shock began in June 2023 after informal discussions between several of the committee members at the 2023 EVECC Congress in Porto, Portugal. A larger working group of participants were solicited via email and through 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 agendas and meeting minutes circulated before and 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,

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was drafted in late 2023 and published in early 2024 [17]. Financial support was solicited from and provided by the American College of Veterinary Emergency and Critical Care to enable open access publication of that article.

Consensus definitions for sepsis and septic shock were developed by a modified Delphi process [18]. Initially, each committee member separately and independently drafted a definition for sepsis. These were collated, with keywords highlighted to aid identification of consistent terms, phrases, or components, and circulated for discussion. From the initial set of 12, a subsequent distilled list of four possible definitions was constructed, circulated, and discussed. These four definitions were then subjected to three rounds of modified Delphi surveys, resulting in the consensus definition below. Separately, each committee member also individually drafted a definition for septic shock. These too were collated, and consistent aspects were determined, as for sepsis. From that initial list, four possible consensus definitions of septic shock were drafted, discussed, and then refined via four rounds of modified Delphi surveys, resulting in a consensus definition for septic shock.

As discussed in the introduction, this process was modeled on that of the Pediatric Sepsis Definition Taskforce [14, 15]. 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 infection, 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 or other important patient-centered outcomes such as the development of multiple organ dysfunction syndrome (MODS). The first question was used to identify clinical sepsis predictors and the second to identify sepsis severity criteria. Within each Domain, a series of questions using a Population, Exposure or Intervention, Comparator, Outcome (PECO/PICO) format was generated as previously reported by other consensus efforts [19–22]. Specifically, for Domain 1, we defined the population of interest as dogs and cats with infection.

For the purposes of the systematic review, some specific diseases and certain infectious agents or pathogens were excluded (see Data S2), albeit 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 the group considered that the pathophysiology of the disorder was sufficiently distinct from most cases of sepsis encountered in clinical practice, and that the FIP literature might have little bearing on the guidelines or potentially distort the final recommendations. Endoparasite infections were excluded because these infections (or infestations) were not deemed plausible causes of sepsis by the committee. For Domain 2, we defined the population of interest as dogs and cats with sepsis; however, that was defined by the authors of the studies reviewed. Typically, sepsis was codified using the definition prevailing at the time the study was conducted. In most cases, the definition was based on identification of infection concurrent with the systemic inflammatory response syndrome adjudicated using established leukocyte count, heart rate, respiratory rate, and temperature criteria.

The electronic database search strategies were developed in consultation with two expert librarian information specialists (J.B., E.F.). Trial searches were initially 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 that would need to be screened. 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 and Scielo). The search was limited to sepsis and related conditions as well as outcomes in dogs and cats. The complete search strategy can be found in the Supporting Information (Data S3). The search used NOT to exclude diseases such as rabies and helminths, and was limited with filters to the publication years 1997–2023. Reviews and guidelines were also excluded by filters. No language filter was applied.

An online software platform (Covidence Systematic Review Software, Veritas Health Innovation) was used to facilitate the systematic literature review [23]. Into this platform, 19,030 citations were imported from the three database sources (MEDLINE via PubMed $n = 6782$; Web of Science $n = 6267$; and CAB Abstracts $n = 5981$) from the original 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 an additional 1280 articles were imported into Covidence, from which 312 duplicates were removed, leaving an additional 968 articles for initial screening. A further 41 duplicate articles were identified manually and removed, leaving 16,601 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.

The Covidence software was used to tag articles as relevant to Domain 1 or 2 or both, and to label articles as needing additional scrutiny, to identify duplicates missed by automated processes, and to highlight studies where a second opinion was needed to adjudicate suitability for inclusion.

The group developed a manuscript screening protocol (Data S4) detailing a priori methods for assessing eligibility for inclusion or exclusion. Two rounds of concordance analysis were performed to determine how consistent independent reviewers were in their assessments of article suitability. The results of these analyses were used to refine the manuscript screening protocol. The group reached consensus regarding 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.

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, S6).

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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 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 Septic Shock in Dogs and Cats

Septic shock is a subset of sepsis with increased mortality, associated with cardiovascular instability and metabolic abnormalities indicative of impaired tissue perfusion despite adequate fluid resuscitation.

Clinically, septic shock can manifest as hyperlactatemia, persistent hypotension, and progressive organ dysfunction.

With this consensus definition, the committee sought to highlight the greater illness severity and consequent higher risk of mortality in this subset of dogs and cats with sepsis, and it encompasses the cardiovascular dysfunction and microcirculation abnormalities that contribute to the impairment of tissue perfusion characteristic of shock. We recognize that there is considerable similarity to the 2016 Sepsis-3 definition of septic shock, but one important difference is that we did not include cellular dysfunction. This element was not included because it was not clear to us how veterinary clinicians or researchers would currently identify cellular dysfunction as separate from metabolic dysfunction or organ dysfunction, and because our review of the literature did not indicate that specific cellular dysfunction or damage variables were predictive of mortality in dogs or cats with sepsis.

While not strictly part of a definition, we felt it necessary to add common manifestations of septic shock to enable application of the definition in clinical settings. These findings might be frequent occurrences in this group of patients, but they are not required for septic shock to be present. Note, the term "persistent hypotension" is intended to refer to hypotension that persists despite adequate fluid resuscitation and hence requires other therapeutic interventions such as vasopressor or inotropic drugs for management.

The committee recognizes that the definition does not specify how cardiovascular instability should be recognized or what metabolic abnormalities indicate that tissue perfusion is impaired. This provides veterinarians latitude to adjudicate for individual patients using all available information. For clinical researchers, this definition should reduce bias in data derived from future patient populations because it does not require that certain parameters be fulfilled. Conversely, this makes collecting and reporting as much data as feasible more important, in order to allow future statistical assessment of the predictive value of potential indicators of cardiovascular instability or impaired tissue perfusion.

4 | Evidence Summaries

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

4.1 | Systemic Inflammatory Response Syndrome (SIRS) Criteria

4.1.1 | PICO Question

In dogs and cats with sepsis (**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., cardiovascular instability, multiple organ dysfunction) or nonsurvival (**O**)?

4.1.2 | Summary of Evidence

The summary of evidence is as follows:

- Seventeen studies (three moderate quality [24–26], 14 low quality [27–40]) provided evidence that supports the use of

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SIRS criteria for prediction of sepsis severity or nonsurvival in dogs and cats.

- Seventeen studies (all low quality [41–57]) were not supportive of the use of SIRS criteria for prediction of sepsis severity or nonsurvival in dogs and cats.
- One hundred fourteen studies were considered irrelevant to this PICO question. (Please note, for clarity, citations for this large number of irrelevant studies have been omitted.)

4.1.3 | Conclusions

Approximately equal numbers of studies observed that SIRS criteria aided identification of worsening illness severity as observed that they did not, suggesting that a state of equipoise exists regarding the utility of SIRS criteria in dogs and cats with sepsis. However, the overall quality of evidence is low, as many studies are likely underpowered. Moreover, use of the SIRS criteria to define sepsis confounds many of the assessments of associations with outcome. Some studies focused on specific populations where pathophysiological effects likely underpin the associations identified. For instance, associations between outcome and leukopenia in dogs with canine parvovirus infection (CPV), or between outcome and hypothermia in neonates. Finally, the use of mortality as an outcome measure is problematic given the high prevalence of euthanasia. Future research in this area would be aided by some straightforward steps that would enable meta-analysis and strengthen future guideline recommendations. Temperature, heart rate, respiratory rate, and leukocyte counts are easily and cheaply measured, and these data should be routinely recorded and included in all future small animal sepsis-related studies. Raw data should be provided whenever possible to enable future meta-analysis. At minimum, descriptive statistics (e.g., median, interquartile range, min–max, or mean and standard deviation) for the SIRS variables of temperature, heart rate, respiratory rate, and white blood cell count should be provided. Inclusion of the numbers of animals with values above and below local reference intervals would aid identification and assessment of bimodal distributions for heart rate and temperature. Researchers are encouraged to compare SIRS variable values with relevant patient-centered outcomes and to provide the associated illness severity scores.

4.1.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with sepsis, evaluation of SIRS criteria is not recommended for the assessment of illness severity or prognosis in clinical settings.
- In dogs and cats with sepsis, we suggest evaluation of SIRS criteria for the assessment of illness severity or prognosis in research settings.
  - We recommend reporting SIRS criteria in all future studies of dogs and cats with sepsis.
  - We recommend that raw data or summary statistics for heart rate, respiratory rate, core temperature, and leukocyte and band neutrophil counts be provided in all future reports on sepsis in dogs and cats.

4.2 | Organ Dysfunction and Illness Severity Scores

4.2.1 | PICO Question

In dogs and cats with sepsis (**P**), does assessment of organ dysfunction or illness severity (**I**), compared to not assessing organ dysfunction or illness severity (**C**), improve prediction of nonsurvival (**O**)?

4.2.2 | Summary of Evidence

The summary of evidence is as follows:

- Nine studies (two high quality [55, 58], seven moderate quality [38, 59–64]) provided evidence that supports the use of organ dysfunction assessments or illness severity scores for prediction of severity or nonsurvival in dogs with sepsis.
- Three studies (two high quality [56, 65], one moderate quality [66]) were not supportive of the use of organ dysfunction assessments or illness severity scores for prediction of severity or nonsurvival in dogs with sepsis.
- Two studies in dogs were considered irrelevant to the PICO question [67, 68].
- One study in cats (high quality, not supportive [69]) provided evidence relevant to the PICO question.

4.2.3 | Conclusions

In general, available information on cats is very limited; hence, the information presented is focused on dogs. Fifteen studies were evaluated that described organ dysfunction assessments or illness severity scores in dogs with sepsis or critically ill dogs considered at risk of sepsis or death. Example systems included the Acute Patient Physiologic and Laboratory Evaluation (APPLE) score [62, 70, 71], the Sequential Organ Failure Assessment (SOFA) score [61, 72], the "quick" version of SOFA (qSOFA) [58], and the survival prediction index-2 (SPI2) [59, 73]. Nine studies support the use of scoring schemes, whereas six were not supportive. The major confounder in most studies was the generally small sample size, which might be a frequent cause of both type I and type II errors. For instance, the largest study reviewed included 204 dogs. This stands in contrast to comparable human studies that can involve thousands of patients. Irrespective, there is no indication that scoring is detrimental or harmful, such that any additional insights provided to clinicians by these scores might be useful.

Overall, the body of evidence suggests that scoring schemes can help predict outcomes, but their clinical utility is limited. Commonly, scores of survivors and nonsurvivors overlapped substantially, such that the score alone was not adequate for discrimination between outcomes for individual patients. Additionally, most veterinary studies are complicated by the possibility

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of elective euthanasia that could reflect futility but likely frequently incorporates ethical, moral, and financial dimensions that are specific to the pet and the client. Current evidence is too sparse to recommend universal severity score use for septic dogs, but when available, the requisite data should be routinely recorded for all critically ill dogs and cats to maximize availability for future studies.

4.2.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with sepsis, we suggest scoring organ dysfunction and illness severity using validated instruments for the assessment of prognosis in clinical settings.
- In dogs with sepsis, we recommend scoring organ dysfunction and illness severity using validated instruments for the assessment of prognosis in research settings.
- In cats with sepsis, there is insufficient evidence to recommend scoring organ dysfunction or the use of illness severity scores for the assessment of prognosis in clinical settings.
- In cats with sepsis, we suggest scoring organ dysfunction and illness severity using validated instruments for the assessment of prognosis in research settings.

4.3 | Additional Physiological or Objective Patient Parameters

As with our assessments of the evidence for sepsis diagnosis, these two PICO questions were considered individually, and separate guidelines were drafted. 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). The PICO questions, evidence summaries, and discussions are presented sequentially and the combined guidelines are duplicated at the end of each section.

4.3.1 | PICO Question

In dogs and cats with sepsis (**P**), does measurement of objective physiologic parameters (e.g., mean arterial pressure, cardiac output, or systemic vascular resistance) (**I**), compared to not measuring objective physiologic parameters (**C**), improve prediction of severity (e.g., development of cardiovascular instability, new organ dysfunction) or nonsurvival (**O**)?

4.3.2 | Summary of Evidence

The summary of evidence is as follows:

- Twelve studies (10 moderate quality [31, 37, 60, 74–81], two low quality [45, 82]) provided evidence that supports the use of objective physiologic parameters for prediction of severity or nonsurvival in dogs with sepsis.
- Four studies (one high quality [83], two moderate quality [24, 33], one low quality [84]) provided evidence that supports the use of objective physiologic parameters for prediction of severity or nonsurvival in cats with sepsis.
- Four studies were not supportive of the use of objective physiologic parameters for prediction of severity or nonsurvival in dogs and cats with sepsis [41, 51, 78, 85].

4.3.3 | Conclusions

Deteriorating physiological parameters are associated with the development of sepsis and subsequently worse outcomes. As such, measurement of objective physiological parameters might aid in the identification of dogs or cats that are developing sepsis or multiple organ dysfunction. No specific physiological parameter is universally associated with mortality, but worsening tissue oxygen delivery is associated with a grave outcome. Specifically, tachycardia, tachypnea, and hypotension are widely documented to be identified in dogs that are treated for sepsis. However, changes in these parameters over time were uncommonly documented in the reviewed studies. Most studies report data collected at the time of sepsis diagnosis or at hospital admission. While it seems logical that monitoring vital signs over time would be helpful, no prospective studies were identified that document this. Available evidence indicates that the development of multiple organ dysfunction and subsequent death is preceded by inadequate tissue oxygen delivery.

In cats, hypotension and hypothermia are associated with sepsis and a poor outcome. The studies that were evaluated were primarily retrospective or observational in nature. No study tracked physiological parameters over time, and frequent assessments were made based on admission vitals. It would be very useful to prospectively track changes in physiological parameters over time in septic cats, including subgroups that died and those that survived. Tachycardia, while common in dogs, may likely be blunted in cats due to hypothermia and challenges in accurately and repeatably measuring blood pressure in cats, which hampers prognostic assessments.

4.3.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with sepsis, we suggest measurement of objective physiologic parameters for the assessment of prognosis in clinical and research settings.
- In dogs with sepsis, we recommend measurement of heart rate, respiratory rate, and blood pressure at regular intervals.
- In cats with sepsis, we recommend measurement of core body temperature and blood pressure at regular intervals.

4.4 | Additional Physiological or Objective Patient Parameters

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4.4.1 | PICO Question

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

4.4.2 | Summary of Evidence

The summary of evidence is as follows:

- Ten studies (five high quality [80, 86–89], five moderate quality [34, 76, 90–92]) provided evidence that supports the use of additional objective parameters for prediction of severity or nonsurvival in dogs and cats with sepsis.
- One study (moderate quality [93]) was not supportive of the use of additional objective parameters for prediction of severity or nonsurvival in dogs and cats with sepsis.

4.4.3 | Conclusions

4.4.3.1 | Cortisol. Three studies assessed the prognostic value of cortisol measurements. Basal hypercortisolemia >5 μg/dL (>138 nmol/L) was more frequent in nonsurvivors than survivors in one study of 21 dogs with SIRS, although it is uncertain whether every dog had sepsis. A delta cortisol value ≤3 μg/dL (≤83 nmol/L) after adrenocorticotropic hormone (ACTH) administration was associated with vasopressor administration and hypotension, suggesting it might be a useful indicator of cardiovascular dysfunction. However, there is currently insufficient evidence to recommend cortisol measurement or the use of the ACTH stimulation test for all septic patients. Further investigation of cortisol concentrations as predictors of cardiovascular dysfunction might be warranted, although it is notable that the ACTH stimulation test is not recommended for this purpose in people.

4.4.3.2 | Thyroid Hormones. A single study in dogs with CPV showed an initial decrease (Day 3), followed by an increase (Day 5), in total thyroxine (T4) concentrations among survivors. Study quality was limited, however, such that further research is needed before these findings can be applied more broadly.

4.4.3.3 | Cardiac Biomarkers. Various studies have measured distinct troponin proteins, making comparisons difficult. One study assessed the role of cardiac troponin I (cTnI) in dogs with CPV; no association with outcome was identified. Similarly, one study evaluated N-terminal-pro-C-type natriuretic peptide (NT-pCNP) in dogs with various sources of sepsis; no association with outcome was identified. As such, cTnI or NT-pCNP cannot be recommended currently, but there remains scope for further investigation in this area.

4.4.3.4 | Echocardiography. Certain echocardiographic measurements in dogs with CPV have potential as prognostic markers; however, the technical complexity of acquiring the relevant measurements might limit widespread application. Further investigations are required for validation across different patient populations and clinical care settings.

4.4.3.5 | Organism Culture. Performing microbiological culture of suitable clinical samples and assessing the appropriateness of antimicrobial drug therapy are considered central to antimicrobial stewardship but do not currently offer prognostic information.

4.4.3.6 | Proteomics and Lipidomics. Unbiased omics technology approaches for the assessment of pathophysiologic alterations or metabolic derangements and the identification of possible prognostic biomarkers appear promising but are not applicable to clinical practice; hence, they are only relevant to clinical research settings at present. Two studies have evaluated their use in babesiosis and in dogs with bacterial sepsis. More data across diverse patient populations are needed to identify potential biomarkers for outcome prediction and disease severity assessment and ultimately will likely need to be translated into other platforms such as ELISA, bead-based multiplex assays, or immunoturbidometric methods to be useful in the context of clinical care.

4.4.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with sepsis, we suggest measurement of objective physiologic parameters for the assessment of prognosis in clinical and research settings.
  - In dogs with sepsis, we recommend measurement of heart rate, respiratory rate, and blood pressure at regular intervals.
  - In cats with sepsis, we recommend measurement of core body temperature and blood pressure at regular intervals.

4.5 | Acute Phase Proteins (APPs)

4.5.1 | PICO Question

In dogs and cats with sepsis (**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., cardiovascular instability, multiple organ dysfunction) or nonsurvival (**O**)?

4.5.2 | Summary of Consensus on Evidence

The consensus on the evidence is summarized as follows:

- Eight studies (four high quality [26, 94–96], three moderate quality [36, 97, 98], one low quality [99]) provided evidence that supports the use of APPs for prediction of severity or nonsurvival in dogs with sepsis.
- One study (low quality) provided evidence that supports the use of APPs for prediction of severity or nonsurvival in cats with sepsis [100].

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- Nine studies (four high quality [64, 101–103], four moderate quality [30, 34, 104, 105], one low quality [106]) were not supportive of the use of APPs for prediction of severity or nonsurvival in dogs and cats with sepsis.
- Seven studies were considered irrelevant to the PICO question [107–113].

4.5.3 | Conclusions

A total of 18 studies were considered relevant to the PICO question, with equal numbers providing evidence that is not supportive of the use of APPs for prognostication in sepsis and providing evidence that supports their use. Most reviewed studies included cohorts of animals with various causes of sepsis. Some focused solely on bacterial sepsis yet included several sources of infection. Other studies included a myriad of sources and causes of sepsis due to both bacterial and viral pathogens. For the formulation of general recommendations, this heterogeneity is likely a strength because it increases the external validity of the findings.

All studies deemed "not supportive" evaluated CRP, SAA, or both. In addition, two studies that observed apolipoprotein A1 (Apo-A1) to be useful for prognostication simultaneously observed that CRP or SAA was not predictive of outcome. The reviewed evidence suggests that in dogs with sepsis, concentrations of CRP and SAA are increased, while in cats with sepsis, SAA concentrations are increased. However, the available data indicate that single-time-point measurements of these APPs are not predictive of outcome. If CRP or SAA is to be evaluated to enable patient management (separate from clinical research), then serial measurement will likely be necessary to maximize the utility of the information provided about patient outcome.

The APPs for which reviewed evidence best supports their use for prognostication in sepsis are procalcitonin (PCT) in dogs and cats and Apo-A1 in dogs, yet data here are sparse. These studies need to be replicated, particularly because multiple methods were used to measure PCT concentrations or expression, and none are suitable for use in the context of clinical care. One study also suggested that PCT performed better when measured daily. Some data support the use of CRP concentrations, but only when CRP is measured serially and the changes in concentration are charted over time. As such, APP measurement in sepsis warrants further study using targeted and potentially serial assessment of promising biomarkers in larger cohorts. Further assay development for Apo-A1 and PCT will be necessary to enable widespread clinical accessibility.

4.5.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with sepsis, single-time-point measurements of CRP and SAA are not recommended for the assessment of prognosis in clinical settings.
- In dogs with sepsis, we suggest serial quantitation of APPs for the assessment of disease severity and prognosis in clinical and research settings.
- In cats with sepsis, quantitation of APPs is not recommended for the assessment of prognosis in clinical settings.
- In cats with sepsis, we suggest quantitation of APPs for the assessment of prognosis in research settings.

4.6 | Blood Gases, Electrolytes, and Lactate

4.6.1 | PICO Question

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

4.6.2 | Summary of Consensus on Evidence

The consensus on the evidence is summarized as follows:

- Ten studies (eight high quality [24, 30, 31, 48, 74, 85, 86, 114], two moderate quality [29, 36]) provided evidence that supports the use of blood gases, electrolytes, or lactate for prediction of severity or nonsurvival in dogs and cats with sepsis.
- Nine studies (two high quality [38, 115], seven moderate quality [41, 51, 67, 76, 116–118]) were not supportive of the use of blood gases, electrolytes, or lactate for prediction of severity or nonsurvival in dogs and cats with sepsis.
- Five studies were considered irrelevant to the PICO question [42, 80, 119–121].

4.6.3 | Conclusions

4.6.3.1 | Dogs. Fourteen studies reported blood gas measurements, acid–base variables, and concentrations of lactate or electrolytes in dogs with sepsis. Five studies enrolled dogs with CPV, two enrolled dogs with septic peritonitis, two enrolled dogs with pyometra, one study enrolled dogs with endocarditis, and four involved heterogeneous causes of sepsis.

Considering all dogs with sepsis, 10 studies evaluated the association of blood lactate concentrations with outcome. Of these, three identified a positive association with mortality (higher lactate in nonsurvivors), and seven reported no difference in lactate concentrations between survivors and nonsurvivors. An increase in lactate during hospitalization was associated with mortality in three studies and was not associated with mortality in three studies. The association of base deficit with outcome was reported in five studies. Two studies demonstrated an association between base deficit (lower base excess) and outcome, whereas three found no association with outcome. There was no association of pH or partial pressure of carbon dioxide ($PaCO_2$) and outcome in two studies, while one of two studies demonstrated an association of bicarbonate (HCO_3^-), partial pressure of oxygen (PaO_2), and blood oxygen saturation (SpO_2) with outcome; HCO_3^-, PaO_2, and SpO_2 were lower in nonsurvivors. Five studies found no association between sodium and potassium and outcome, whereas two

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out of four studies found an association between lower ionized calcium and mortality. One study found no association of total calcium with outcome. Only one study assessed chloride and outcome and found an association between lower chloride and mortality, but since this study enrolled dogs with CPV, it might be confounded by the pathogenesis of CPV-induced gastrointestinal disease. None of the studies of dogs with CPV identified an association with ionized calcium, sodium, or potassium.

In summary, in dogs with sepsis due to causes other than CPV, higher lactate concentrations either as single measurements on admission or as trends in response to resuscitation might be associated with mortality, although specific cutoffs could not be extrapolated. Similarly, in dogs with sepsis due to causes other than CPV, measurement of blood gases, electrolytes, or lactate, in particular ionized hypocalcemia, can be used for the assessment of prognosis. As such, measurement of blood gases, electrolytes, or lactate can be used for the assessment of prognosis, either as a single measurement on admission or as trends in response to resuscitation. As with most biomarkers, additional prospective studies including large, diverse populations will be required to fully clarify the roles of these parameters as therapeutic guides or markers of illness severity.

4.6.3.2 | Cats. Six studies evaluated cats with sepsis, including two studies on septic peritonitis, one on pyothorax, and three including cats with a variety of sources of sepsis. Increased magnesium concentration and methemoglobin fraction were observed in nonsurvivors in one study, but these observations have not been replicated to date. Decreased chloride was found to be associated with mortality in one study, while two studies did not find any association. Higher phosphorus concentrations were found in nonsurvivors in one study, but this was not replicated in two others. Unlike dogs, abnormalities of ionized calcium and total calcium have not been associated with outcome in cats. Hyperlactatemia is associated with the presence of shock in cats, but not with mortality in any of the three studies reviewed, suggesting that lactate might be of limited use in cats. Lower bicarbonate concentrations were associated with the presence of shock, but only in a single study. Further investigations of the utility of base deficit and HCO_3^- concentration in cats with sepsis are warranted to assess their prognostic utility.

4.6.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with sepsis, we suggest serial quantitation of lactate and ionized calcium for the assessment of prognosis in clinical and research settings.
- In dogs with sepsis, we suggest serial quantitation of blood gases and electrolytes for the assessment of prognosis in research settings.
- In cats with sepsis, quantitation of blood gases, electrolytes, or lactate is not recommended for the assessment of prognosis in clinical settings.
- In cats with sepsis, we suggest quantitation of blood gases, electrolytes, or lactate for the assessment of prognosis in research settings.

4.7 | Complete Blood Counts

4.7.1 | PICO Question

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

4.7.2 | Summary of Evidence

The summary of evidence is as follows:

- Sixteen studies (seven high quality [24, 30, 31, 64, 85, 114, 122], seven moderate quality [36, 42, 47, 49, 116, 117, 121], two low quality [120, 123]) provided evidence that supports the use of CBCs for prediction of severity or nonsurvival in dogs and cats with sepsis.
- Nine studies (two high quality [38, 48], six moderate quality [41, 51, 67, 76, 118, 124], one low quality [68]) were not supportive of the use of CBCs for prediction of severity or nonsurvival in dogs and cats with sepsis.
- Four studies were considered irrelevant to the PICO question [80, 119, 125, 126].

4.7.3 | Conclusions

A total of 25 studies evaluated associations between hematology variables and outcome. Most assessed associations with mortality, and some also evaluated associations with outcomes, including duration of hospitalization and development of septic shock.

Eight studies included dogs with CPV. Of these, two observed an association between leukopenia and nonsurvival, whereas two observed an association between leukopenia and disease severity, illness score, and duration of hospitalization. One study demonstrated that increasing leukocyte counts during hospitalization was associated with survival. The remaining three studies found no association between leukocyte count and disease severity or survival. In the six CPV studies that assessed segmented neutrophils, three found that neutropenia was associated with increased mortality, or with severity or duration of hospitalization, but not mortality. Associations between outcomes and monocyte and lymphocyte counts were assessed in three of eight and four of eight studies, respectively. Only one study found that lymphopenia and monocytopenia were associated with death, while another observed a negative correlation between lymphocyte count and duration of hospital stay. One study observed higher mean platelet volume (MPV) and platelet distribution width (PDW) in CPV nonsurvivors versus survivors. No other blood count parameters were found to be associated with disease severity or mortality in dogs with CPV.

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Excluding CPV, 11 studies described CBC parameters in dogs with sepsis of heterogeneous causes ($n = 5$) or resulting from pyometra ($n = 2$), surgical sepsis ($n = 2$), endocarditis ($n = 1$), and babesiosis ($n = 1$). One study observed a difference in leukocyte count between dogs that developed septic shock (but not mortality) compared with those that did not. This association was not observed in the remaining 10 studies, however. Two studies observed an association between neutropenia and disease severity, one study reported an association between neutropenia and nonsurvival, and one study observed an association between band neutrophil counts and mortality. In a study of dogs with various causes of sepsis, occurrence of lymphopenia, eosinopenia, and monocytopenia was associated with the development of septic shock but not mortality. One study of a heterogeneous group of dogs with sepsis found an association between MPV and the development of septic shock but not with survival, while a study of dogs with septic peritonitis found that increased MPV was associated with nonsurvival. No other CBC parameter was associated with nonsurvival. Some studies have evaluated CBC-derived indices, such as the delta neutrophil index (DNI) or cell count ratios. The DNI was not associated with mortality but was correlated with septic shock development. The two studies focused on cell count ratios suggest these derivative parameters, particularly the platelet–lymphocyte and monocyte–lymphocyte ratios, warrant further investigation as potential prognostic markers in dogs with sepsis.

A total of seven studies of sepsis in cats provided useful evidence for this PICO question, including three studies of septic peritonitis, three with heterogeneous populations, and one study of pyothorax. There was little consistency in findings between studies; however, this was potentially because of widely different study populations. Moreover, not all CBC parameters appeared to have been consistently evaluated in all studies. The following changes have been associated with mortality in cats with sepsis: severe neutrophil toxic change, lymphopenia, monocytosis, eosinopenia, and anemia. Lymphopenia has also been associated with the presence of MODS in cats with sepsis.

In summary, there is no consistent evidence to suggest that any specific CBC-derived value provides prognostic information regarding MODS development or mortality. However, the available data suggest that leukocyte parameters might be useful in dogs, particularly those with CPV. In dogs with other causes of sepsis, the evidence to support the use of neutropenia and thrombocytopenia as prognostic indicators is currently too weak to recommend their clinical application, but evaluation of MPV and specific leukocyte ratios warrants further investigation in dogs with sepsis. In cats, lymphopenia warrants further assessment as a prognostic indicator.

4.7.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with sepsis due to CPV, we recommend performing a CBC for the assessment of prognosis in clinical and research settings.
  - Leukocyte and neutrophil counts might be the most useful variables.
- In dogs with sepsis due to causes other than CPV, we suggest performing a CBC for the assessment of prognosis in clinical and research settings.
  - Neutrophil count is most associated with severity, but not consistently with mortality.
  - Leukocyte count ratios warrant further investigation as potential prognostic markers.
- In cats with sepsis, performing a CBC is not recommended for the assessment of prognosis in clinical settings, except where necessary to aid illness severity scoring and identification of organ dysfunction.
- In cats with sepsis, we suggest performing a CBC for the assessment of prognosis in research settings.
  - Lymphocyte count warrants further investigation as a biomarker for organ dysfunction and mortality.

4.8 | Serum Biochemistry Profile and Urinalysis

4.8.1 | PICO Question

In dogs and cats with sepsis (**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 cardiovascular instability, new organ dysfunction) or nonsurvival (**O**)?

4.8.2 | Summary of Evidence

The summary of evidence is as follows:

- Fourteen studies (four high quality [24, 31, 48, 85], eight moderate quality [36, 41, 42, 51, 67, 116–118], two low quality [68, 123]) provided evidence that supports the use of serum biochemistry profiles and urinalysis results for prediction of severity or nonsurvival in dogs and cats with sepsis.
- Six studies (four high quality [30, 64, 114, 122], two moderate quality [29, 76]) were not supportive of the use of serum biochemistry profiles and urinalysis results for prediction of severity or nonsurvival in dogs and cats with sepsis.
- Eleven studies were considered irrelevant to the PICO question [80, 101, 112, 113, 119–121, 124, 125, 127, 128].

4.8.3 | Conclusions

In dogs, 14 studies relevant to the PICO question were identified, of which six focused on CPV. In these studies, one observed lower cholesterol in nonsurvivors, but this association was not assessed or identified in any other study. Two studies observed an association between hypoalbuminemia and hypoproteinemia and duration of hospitalization ($n = 1$) and nonsurvival ($n = 1$), whereas three studies found no association. The only other outcome association identified in CPV studies was between increased urea and mortality, but interestingly, creatinine was not prognostic.

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The other eight studies of sepsis in dogs included four of heterogeneous causes, two on pyometra, one on septic peritonitis, and one on endocarditis. Creatinine concentration was positively associated with mortality in two studies and with duration of hospitalization in another. Three studies assessed associations of liver enzymes, with one finding an association between alanine aminotransferase (ALT) and duration of hospitalization. In the two studies that assessed hypocholesterolemia, one observed an association with mortality, whereas the other did not. One study observed an association between hypoalbuminemia and mortality, whereas four did not. Glucose concentrations were not prognostic in any of the six studies that investigated them.

In cats with sepsis, six studies were relevant to the PICO question, including three on cats with heterogeneous causes, two on septic peritonitis, and one on pyothorax. Cats with MODS and septic shock were specifically investigated in one study, wherein cats with cardiovascular dysfunction (septic shock) had higher ALT, bilirubin, aspartate aminotransferase (AST), and creatine kinase (CK), and lower total protein and albumin compared to cats with uncomplicated sepsis. Five studies in cats investigated bilirubin concentration, of which two found that hyperbilirubinemia was associated with mortality and cardiovascular dysfunction (septic shock). No such association was identified in the remaining studies. In one study, hypoproteinemia was identified in cats with complicated sepsis, and total protein was lower in nonsurvivors than in survivors. Albumin was analyzed in five studies; hypoalbuminemia was associated with cardiovascular dysfunction and mortality in one study. Four studies found no association between albumin and outcome.

Four studies in cats assessed the association between urea and mortality; a relationship was identified in two studies and not in two others. Creatinine concentration was positively associated with mortality in one study, but not in the other three. Glucose concentration was associated with mortality in one study, but not in two others. Cholesterol concentration was associated with mortality in one study but not in another. The muscle-derived enzymes AST and CK have been associated with complicated sepsis in one study but not with mortality.

In summary, performing a biochemistry profile in dogs and cats with sepsis is crucial for the identification of MODS, and individual variables may also provide separate prognostic information. However, no specific biochemistry parameter reliably predicts disease severity or outcome in small animals. For dogs, creatinine, albumin, and cholesterol might be the best individual predictors of outcome, but additional studies involving larger cohorts are needed to strengthen the currently available evidence. In cats, total bilirubin might be a useful prognostic marker, but even for this variable, study findings are not wholly consistent, and larger studies will likely be required to confirm current preliminary data. Insufficient evidence exists to define the role of urinalysis in dogs or cats with sepsis, with the only relevant study reviewed finding no evidence of an association with outcome.

4.8.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs and cats with sepsis, we recommend performing a serum biochemistry profile to aid illness severity scoring and identification of organ dysfunction in clinical settings.
- In dogs with sepsis, we suggest performing a serum biochemistry profile for the assessment of prognosis in clinical and research settings.
  - In dogs, concentrations of creatinine, albumin, and cholesterol might be the most useful variables.
- In cats with sepsis, we suggest performing a serum biochemistry profile for the assessment of prognosis in clinical and research settings.
  - In cats, total bilirubin concentration and ALT activity might be the most useful variables.
- In dogs and cats with sepsis, there is insufficient evidence to make a recommendation regarding performing urinalysis for the assessment of prognosis.

4.9 | Coagulation Parameters

4.9.1 | PICO Question

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

4.9.2 | Summary of Evidence

The summary of evidence is as follows:

- Six studies (two high quality [62, 87], four moderate quality [47, 129–131]) provided evidence that supports the use of coagulation system variables for prediction of severity or nonsurvival in dogs with sepsis.
- One study (high quality [24]) provided evidence that supports the use of coagulation system variables for prediction of severity or nonsurvival in cats with sepsis.
- Two studies (moderate quality [132, 133]) were not supportive of the use of coagulation system variables for prediction of severity or nonsurvival in dogs with sepsis.
- Two studies (high quality [33, 85]) were not supportive of the use of coagulation system variables for prediction of severity or nonsurvival in cats with sepsis.
- Two studies were considered irrelevant to the PICO question [134, 135].

4.9.3 | Conclusions

In dogs, seven studies including a total of 213 dogs provided moderate- or high-quality evidence that supports the use of coagulation system variables for prediction of severity or nonsurvival in dogs with sepsis. Of these, three studies (n = 139 dogs) were considered to provide only limited support for the incorporation

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of coagulation system variables into prognostic assessments of dogs with sepsis. One study used proteomics techniques that have limited clinical relevance but identified altered prothrombin expression in dogs with babesiosis. The available evidence suggests that protein C and antithrombin activity (AT) measurements, thromboelastography, platelet aggregometry, platelet count, and MPV are the most useful for prognostication in dogs with sepsis, but only decreased protein C and AT activities were supported by more than one study. In cats, only one study provided evidence that supports the use of activated partial thromboplastin time (aPTT) measurement for the prediction of severity or nonsurvival in cats with sepsis. However, this association is tempered by the lack of association of this variable in cats in a separate study from the same group. As such, the evidence reviewed suggests that coagulation system variables provide limited insights into prognosis in dogs with sepsis and could be considered as markers of organ dysfunction. 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 with sepsis. Wide availability, low cost, and ease of use suggest that clotting times should be considered for the assessment of dogs and cats with sepsis and that, when available, protein C and AT activities should be measured in dogs with sepsis.

4.9.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with sepsis, we suggest measurement of coagulation system variables, in particular protein C and AT, for the assessment of prognosis in clinical and research settings.
- In cats with sepsis, measurement of coagulation system variables is not recommended for the assessment of prognosis in clinical settings.
- In cats with sepsis, we suggest measurement of clotting times for the assessment of prognosis in research settings.

4.10 | Cytokines

4.10.1 | PICO Question

In dogs and cats with sepsis (**P**), does measurement of cytokine concentrations (**I**), compared to not measuring cytokine concentrations (**C**), improve prediction of severity (e.g., cardiovascular instability, multiple organ dysfunction) or nonsurvival (**O**)?

4.10.2 | Summary of Evidence

The summary of evidence is as follows:

- Six studies (three high quality [103, 114, 136], three moderate quality [27, 137, 138]) provide evidence that supports the use of cytokine concentrations for prediction of severity or nonsurvival in dogs and cats with sepsis.
- Three studies (one high [139], two moderate [42, 140]) were not supportive of the use of cytokine concentrations for prediction of severity or nonsurvival in dogs and cats with sepsis.
- One study was considered irrelevant to the PICO question [113].

4.10.3 | Conclusions

The overall body of evidence suggests that cytokine concentrations in dogs at the time of admission to either the emergency room or the ICU have potential utility for identifying disease severity and nonsurvival. In dogs, five out of eight studies reported positive associations between cytokines, such as interleukin (IL)-6, monocyte chemoattractant protein-1 (MCP-1, also known as C–C motif chemokine ligand 2 [CCL2]), and tumor necrosis factor (TNF)-α, and either disease severity or nonsurvival. However, three studies found no significant prognostic value, particularly for cytokines like IL-10 or IL-8 (also known as CXC-motif ligand 8, CXCL-8). The variability in study designs, timing of cytokine measurements, and patient populations highlights the need for further research before cytokine concentrations can be reliably applied to clinical prognostication in sepsis.

In cats, limited data indicate that certain cytokines, such as IL-1β, IL-6, IL-12, MCP-1 (CCL2), and Fms-like tyrosine kinase 3 ligand (Flt-3L), may help distinguish disease severity (e.g., sepsis vs. septic shock) but were not able to help determine outcome. In another study, moderate, positive correlations between nonsurvival and plasma IL-1β activity and IL-6 concentration were found in cats with sepsis. As such, no specific recommendation can be made about the use of specific cytokine concentration measurement at admission to inform the identification of disease severity or outcome in cats.

The evidence suggests that cytokine concentrations are useful for the prognostication of sepsis in dogs, as five of eight studies demonstrated associations between specific cytokines and disease severity or nonsurvival. However, additional studies are necessary in cats to determine with greater certainty whether cytokine concentrations are reliable for prognostication in feline sepsis. Currently, the data are less conclusive. While some cytokines (e.g., IL-1β, IL-6, IL-12, MCP-1 [CCL2], Flt-3L) showed potential for distinguishing disease states or identifying nonsurvival, the small sample sizes and inconsistent findings highlight the need for further studies with larger cohorts. Additionally, investigation of cytokine concentrations in the context of clinical sepsis research should involve measurement of multiple cytokines using validated, robust methods of quantitation.

4.10.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with sepsis, we suggest measurement of cytokine concentrations, in particular IL-6, MCP-1 (CCL2), and TNF-α, for the assessment of prognosis in clinical or research settings.

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- In cats with sepsis, measurement of cytokine concentrations is not recommended for the assessment of prognosis in clinical settings.
- In cats with sepsis, we suggest measurement of cytokine concentrations for the assessment of prognosis in research settings.

4.11 | Novel Biomarkers

4.11.1 | PICO Question

In dogs and cats with sepsis (**P**), does measurement of novel biomarkers (**I**), compared to not measuring novel biomarkers (**C**), improve prediction of severity (e.g., cardiovascular instability, multiple organ dysfunction) or nonsurvival (**O**)?

4.11.2 | Summary of Evidence

The summary of evidence is as follows:

- Six studies (one moderate quality [141], five low quality [39, 89, 105, 142, 143]) provided evidence that supports the use of novel biomarkers for prediction of severity or nonsurvival in dogs with sepsis.
- Five studies (one moderate quality [93], four low quality [96, 98, 144, 145]) were not supportive of the use of novel biomarkers for prediction of severity or nonsurvival in dogs with sepsis.
- Two studies were considered irrelevant to the PICO question [113, 146].

4.11.3 | Conclusions

There is very little evidence supporting the use of novel biomarkers in sepsis in general. There is no evidence for their use in cats. Of the biomarkers evaluated, cell-free DNA indexed to neutrophil count has some support as a prognostic indicator in dogs, but data do not support sensitivity or specificity calculations that would inform clinical decision making. Currently, the major value of this body of literature is in identifying potentially promising biomarkers that warrant further assessment and in limiting further evaluation of markers that might be of little value even in larger study populations.

4.11.4 | Guideline Recommendations

The recommendations are as follows:

- In dogs with sepsis, measurement of novel biomarkers is not recommended for the assessment of prognosis in clinical settings.
- In dogs with sepsis, we suggest measurement of novel biomarkers, including cell-free DNA, serum histones, metabolomic and lipidomic profiles, and vascular endothelial growth factor for the assessment of prognosis in research settings.
- In cats with sepsis, there is insufficient evidence to make a recommendation regarding measurement of novel biomarkers for the assessment of prognosis in clinical settings.
- In cats with sepsis, we suggest measurement of novel biomarkers for the assessment of prognosis in research settings.

5 | Discussion

The second domain of the sepsis definitions consensus effort aimed to use the veterinary literature to determine what patient factors, biomarkers, or clinicopathologic parameters predict mortality in dogs and cats with sepsis. Our aspiration was that these criteria would aid in the assessment of sepsis severity and outcome prediction. In addition, we sought to establish a consensus definition of septic shock to describe the state of patient cardiovascular compromise that is recognized clinically in human and veterinary medicine as a severe manifestation of the syndrome. While this was not essential to fulfill the a priori aims of Domain 2, it enabled us to encapsulate our collective understanding of the processes involved in the progression of sepsis. Moreover, the consensus definition of septic shock maintains alignment with human medical definitions of sepsis and provides a tangible link to prior sepsis severity grades derived from the 1991 and 2001 definitions.

The systematic review of the veterinary literature evaluated more than 350 articles. Some articles were relevant only to Domain 1, some only to Domain 2, while others were germane to both. Across these publications, we were able to use data on various infections, patient types, and study settings across numerous countries. We believe that this will enhance the generalizability of our recommendations. As with the accompanying sepsis definition article, we extracted more data from the publications than we could ultimately use, and these are provided in the Supporting Information should other investigators wish to analyze them further.

As for sepsis, a stronger evidence base supported recommendations and suggestions for dogs than for cats. There were sufficient data available to support recommendations for the use of readily available tests, including CBCs and serum biochemistry profiles for the assessment of illness severity and outcome prediction. We also made various suggestions for measurement of other parameters, including organ dysfunction scoring, measurement of physiologic parameters, APPs, lactate, ionized calcium, several coagulation parameters, and some cytokine concentrations. Of these, only lactate and the cardiovascular components of organ function assessment were highlighted in our proposed definition of septic shock. This disparity should not be interpreted as an inconsistency between predictors of outcome and the consensus definition because these two elements have distinct goals. The factors that we identified as predictive of outcome in dogs and cats with sepsis represent parameters that clinicians and researchers can measure, assess, study, and report to better identify patients with sepsis at the highest risk. The septic shock definition and commonly associated clinical findings provide a means to

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understand and recognize patients with sepsis that have a form of sepsis that will require intensification of management to successfully treat.

As with our efforts to define sepsis, we intend that this systematic review is a first step on the path to data-driven definitions of sepsis and septic shock and to the validation of the criteria proposed to identify the animals at greatest risk of mortality. In the future, we hope that large veterinary databases will allow us to test these associations more fully. Consistent and comprehensive data collection and reporting by future sepsis studies will be necessary, and we have laid out the recommendations for clinical research settings clearly and separately in the accompanying summary document in the Supporting Information.

Our review has limitations. While systematic and thorough, our ability to draw strong conclusions, particularly for cats, was limited by the available evidence. Many studies were small, heterogeneous, or inadequately controlled, or did not provide all the data necessary to fully address our PICO questions. For Domain 2, we included populations of animals with documented sepsis; however, that was defined by the study investigators. Certainly, the illness severity in these studies varied, and some included animals would not meet the organ dysfunction criteria we now recommend. This may have blunted or obscured associations between potential prognostic indicators and survival. This makes further investigation of sepsis populations using the new sepsis consensus definition essential to solidly establish which parameters are consistent predictors of survival in a more homogenous population of severely affected dogs and cats. Despite these potential shortcomings, we hope that this systematic review enables clinicians to better identify and manage dogs and cats with septic shock and multiple organ dysfunction. We hope that clinical researchers can continue to build on the evidence base collated here to enhance prognostication and enable therapeutic strategies to be tested in severely affected animals, where the need is great and the potential for positive impact is substantial.

Author Contributions

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

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Disclosure

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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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