

Clinical trials in spontaneous disease in dogs: a new paradigm for investigations of sepsis

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Abstract

Objective: To provide evidence that naturally occurring sepsis in dogs provides a unique opportunity to test new therapies in clinically relevant settings.

Data sources: Human and veterinary literature.

Human data synthesis: Sepsis is a devastating condition responsible for most intensive care unit deaths. Most clinical trials targeting inflammatory mediators of sepsis have failed to improve outcome in clinical patients despite promising results in laboratory animal models. Animal models of sepsis fail to reproduce the clinical syndrome and therefore lead to conclusions that may not be relevant to clinical care.

Veterinary data synthesis: Sepsis is recognized but not well-characterized in companion animal species. Despite some species variability, the cardiopulmonary response to sepsis in dogs is similar to humans. Additionally, inflammatory and coagulation changes that accompany canine sepsis are consistent with those documented in humans. Sepsis secondary to canine parvoviral infection offers the advantages of relative population homogeneity, predictable course, and easy early diagnosis. The disadvantages of canine parvovirus are that it affects a predominantly young and healthy population and results in low mortality with aggressive supportive care. Septic peritonitis and pneumonia have high mortality but can be challenging to diagnose, have a variable course, and affect a heterogeneous population, which can be an advantage or a disadvantage.

Conclusions: Similar to trials currently being performed in canine cancer patients, veterinary clinical trials of new sepsis therapeutics may provide a unique opportunity to advance the treatment of sepsis in dogs, humans, and other species. Spontaneous sepsis from canine parvovirus, peritonitis, and pneumonia are common clinical conditions in which therapeutics can be tested.

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The Holy Grail of Curing Sepsis

Sepsis is not a specific disease entity but rather the systemic inflammatory response to infection.¹ Sepsis carries with it a high morbidity, high mortality, and high health care costs. Septic shock is a major cause of death in human intensive care unit (ICU).² Although the mortality rate associated with sepsis has decreased in the last 20 years, the total number of cases has increased.² In 2002, sepsis was the 10th most common

cause of human death in the United States.³ The serious economic and health impact of sepsis has resulted in numerous investigations to identify targeted treatment strategies. The history of potentially promising interventions can be traced back over 50 years to the early recommendations for the use of pharmacologic doses of corticosteroids in the treatment of sepsis.⁴ This intervention, like many of the ones that followed, was thought to be the Holy Grail. The dramatic effects of high-dose corticosteroids in animal models were compelling.⁵ It was only when clinical trials failed to show a benefit (and some showed an increased risk of mortality⁶) that the search moved to more glamorous agents, such as anti-endotoxin^{7–13} and anti-cytokine therapies.^{14–23} These agents also appeared to generate miraculous results in animal models^{24–27} but failed miserably in human clinical trials (Table 1).²⁸ After over 30 years of repeated disappointment, investigators started to

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Table 1: Agents that have failed in human sepsis clinical trials^{28,29}

Anti-endotoxin strategies
Antibodies ^{7–13}
Polymyxin B ³⁰
Mediator blocking strategies
Anti-tumor necrosis factor (TNF) ^{14–19}
Soluble TNF receptor ^{20,21}
Interleukin 1 receptor antagonist ^{22,23}
Platelet activating factor receptor antagonist ^{31–33}
Nitric oxide synthase inhibition ³⁴
Bradykinin inhibition ³⁵
Prostaglandin inhibition ^{36,37}
High dose glucocorticoids ^{38–42}
Immune enhancement
Granulocyte colony stimulating factor administration ⁴³
Coagulation inhibitors
Antithrombin administration ⁴⁴
Tissue factor pathway inhibitor administration ⁴⁵

question the value and appropriateness of animal models of sepsis.^{46–49}

Proposed explanations for the disparity between animal models of sepsis and clinical treatment of septic human patients highlight several key issues. The three main issues are faulty design of the intervention, unnatural experimental source of sepsis, and clinical relevance of the animal model.

Many of the original animal models of sepsis were designed to define the pathophysiology. As knowledge grew, the same models were used for preclinical evaluation of novel therapies. Over time it has become evident that many animal models of sepsis have substantial methodological shortcomings that limit application to clinical disease. For example, early recommendations for the use of high-dose glucocorticoids in sepsis stemmed from research studies in which treatment occurred before initiation of the septic insult.²⁹ The clinical trials of high-dose glucocorticoids, which relied on treatment after clinical signs of sepsis, failed to demonstrate a benefit (Table 1). While the information gained from such pre-treatment approaches is invaluable in defining the inflammatory and physiologic response during sepsis, the use of this methodology has limited clinical applicability. It is the rare instance in which a clinician can predict that a patient will develop sepsis and therefore implement pretreatment-based therapy. Therefore, a clinically relevant intervention must be effective and safe after clinical signs of sepsis are apparent.

Inflammatory mediators have frequently been classified as either good or evil, with the latter targeted for elimination. The erroneous nature of this philosophy became clear in the early human clinical trials of strategies directed against tumor necrosis factor α (TNF- α)

trials in which inhibition of TNF lead to a crippling of the immune response and severe complications from uncontrolled infections.²¹ Sepsis is a dynamic condition in which there are hyper-inflammatory phases and anti-inflammatory phases which are not mutually exclusive.^{50,51} Therefore, a simplistic approach of reducing inflammation without knowing the stage or inflammatory milieu of sepsis could lead to benefit, harm, or no effect at all.

The characterization of the patient response and selection of appropriate therapy based on a panel of biomarkers is a trend in clinical management of sepsis.⁵² In fact, the positive outcome of a recent anti-TNF trial was based on identifying and treating patients with elevated interleukin (IL)-6.⁵³ This approach is one of the first to implement the use of IL-6 as a biomarker to identify patients in the hyperinflammatory phase of sepsis that might benefit from a specific anti-inflammatory treatment strategy. Classification schemes like the systemic inflammatory response syndrome (SIRS)¹ are recognized as overly simplistic for such a complex and variable syndrome as sepsis. New classification recommendations account for the array of factors that influence outcome in clinical sepsis in humans.⁵² Although elevated IL-6 at 6 hours after intra-abdominal infection was shown to be a reliable predictor of mortality in mice,⁵⁴ these classification strategies and implementation of biomarkers are often impractical or overlooked in animal studies. A further potential limitation of many experimental animal models is that they are extremely homogeneous, which allows high reproducibility. Although sound science requires repeatable and consistent results, this approach is not representative of the highly variable clinical syndrome. The challenge is to identify which patient will benefit from which treatment observed in which experimental model.

The early sepsis models were among the most reproducible and least representative of clinical disease. Indeed, rather than models of sepsis, they were models of endotoxemia.⁵⁵ Animals were given an injection, typically as a bolus, of lipopolysaccharide (LPS). Intravenous injection of this gram-negative bacterial cell wall component produces rapid and reproducible signs of septic shock. While a valuable tool for defining the progression of an inflammatory response, this approach is not clinically relevant (except in rare and bizarre cases⁵⁶). Most causes of clinical sepsis are the result of bacterial infections. These live bacteria continue to proliferate if not appropriately treated and trigger the release of a multitude of inflammatory mediators. The use of live bacteria to create the model of sepsis is clearly much more relevant to the clinical scenario than use of bacterial products such as LPS.

The route of exposure to the bacterial insult also influences the response and may therefore impact the model.⁴⁷ A sudden intravenous exposure to bacteria or their products is unusual in natural infections. More typically, local defenses are overwhelmed gradually and inflammation smolders before bursting into a full systemic response. To achieve reproducible results, known amounts of bacteria may be injected into the peritoneum or trachea. While such administration of live bacteria is more similar to the clinical situation, clinical sepsis is most often the result of a breakdown of the normal host barrier to infection.⁴⁷ Aberrations of the host defenses can result from loss of intestinal integrity, immune suppression, tissue damage, and other risk factors such as hospitalization and placement of catheters or other devices that bypass or overwhelm the normal defenses.

The most frequently reported source of sepsis in humans is the respiratory tract followed by the gastrointestinal tract,⁵⁷ whereas in dogs, the gastrointestinal tract is the most common source.⁵⁸ Most gastrointestinal sources of sepsis are created by the host's own endogenous flora; therefore, in the late 1970s, a group of trauma surgeons developed a model of intra-abdominal sepsis in the mouse. This surgical model combines ischemia of the cecum through ligation at its base followed by penetration of the cecum with a hypodermic needle to allow leak of cecal contents into the abdomen.⁵⁹ Although within a laboratory, the technique is highly reproducible based on the size of the hypodermic needle and number of perforations, there is variation across investigators. The popularity of this model of intra-abdominal sepsis stems from the endogenous source of infection, moderately high level of reproducibility, and the prolonged duration of the response with hemodynamic and metabolic responses similar to human clinical sepsis.^{59,60}

Although cecal ligation and puncture (CLP) in mice is currently the gold standard for sepsis research, this model has important limitations. Species, strain, gender, age, and size of the animals are important to the relevance of any sepsis study.^{48,49,60-63} The small size of rodents makes serial sampling and cardiopulmonary monitoring difficult. The question of scale must always be considered, does a drug dose increase linearly with increasing size? Not only is there a question of size, but the influence of life span may also impact interpretation. In addition, laboratory rodents are highly inbred, making them genetically similar.⁶⁴ The recent interest in the genetic predisposition to sepsis in humans⁶⁵ would not play a significant role when using inbred rodent strains.

Another important factor is the gender difference between animal models and clinical sepsis; premeno-

pausal women are more resistant to complications of trauma-induced sepsis.⁶⁶ The effects of estrogen are typically not included in animal studies of sepsis, since most studies are performed on juvenile male rodents. The impact of age is also potentially important. Most human cases of sepsis occur in the elderly.² Aging is associated with alterations in the inflammatory response⁶⁷ and as a result treatment of elderly septic patients may be different than treatment of younger patients. In fact, the beneficial effects of activated protein C in the PROWESS study were demonstrated in elderly patients⁶⁸ and experimental CLP studies in mice with normal or reduced protein C (i.e., mutant mice heterozygous for the protein C gene) demonstrated that lack of protein C increased mortality in old mice, but not young mice.⁶⁹ The benefit of activated protein C in sepsis in pediatrics and other demographic groups is still debated.⁷⁰

Interestingly, although rodents are the most commonly used animals for studies of sepsis, compared with humans, baboons and dogs, mice and rats are highly resistant to endotoxin.⁷¹ Baboons have been promoted as a highly relevant species to investigate the response to sepsis and much of the seminal work was performed in baboons.⁶³ There are, however, many constraints in the use of baboons.⁴⁹ Canine laboratory models of sepsis are known to share the early hyperdynamic cardiovascular response to sepsis with humans and this response can be observed and documented.⁷² Similarities between dogs and humans in the later response to sepsis are not well documented. Although dogs have several beneficial features that make them excellent experimental models for sepsis,⁷³ the use of dogs in research has fallen out of favor. This move away from canine models may be due to the increased awareness of the human-canine bond as well as the high costs associated with large animal species. Canine experimental models such as the fecal peritonitis model used by Natanson's group^{72,73} also shares many of the drawbacks of other laboratory models⁴⁶ including the need for anesthesia and the artificial nature of the insult. It is possible to capitalize on the information that can be gained from canine sepsis without artificially creating disease in dogs. Information derived from spontaneous diseases that lead to sepsis in dogs can lead to a new understanding of sepsis in animals and humans.

Naturally occurring parvovirus-, peritonitis-, and pneumonia-induced sepsis in dogs fulfill many of the criteria necessary to be a clinically relevant model of human sepsis (Table 2). In general, sepsis in dogs parallels the human syndrome and leads to coagulopathy, multiple organ failure, acute respiratory distress syndrome (ARDS), and death.^{58,74-76} The septic origin is often diverse and the evolving inflammation may result

Table 2: Criteria for clinically relevant models of sepsis⁴⁶

Natural route of infection
Treatment is initiated after development of clinical signs
Appropriate adjunctive care is provided
Target outcome is survival
Genetic, gender and age diversity

in complex metabolic and hemodynamic abnormalities. Dogs that are brought to veterinary hospitals with diseases associated with naturally occurring sepsis are genetically and gender diverse, and the goal of the intervention is survival. Dogs, like humans, are treated for sepsis with appropriate supportive care, such as fluids, antibiotics, and if indicated, surgery. Dogs, however, lack the complicating factors of drug and alcohol addiction, which can influence the incidence of sepsis and the outcome,^{77,78} whether this is an advantage or disadvantage for canine clinical trials is not known.

Translational medicine, defined as the application of basic science (i.e., the 'bench') to clinical problems (i.e., the 'bedside'), is a concept promoted by the National Institutes of Health (NIH) to increase the impact of basic research on management of clinical disease.^a Veterinary clinical trials represent an excellent mechanism to translate research information into clinical practice. Translational clinical trials are conducted in many veterinary oncology centers and are currently receiving significant attention.^{79,80} These trials are subject to the same oversight and regulation as human clinical trials. They require institutional approval and owner consent. Drugs or devices that are being tested in client-owned animals must meet safety requirements in that species. The proper implementation of veterinary clinical trials offers the opportunity to improve or subsidize patient care, advance veterinary medicine, and benefit human health.

Canine Sepsis

Regardless of the species, sepsis is defined as the presence of the systemic inflammatory response to an infectious agent.¹ Sepsis is a syndrome that spans a wide range of disease processes. In dogs, there are well-defined diseases like parvovirus that lead to bacterial translocation, bacteremia, and endotoxemia in a predictable pattern.^{76,81,82} There are also more heterogeneous manifestations of sepsis as seen with peritonitis and pneumonia. Each of these conditions provides a potential opportunity to investigate aspects of treatment or disease progression.

In 1978, a new pathogenic virus emerged in dogs, canine parvovirus (CPV), resulting in fatal hemorrhagic diarrhea and leukopenia.⁸³ Parvovirus primarily affects

puppies between 6 weeks and 6 months of age.⁸³ The Ryan Veterinary Hospital at the University of Pennsylvania treats approximately 150 cases of CPV each year. Currently, treatment of CPV is limited to supportive care, fluid therapy, and antibiotics.⁸⁴ Even though the initial insult in CPV is viral, the mortality is associated with bacterial translocation, *Escherichia coli* septicemia, a systemic inflammatory response, and shock.^{76,81,82,85} Therefore, CPV represents a disease with intestinal-origin sepsis, and clinical trials in this population may provide information about sepsis that originates from primary epithelial barrier compromise or intestinal ischemia.

Several clinical aspects of CPV have been characterized⁸⁴ and clinical trials have been reported in this population.⁸⁶⁻⁹¹ In a double-blinded randomized trial of 40 dogs with CPV, plasma endotoxin, as measured by a modified version of the QCL-1000 quantitative chromogenic *Limulus* Amebocyte Lysate (LAL) Assay,^b was significantly higher in dogs with CPV than in either healthy puppies or the CPV dogs at 30 days after recovery.⁸⁸

The initiation of the inflammatory cascade through endotoxin binding to its circulating binding protein (LBP) interacting with the surface receptor CD-14 leading to activation of the Toll-like receptor (TLR) 4 results in increases in TNF and other cytokines.⁶⁵ In acute endotoxin exposure, TNF is an early and often transient marker.⁹² In human sepsis studies, plasma TNF is not consistently detected.^{93,94} The variability in measurable TNF response is thought to be a result of predominantly local production, short half-life, and the presence of circulating inhibitors.⁹⁵ In one clinical CPV study, plasma TNF activity was present in 7 of 17 dogs. In that study, there was a significantly increased risk of mortality with increasing TNF ($P = 0.041$).

The recently recognized genetic predisposition to sepsis in humans⁶⁵ may also apply to dogs. It is well recognized that some breeds (e.g., Doberman Pinschers, Rottweilers, and Pit Bulls) are more severely affected or more likely to contract CPV.^{96,97} Some breeds may be predisposed to an increased pro-inflammatory response.⁹⁸ In one study, 4/5 Rottweilers with CPV had measurable endotoxin but none had measurable TNF. There were no Doberman Pinschers in that study. The failure to demonstrate an increased pro-inflammatory response in Rottweilers may have resulted from differences in disease severity, timing, and local *versus* systemic production of inflammatory mediators.

One distinct advantage of evaluating new therapies for sepsis in clinical trials conducted in dogs with parvovirus is the ease of diagnosis. The diagnosis of parvoviral enteritis is based on the presence of clinical

signs and, in most cases, the diagnosis can be confirmed by with a cage-side ELISA assay for CPV antigen in the patient's feces.⁸⁴ In humans and other canine conditions associated with sepsis, even though the clinical suspicion may be high, confirmation of the diagnosis of sepsis is often delayed until culture results are available. The resulting delay in patient enrollment may contribute to failure to demonstrate a treatment benefit in some trials. The rapid ability to diagnose CPV could also be considered a disadvantage in that dogs would be enrolled into treatment studies more rapidly than humans might be. This concern, however, can be balanced by the variable duration of clinical signs prior to presentation to the hospital.

A major shortcoming of enrolling dogs in clinical trials of agents for the treatment of sepsis is the lack of a validated canine scoring system to document severity of acute illness. Similar to the lack of sensitivity and specificity in humans, the use of SIRS criteria to stratify dogs with CPV does not appear to be useful. Depending upon which criteria are applied, 84% of dogs in one retrospective study⁹⁷ would have fulfilled the criteria of Hauptman,⁹⁹ whereas if the more stringent criteria of Okano¹⁰⁰ were applied, only 29% of cases would have been diagnosed with SIRS. In a prospective observational study of 3,708 human patients in a tertiary care ICU and medicine ward, 68% met 2/4 SIRS criteria, however only 26% of those developed clinical sepsis, and only 4% developed septic shock.¹⁰¹ Consistent with the low incidence of septic shock in human SIRS patients, in the retrospective study of 77 CPV positive dogs of which 49% met 2/3 (WBC counts were omitted due to inconsistent availability) SIRS criteria (heart rate >140 beats/min; respiratory rate >30 breaths/min; temperature >39.2 °C [102.5 °F] or <37.8 °C [100.0 °F]), no individual or combination of SIRS criteria was able to predict mortality or duration of hospitalization.⁹⁷ Non-survivors, however, were more likely to meet 2/3 criteria for a greater percentage of their hospitalization, suggesting that failure to resolve the metabolic derangements of SIRS may be a negative prognostic indicator and those may have been the dogs more likely to progress to septic shock.⁹⁷

Biomarkers to evaluate the systemic response to CPV may be useful in developing a scoring system. Endotoxemia is known to result in activation of the coagulation cascade. Recent studies of activated protein C have clearly shown an interaction between inflammation and coagulation.⁶⁸ Early sepsis is associated with a hypercoagulable state that historically has been difficult to diagnose due to the lack of available laboratory tests. Thrombelastography (TEG) is a tool that can identify hypercoagulable states.¹⁰² In a small prospective study, 9/9 dogs with CPV had TEG evidence

of hypercoagulability.¹⁰³ Additionally, compared to age-matched controls, dogs with CPV had hyperfibrinogenemia, low antithrombin activity, and prolongation of the activated partial thromboplastin time.¹⁰³ Although additional studies are necessary to determine if any of these biomarkers can predict morbidity or mortality, 5/9 dogs with evidence of hypercoagulability did develop thrombotic complications.¹⁰³

In reports of treatment of dogs with CPV at a tertiary care hospital, median duration of hospitalization was 6 days and survival was 92–96%.^{88,97} An aggressive approach to supportive care may be a predictor of outcome because dogs treated at primary care facilities had a 67%⁸⁸ to 75%¹⁰⁴ survival. In humans, early aggressive intervention has been associated with improved survival.¹⁰⁵

Clinical trials in dogs with CPV have been successfully performed. In addition to numerous observational studies^{81,103,104,106,107} and at least one uncontrolled clinical trial in this population of dogs,⁸⁶ there have been several randomized controlled clinical trials^{87–90} of which 2 were blinded and placebo controlled.^{88,90} These clinical trials have addressed interventions directed at the initiating viral insult, at the secondary bacteremia, or at supportive care. The investigation of feline interferon ω for enhanced antiviral activity is one such trial. In a randomized, double-blinded, placebo-controlled trial in France, survival was improved with this therapy.⁹⁰ A similar randomized, controlled double-blinded study failed to demonstrate benefit in a US trial, however, the dose tested was lower and the overall survival was higher (unpublished data). Of the investigations of anti-endotoxin agents,^{86,88,104} only one was conducted as a randomized double-blinded, placebo-controlled trial.⁸⁸ This trial investigated a recombinant form of bactericidal permeability increasing (BPI) protein. In this limited group of dogs (20 in each group), the treatment failed to demonstrate a benefit to morbidity or mortality. In a human clinical trial in which 190 children with meningococemia received BPI, the study failed to demonstrate a significant survival effect.¹⁰⁸ In a randomized controlled trial of granulocyte-colony stimulating factor (G-CSF) in dogs with parvovirus, no benefit on white blood cell count or outcome was identified.⁸⁷ These findings are consistent with those reported from a large multicenter trial of G-CSF in humans with pneumonia and severe sepsis.⁴³ Failure of similar trials in both dogs and humans, however, does not prove that the CPV model is relevant to human sepsis. Further investigation is warranted to determine if trials in dogs with CPV can be used to screen novel sepsis therapies before embarking on human clinical trials.

Evaluation of supportive care strategies can also be tested in dogs with CPV. Early enteral nutrition,

particularly with immune-modulating components has been the subject of extensive debate in critical care circles. Dogs with naturally occurring sepsis may provide an excellent model to address some of the persistent questions. In a randomized controlled trial of early enteral feeding in dogs with parvovirus, earlier resolution of clinical signs and a reduction in some markers of intestinal permeability, but no effects on outcome were documented.⁸⁹ Future studies in dogs with naturally occurring sepsis could address the role of disease severity and specific immunomodulating components on markers of inflammation and outcome.

Although CPV has several advantages for clinical trials of sepsis, there are also certain constraints associated with this disease if it were to be used as the only model for sepsis. The advantages are that it meets most of the criteria for a clinically relevant model of sepsis (Table 2). In addition, CPV is easily diagnosed, it has a highly predictable course, and many of the physiologic responses have been characterized. In human sepsis trials, one major limitation is the inability of critically ill (i.e., unconscious) patients to sign informed consent forms. Even if the dog is unconscious, the owner is capable of making the informed decision about enrolling their pet in a clinical trial. The primary limitation of CPV for sepsis trials is that with aggressive supportive care, the survival rate reaches over 90%. Therefore a trial to demonstrate an improvement in outcome would require large numbers of dogs. In the BPI trial, it was estimated that over 300 dogs would be required to confidently demonstrate that BPI did not provide a survival advantage over standard care.⁸⁸ Improvement in morbidity (i.e., duration of hospitalization) may be a more appropriate outcome in CPV trials. Other intermediate outcome parameters (i.e., serum biomarkers) might be able to demonstrate benefit; however, the relatively small size of puppies may preclude frequent blood sampling. Another limitation that might prevent direct broad translation to human sepsis is that the affected dogs are immature, whereas most human sepsis cases occur in older adults. Additionally, the CPV-induced leukopenia may influence the immune response or at least make white blood cell count an unreliable marker of SIRS.

Although CPV is one canine disease that can be of value in testing new therapeutic strategies for sepsis, there are other common septic conditions that might be considered for additional or complementary clinical trials. Septic peritonitis is the most commonly reported cause of sepsis in dogs.⁵⁸ There have not been any published veterinary clinical trials in this population of dogs. The majority of septic peritonitis studies have focused on surgical interventions.^{109–112} This population of dogs is more heterogeneous than dogs with CPV.

The cause of peritonitis may be intestinal perforation due to foreign bodies, ulcers or tumors, trauma, intra-abdominal abscesses, or infection associated with the reproductive tract.^{109–112} Typically, dogs with peritonitis are older, on average between 5 and 7 years of age.^{75,109–112} The diagnosis of peritonitis may also be more difficult than CPV.¹¹³ Bacterial pneumonia is even more heterogeneous and can be more challenging to diagnose. There are no reported veterinary clinical trials for the treatment of sepsis associated with pneumonia. Community-acquired pneumonia may be more common in young dogs and has a relatively low mortality rate.¹¹⁴ Pneumonia from aspiration or immune suppression is typically found in older dogs and perhaps, similar to human cases, mortality is commonly influenced by underlying disease.¹¹⁵ Many human patients develop ARDS secondary to pneumonia or sepsis.¹¹⁶ Similarly, pathologic evidence of ARDS has also been reported in dogs with parvovirus, pneumonia, and sepsis.^{74,76} Clinical trials in these spontaneous diseases can be tailored to address important questions. The relatively homogeneous, low-mortality disease CPV may be valuable for evaluating biomarkers and impact of new treatment on morbidity. Mortality benefits are likely to be more obvious in the population of dogs with peritonitis or pneumonia. The heterogeneity of these conditions allows for translation to broader clinical situations, but it necessitates severity of illness scoring for staging disease and to allow comparison between treatment groups.

Conclusions

Sepsis is a syndrome with increasing incidence, high mortality, and astronomical expense in humans and companion animals. Despite all of the medical advances, current therapy for sepsis, in most cases, regardless of the species, is limited to supportive care. New therapeutic options are essential, however the cost of development and failure to show therapeutic benefit in most human clinical trials are intimidating realities. A population of animals with a spontaneous and parallel disease that results in a predictable septic insult, such as CPV, and more heterogeneous conditions such as septic peritonitis and bacterial pneumonia will provide important screening tools to determine which therapies should be taken into human clinical trials and can also be used effectively for treatment of dogs with sepsis.

Incorporation of spontaneous canine sepsis into a preclinical screening strategy of therapies for human sepsis can have multiple benefits. Drug companies will be able to obtain valuable information unavailable from laboratory studies. The extensive financial and public relations costs of failed trials may be avoided. Physi-

cians will have increased confidence in therapies that proceed into clinical trials. Veterinarians will be able to increase their level of patient care and advance the knowledge of sepsis therapy. Both humans and animals with sepsis will benefit from drugs developed. In summary, spontaneous canine sepsis represents a logical, clinically relevant, cost-effective model for evaluation of therapies for sepsis for all species.

Footnotes

^a <http://nihroadmap.nih.gov>

^b QCL-1000 quantitative chromogenic *Limulus* Amebocyte Lysate Assay, BioWhittaker Inc., Walkersville, MD.

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