

## Multiple Organ Dysfunction Syndrome in Humans and Animals

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Multiple organ dysfunction syndrome (MODS), defined as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention, is a cause of high morbidity and mortality in humans and animals. Many advances have been made in understanding the pathophysiology and treatment of this syndrome in human medicine, but much still is unknown. This comparative review will provide information regarding the history and pathophysiology of MODS in humans and discuss how MODS affects each major organ system in animals.

**Key words:** Acute respiratory distress syndrome; Disseminated intravascular coagulation; Multiple organ failure; Sepsis.

**M**ultiple organ dysfunction syndrome (MODS) is defined as “the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.”<sup>1</sup> In people, MODS is most commonly a sequela to severe sepsis or septic shock, but it also develops secondary to trauma, neoplasia, or other causes of the systemic inflammatory response syndrome (SIRS). The exact incidence of MODS in people is difficult to estimate because there is no true consensus for the definition of dysfunction in each individual organ system<sup>2</sup>; but it has been estimated that 15% of all people admitted to the intensive care unit (ICU) will develop MODS.<sup>3,4</sup> Mortality rates for surgical and medical ICU patients with MODS range from 44 to 76%.<sup>5</sup> A reported incidence of MODS in dogs is approximately 4% with trauma and approximately 50% with sepsis; in both cases MODS is associated with a poor outcome.<sup>6,7</sup> This comparative review will outline the history and pathophysiology of MODS, discuss similarities and differences in the epidemiology of MODS in humans and animals and review how MODS manifests itself in each organ system.

### History

Multiple organ dysfunction syndrome is a relatively new concept in both human and veterinary medicine and it has been described as an iatrogenic disorder.<sup>8</sup> Application of advanced medical knowledge and technology has allowed people and animals to survive initial insults that at one time would have been fatal so relatively long-term sequela like MODS can be manifested. The 1st reports of individual forms of organ dysfunction were during World War II and the

### Abbreviations:

ACTH	adrenocorticotropin hormone
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine transaminase
ARDS	acute respiratory distress syndrome
ATP	adenosine triphosphate
CARS	compensatory anti-inflammatory response syndrome
CIRCI	critical illness-related corticosteroid insufficiency
DAMP	danger-associated molecular pattern
DIC	disseminated intravascular coagulation
FDP	fibrinogen degradation product
GFR	glomerular filtration rate
HMGB-1	high-mobility group box-1
ICU	intensive care unit
IL	interleukin
LPS	lipopolysaccharide
MODS	multiple organ dysfunction syndrome
MPT	mitochondrial permeability transition
NO	nitric oxide
PAMP	pathogen-associated molecular pattern
PT	prothrombin
PTT	partial thromboplastin
SAE	sepsis-associated encephalopathy
SIRS	systemic inflammatory response syndrome
TNF	tumor necrosis factor

Vietnam War when improved resuscitation techniques allowed soldiers to survive the initial battlefield injury only to go on to die from renal failure or respiratory failure (ie, Da Nang Lung or Vietnam Lung).<sup>9</sup> In 1969, multiple organ dysfunction was first reported in 8 people with acute gastric ulcerations and sepsis that developed a clinical syndrome associated with respiratory failure, hypotension, and icterus.<sup>10</sup> Similarly, in a 1973 retrospective study of 18 people with abdominal aortic aneurysms, 17 died from sequential multiple organ dysfunction starting with pancreatic and pulmonary failure which progressed to cardiac and upper gastrointestinal hemorrhage. In these patients, pulmonary failure was considered to be the primary cause of death.<sup>11</sup> As life-support technology continued to improve, the incidence of multiple organ dysfunction secondary to infectious<sup>10,12–14</sup> and noninfectious<sup>15–17</sup> diseases became increasingly more common.

In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine held a

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consensus conference to develop definitions for clinical syndromes including MODS with the goal of improving disease detection, and to allow early therapeutic intervention and patient stratification in clinical trials.<sup>2</sup> The syndrome of multiple organ dysfunction and failure that had been described over the previous 20 years was officially termed “MODS.” The term “failure” was excluded from the name because it implied an absolute presence or absence of function as opposed to a continuum. MODS was defined as the “presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.”<sup>2</sup> Furthermore, MODS was described as a primary process in which the organ dysfunction could be directly attributable to the insult itself or as a secondary process in which the organ dysfunction was a consequence of the systemic response to a distant insult. Specific criteria for clinical identification of MODS were not described.<sup>2</sup>

### Epidemiology

Sepsis is the most common inciting cause of MODS in people, and MODS is more common in people with sepsis compared to other forms of critical illness (75% versus 43%).<sup>18</sup> In 1995, it was estimated that 9.3% of all human deaths in the United States were related to severe sepsis with a total healthcare cost of \$16.7 billion dollars.<sup>5</sup> The incidence of sepsis has increased over time. In a review of 750 million hospitalizations, there was an annualized increase in the episodes of sepsis from 82.7 episodes/100,000 hospital admissions in 1979 to 240.4 episodes/100,000 hospital admissions in 2000.<sup>19</sup>

There is a limited amount of information regarding the epidemiology of MODS in animals, although sepsis and trauma appear to be common inciting causes. A multicenter report of 114 dogs treated surgically for abdominal sepsis found 78% of dogs had dysfunction of  $\geq 1$  organ systems and 50% had dysfunction of  $\geq 2$  organ systems.<sup>6</sup> In a smaller study of dogs with abdominal sepsis, 5/14 (35.7%) met the criteria for MODS.<sup>20</sup> A retrospective study of 235 dogs with severe blunt trauma reported MODS in 4% of dogs.<sup>7</sup>

### Pathophysiology

The pathophysiology of MODS is complex, multifactorial, and poorly understood. Three models to explain the initiation of MODS have been proposed. The first is the “one-hit” model in which organ failure develops as the direct result of a massive initial insult, such as sepsis, polytrauma, or burn injury. The 2nd model, or the “two-hit” model, describes a priming insult (1st “hit”) which is followed by a subsequent insult (2nd “hit”). The subsequent insult may seem small, such as a catheter-related infection, and it induces enhanced inflammation and immune dysfunction. An experimental “two-hit” canine model of MODS has been described and involves hemorrhagic shock followed by *Escherichia coli* endotoxin given

IV.<sup>21</sup> The 3rd model is known as the “sustained-hit model.” This model describes a continuous insult such as ventilator-associated pneumonia which causes both the initial insult and sustains the dysfunction.<sup>22</sup>

The current understanding of the pathophysiology leading to MODS involves intricate cross-talk among multiple cell populations, hormonal systems, metabolites, and neural signaling along with alterations in oxygen delivery, derangements in oxygen utilization, and modifications in cell phenotypes. There are several proposed mechanisms for the development of MODS including (1) cell or tissue hypoxia, (2) induction of cellular apoptosis, (3) translocation of microbes or components of microbes from the gastrointestinal tract, (4) immune system dysregulation, and (5) mitochondrial dysfunction. Although MODS likely results from a complex combination of these factors and others yet to be identified, emerging evidence suggests that immune system dysregulation and subsequent mitochondrial dysfunction might be the prevailing pathways.<sup>23</sup> The following sections will describe immune system dysregulation and mitochondrial dysfunction in greater detail.

### Immune System Dysregulation

Immune system dysregulation is the imbalance between proinflammatory and anti-inflammatory counterregulatory mechanisms.<sup>24</sup> To maintain normal homeostasis, the innate immune system is designed to respond rapidly to danger signals including pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). PAMPs are a diverse set of microbial molecules that share a number of different recognizable biochemical features that alert the organism to the invading pathogen. DAMPs are similar to PAMPs, but they are markers of endogenous cell damage.<sup>25</sup>

Pathogen-associated molecular patterns and DAMPs are identified by the innate and adaptive immune systems, most commonly via toll-like receptors, which then activate signaling pathways to incite inflammation.<sup>25</sup> Once activated, first responder cells of the innate immune system (predominantly macrophages) produce proinflammatory cytokines (eg, tumor necrosis factor [TNF]- $\alpha$ , interleukin [IL]-1 $\beta$ ). These early cytokines stimulate the synthesis of other inflammatory mediators and result in the activation of other leukocytes.<sup>23</sup> Late inflammatory mediators (eg, high-mobility group box-1 [HMGB-1], IL-6) provide signaling for ongoing inflammation as appropriate.<sup>23</sup>

In response to the production of proinflammatory cytokines, anti-inflammatory cytokines (eg, IL-10) are produced to help maintain immune system balance, known as the compensatory anti-inflammatory response syndrome (CARS). The purpose of CARS is to limit the damage caused by the proinflammatory response while not interfering with pathogen elimination. CARS can be detrimental and lead to immune system dysregulation when its effects are overexaggerated or poorly timed. An unchecked CARS response

can lead to a phenomenon known as “immunoparalysis,” which leaves the host vulnerable to further injury and infection.<sup>26–28</sup>

Neutrophils are also major contributors to the pathogenesis of innate immune dysregulation. Neutrophil priming by cytokines (eg, TNF- $\alpha$ ) leads to alterations in cell surface protein expression, interaction with vascular endothelium, trafficking to various extravascular sites, and production of superoxides.<sup>29</sup> Neutrophils undergo downregulation of apoptotic pathways during inflammation resulting in relative neutrophil “immortality.” This sets up a scenario in which neutrophils infiltrate tissues, produce superoxides, and induce tissue damage. These changes result in the perpetuation of inflammation through various pathways, including release of HMGB1 from damaged cells.<sup>30</sup>

### *Mitochondrial Dysfunction*

Mitochondrial dysfunction and the resultant cytopathic hypoxia also may be key in the pathogenesis of MODS. Neutrophils contribute to relative cellular dysfunction by activating mitochondrial dysfunction pathways. Superoxide from neutrophils along with nitric oxide (NO) production from vascular endothelium combine to form peroxynitrite. Peroxynitrite causes inhibition of several aspects of mitochondrial respiration and mitochondrial synthesis of ATP by activating the enzyme poly-(ADP-ribose) polymerase.<sup>31</sup> Oxidative stress and proinflammatory cytokine signaling lead to uncoupling of oxidative phosphorylation via mitochondrial permeability transition (MPT). In MPT, a pore is opened in the inner mitochondrial membrane which allows an inappropriate proton gradient within the mitochondria and uncoupling of oxidation from phosphorylation.<sup>32,33</sup> These acquired intrinsic derangements in cellular energy metabolism during MODS are referred to as cytopathic hypoxia.<sup>34</sup> The concept of cytopathic hypoxia was developed to explain the disconnect between adequate oxygen delivery and poor utilization of oxygen at the tissue level.<sup>32</sup>

When mitochondrial energy production is decreased because of cytopathic hypoxia, the result is cellular dysfunction and, in some cases, cell death. Mitochondrial dysfunction has been documented during sepsis-induced MODS in people with naturally developing sepsis and in experimental models.<sup>35–37</sup> Pharmacologic inhibition of mitochondrial derangement prevents the development of MODS in experimental bacterial sepsis indicating that mitochondrial damage is a causative factor in the development of MODS and thus could be a therapeutic target.<sup>38</sup>

Although generally viewed as “bad” clinically, downregulation of mitochondrial function might be a cellular adaptive response to prolonged inflammation.<sup>39</sup> In general, cell death (necrosis) is not a common finding in people with MODS. Instead, it appears that mitochondrial dysfunction causes a transient decrease in cellular activity that can return when the animal recovers. This phenomenon has been referred to as a cellular hibernation-like state. However, if this

phenomenon occurs for too long, irreversible organ damage may result.<sup>23</sup>

## **Individual Organ System Dysfunction**

Several different forms of organ dysfunction have been recognized in people and animals during sepsis and other inflammatory states. The predominant organ systems involved in MODS and those characterized clinically are the hepatic, respiratory, gastrointestinal, cardiovascular, coagulation, renal, central nervous, and endocrine systems.<sup>40</sup> These forms of organ dysfunction are discussed in detail below.

### *Hepatic Dysfunction*

Hepatic damage caused by sepsis or other forms of SIRS typically is divided into primary and secondary stages.<sup>41</sup> In the primary stage, septic shock results in hepatic hypoperfusion leading to decreased protein synthesis, lactate clearance, gluconeogenesis, and glycogenolysis. Hypoglycemia results from decreased gluconeogenesis and glycogenolysis. Blood concentrations of aminotransferases increase as the result of hepatocellular leakage and coagulopathy may become clinically apparent.<sup>42</sup> The secondary stage of hepatic dysfunction results from Kupffer cell activation and subsequent production of proinflammatory cytokines, chemokines, reactive oxygen species, and NO leading to further liver damage and dysfunction.<sup>43</sup>

In the context of MODS, hepatic dysfunction often is defined as hyperbilirubinemia in the absence of pre-existing liver disease. Other definitions such as increased blood concentrations of alanine transaminase (ALT) or alkaline phosphatase (ALP) or the presence of hepatic encephalopathy are sometimes used. These definitions make it difficult to assess the overall incidence of hepatic dysfunction in people and small animals and to compare the incidence of hepatic dysfunction among various studies.<sup>44</sup> Hepatic dysfunction is an inconsistent predictor of mortality in people and dogs with MODS.<sup>6,44–49</sup> The incidence of hepatic dysfunction in people in the ICU approached 11% in 1 multicenter prospective study of critically ill patients. The incidence of hepatic dysfunction, when classified by increases in ALT and ALP or bilirubin concentration in dogs with sepsis ranges from 33 to 72%.<sup>6,50,51</sup>

### *Respiratory Dysfunction*

Acute respiratory distress syndrome (ARDS) is 1 manifestation of respiratory dysfunction in people and animals. ARDS can result from 2 different pathways: (1) direct pulmonary causes (eg, bacterial or aspiration pneumonia, lung contusions, inhalation injury) or (2) indirect causes (eg, sepsis, pancreatitis, trauma, burns, blood transfusions [transfusion-associated acute lung injury]).<sup>52–59</sup> ARDS is characterized by neutrophil infiltration of the lung, alveolar-capillary barrier damage, pulmonary vascular leakage, and alveolar and systemic release of proinflammatory cytokines.

Alveolar–capillary barrier damage and increased vascular permeability result in pulmonary edema while the production of cytokines perpetuates inflammation, promotes atelectasis, and causes structural damage to the type I alveolar pneumocytes.<sup>60,61</sup>

Acute respiratory distress syndrome has been associated with a 4-fold higher risk of in-hospital mortality in people.<sup>62</sup> Mortality rates for ARDS in people are difficult to accurately estimate because of the variability in diseases that cause ARDS, but range from 15 to 80% with no difference in overall mortality between direct and indirect causes of ARDS.<sup>52,63</sup> Survival rates of ARDS in veterinary medicine are thought to be lower than in human medicine, although it is difficult to estimate the true survival rate because of the influence of economic or philosophical confounding variables. In addition, there is limited information available pertaining to ARDS-specific mechanical ventilation in small animals. Description of successful management of dogs with ARDS has been limited to case reports and case series.<sup>64–66</sup> In a retrospective study of dogs and cats that required mechanical ventilation, 12/73 met the criteria for the diagnosis of ARDS and only 1 survived.<sup>67</sup>

### **Gastrointestinal Dysfunction**

Gastrointestinal dysfunction is described in people and animals as hyporexia or anorexia, inability to tolerate enteral feedings, decreased intestinal motility, hemorrhagic diarrhea, increased intestinal permeability, and bacterial translocation.<sup>68–70</sup>

Bacterial translocation often is discussed in the context of MODS and can be defined as the process by which intestinal bacteria or *Candida* cross the intestinal mucosal barrier to reach mesenteric lymph nodes.<sup>71</sup> The principal mechanisms thought to be responsible for bacterial translocation are an alteration in the normal gastrointestinal flora and physical disruption of the gut mucosal barrier.<sup>72</sup> After a severe insult such as polytrauma or cardiac arrest, the gut flora (including obligate anaerobes and *Lactobacillus*) is destroyed immediately and the number of intestinal pathogenic bacteria gradually increases.<sup>73</sup> Destruction of gut flora is detrimental because these commensal organisms are an important defense against pathogenic bacteria colonization and thus aid in the prevention of bacterial translocation.<sup>74</sup>

Bacterial translocation after physical disruption of the gut mucosal barrier is thought to be caused by inflammatory mediator, endotoxin, and NO-induced changes in and decreased production of tight junction proteins.<sup>75</sup> Dogs and cats with experimentally induced endotoxemia have significantly increased gastrointestinal mucosal permeability when compared to control animals.<sup>76</sup> Cats also exhibit jejunal epithelial necrosis and neutrophil infiltration.<sup>76,77</sup>

In addition to barrier dysfunction, sepsis also causes changes in gastrointestinal motility and absorption of nutrients. Endotoxin given IV to dogs causes a decrease in the number and strength of jejunal

contractions as well as decreased net absorption of water, electrolytes, and glucose from the jejunum,<sup>78,79</sup> decreased colonic absorption of water and sodium,<sup>80</sup> and increased colonic motility and contractions.<sup>81</sup> These changes can lead to diarrhea, dehydration, and electrolyte abnormalities. If severe, these changes ultimately may lead to decreased oxygen delivery and tissue perfusion, putting the patients at an increased risk of developing MODS.

The incidence of overall gastrointestinal dysfunction in people and animals is difficult to gauge compared to other forms of organ dysfunction because of the lack of a clear definition and subjective nature of its assessment<sup>69,82</sup>; however, it is considered to be common.<sup>68,69,83</sup>

### **Cardiovascular Dysfunction**

Cardiovascular dysfunction is characterized by biventricular dilatation, decreased ejection fraction, hypotension often despite fluid therapy, and decreased response to catecholamines.<sup>84</sup> The cause of cardiovascular dysfunction is often multifactorial but generally is thought to be associated with the production of substances that lead to decreased cardiac contractility and mitochondrial damage. Endotoxin, cytokines (eg, IL-1 $\beta$ , TNF- $\alpha$ , platelet activating factor), and calcium leak from the sarcoplasmic reticulum, ultimately leading to a decrease in myocardial cell contractility.<sup>85,86</sup> In humans, and canine and guinea pig models, several cardiac abnormalities occur, including decreased contractility, left ventricular dilatation, and decreased left ventricular ejection fraction after exposure to *Staphylococcus aureus* and *E. coli*,<sup>87</sup> TNF- $\alpha$ ,<sup>88–90</sup> IL-1 $\beta$ ,<sup>89</sup> and IL-6.<sup>91</sup> The proinflammatory complement protein C5a also may play a role in myocardial dysfunction by producing reactive oxygen species.<sup>84</sup> NO production leads to decreased cardiac contractility by downregulating the beta-adrenergic myocardial receptors and decreasing cytosolic calcium.<sup>92,93</sup> Peroxynitrite is formed from NO and results in oxidative mitochondrial damage and decreased cardiac contractility.<sup>94</sup>

Critical illness-induced left ventricular dysfunction has been described in 16 dogs in which primary heart disease was not suspected and congestive heart failure was not present; over half of these dogs had bacterial sepsis or cancer.<sup>95</sup> A similar case report described a dog with idiopathic septic arthritis that had evidence of myocardial dysfunction on physical examination and echocardiogram. An echocardiogram performed 3 months later showed resolution of the myocardial dysfunction, indicating the initial echocardiographic abnormalities were a consequence of the septic arthritis and not from underlying heart disease.<sup>96</sup>

In people and small animals, cardiovascular dysfunction often is thought of in the context of the peripheral vasculature. For patient stratification in retrospective or prospective studies, cardiovascular dysfunction has been defined as hypotension requiring vasopressor treatment and is associated with decreased survival.<sup>6,7</sup> Cardiovascular dysfunction occurring

secondary to sepsis is referred to as septic shock, which is defined as sepsis-induced arterial hypotension despite adequate fluid resuscitation.<sup>2</sup>

Cardiovascular dysfunction is common in people with sepsis; some studies report an incidence of up to 66%.<sup>97,98</sup> It is also considered a prognostic factor for poor outcome<sup>98</sup> and is associated with mortality rates as high as 70%.<sup>88,98,99</sup>

Septic shock carries a poor prognosis in veterinary medicine, and several veterinary studies show survival rates of 10% or less.<sup>6,50,100,101</sup> Mortality also is increased in dogs with septic shock that require a greater number of vasopressors.<sup>102</sup>

Literature regarding sepsis-induced cardiovascular dysfunction in cats is lacking. Relative bradycardia is a common and unique finding in cats with sepsis; 19/29 cats with severe sepsis were reported to have an inappropriately low heart rate, and this mechanism is suspected to be secondary to increased vagal tone or cytokine-associated myocardial dysfunction.<sup>103</sup> The combination of bradycardia and hypothermia was a negative prognostic indicator in a case series of 12 cats with primary bacterial septic peritonitis,<sup>104</sup> but another study did not support this conclusion.<sup>103</sup> Recovery of cardiovascular function for cats requiring vasopressor support is variable.<sup>104,105</sup>

### **Coagulation Dysfunction**

Coagulation is a physiologic process intended to localize inflammation at the site of infection, prevent the spread of microorganisms, stop active hemorrhage, and promote wound healing.<sup>106</sup> Disseminated intravascular coagulation (DIC) is the most severe form of coagulation dysfunction and occurs when the appropriate physiologic response is exaggerated by the presence of proinflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . This proinflammatory response leads to fibrin formation and microvascular thrombosis through the upregulation of procoagulant pathways, downregulation of anticoagulant pathways, and suppression of fibrinolysis. The generation of thrombin leads to the production of additional proinflammatory cytokines that act as a positive feedback loop to perpetuate the coagulation cascade.<sup>107</sup> Animals with DIC may develop microvascular thrombosis or hemorrhage resulting from consumption and exhaustion of coagulation factors, or both simultaneously.<sup>108</sup> DIC most commonly occurs in people with sepsis, trauma, and cancer.<sup>109</sup>

In humans and animals, a diagnosis of DIC is not required for the classification of coagulation dysfunction. In dogs, coagulation dysfunction has been defined as prolongation of prothrombin time (PT) or partial thromboplastin time (PTT) >25% above the upper reference limit, a platelet count  $\leq 100,000/\mu\text{L}$  or both.<sup>6</sup>

Coagulation dysfunction is common in humans, affecting 15–30% of patients with severe sepsis,<sup>110</sup> and has been shown to be an independent predictor of mortality in patients with sepsis.<sup>111,112</sup> The incidence

of thrombocytopenia in human patients with sepsis is 35–59% and an inverse relationship exists between severity of disease and platelet count.<sup>113,114</sup>

Coagulation dysfunction is a negative prognostic indicator in dogs with sepsis and trauma.<sup>6,7</sup> Of dogs with sepsis, 60.5% had coagulation dysfunction, and coagulation dysfunction was the most common disorder diagnosed in a recent multicenter retrospective veterinary study.<sup>6,115</sup> Of 10 dogs with septic shock and MODS because of babesiosis, 9 had thrombocytopenia and none of these dogs survived.<sup>50</sup> Other coagulation abnormalities found in dogs with naturally developing sepsis include increased D-dimers, fibrinogen degradation products (FDP), and von Willebrand factor, and depletion of antithrombin and activated protein C.<sup>6,115–117</sup> There is some evidence that decreased antithrombin concentrations are associated with decreased survival in dogs with critical illness including sepsis,<sup>118,119</sup> whereas other studies show no correlation.<sup>115</sup>

There is less information regarding coagulation dysfunction in cats compared to dogs. A retrospective study evaluated the coagulation profiles of 46 critically ill cats in which the most common primary diseases were neoplasia, sepsis, and pancreatitis. Coagulation abnormalities included a prolonged PT (26/34 cats) and PTT (33/33 cats), thrombocytopenia (12/24 cats), increased FDP (10/33 cats), and decreased fibrinogen concentration (22/33 cats).<sup>120</sup> Additional retrospective evaluations of DIC in cats have shown similar coagulation profiles.<sup>121,122</sup>

### **Renal Dysfunction**

Renal dysfunction is referred to as acute kidney injury (AKI). Like many forms of organ dysfunction, AKI is caused by several different pathways. There are 2 main forms of AKI associated with MODS. One form involves a more traditional definition of kidney failure which is characterized by renal epithelial necrosis; renal hypoperfusion and ischemia often are cited in the pathogenesis.<sup>123–126</sup> This form is the least common. A review of 6 studies evaluating AKI caused by sepsis in humans found that only 22% of patients with sepsis-induced AKI had histopathologic evidence of acute tubular necrosis. Similarly, only 37% and 23% of primate and rodent sepsis-induced AKI models, respectively, were consistent with acute tubular necrosis whereas canine and sheep sepsis-induced AKI models had no evidence of acute tubular necrosis. In fact, the majority of animals or people in these studies were reported to have histopathologically normal kidneys.<sup>127</sup>

The 2nd form of AKI is specific to MODS and is not associated with necrosis; this is the most common form in people. Apoptosis caused by inflammatory cytokines (eg, TNF- $\alpha$ ) and endotoxin appears to be a predominant mechanism of this form of sepsis-induced AKI.<sup>128</sup> Apoptosis is difficult to appreciate on routine histopathology, which may explain the lack of histopathologic damage in AKI.<sup>129</sup> Instead of global hypoperfusion during sepsis, renal blood flow is adequate or increased which may explain the lack of acute

tubular necrosis.<sup>130–132</sup> It has been proposed that during sepsis-induced AKI, the efferent arteriole dilates to a greater degree than the afferent arteriole resulting in increased renal blood flow, decreased glomerular capillary pressure, and decreased glomerular filtration rate.<sup>133</sup>

Acute kidney injury is an important form of organ dysfunction in people because it markedly increases mortality.<sup>134–138</sup> A multinational, multicenter study in humans found that AKI had a prevalence of 5–6% and only 40% of these people survived to discharge. Septic shock was the most common cause of AKI in this study.<sup>139</sup> AKI occurs in up to 65% of people with septic shock.<sup>140</sup> A retrospective analysis of critically ill trauma patients found that patients with AKI had a mortality rate of 29.6%, which was significantly higher than the overall mortality rate of 9.2%.<sup>141</sup>

The prevalence of AKI in dogs is unknown, but AKI is considered to decrease survival. In a population of dogs that underwent surgery for septic peritonitis, 12.3% met the investigators' criteria for renal dysfunction (increase in serum creatinine concentrations by  $\geq 0.5$  mg/dL from preoperative concentrations) and only 14% of these dogs survived to discharge.<sup>6</sup> A recent veterinary study evaluated AKI in critically ill dogs. The investigators found 14.6% of dogs met criteria for AKI (increase in serum creatinine concentration of  $>150\%$  from baseline) during hospitalization and the survival rate was 45.8%.<sup>142</sup> The survival rates between these 2 studies are markedly different, and the disparity can most likely be related to differences in patient population. The 1st study involved only patients with septic peritonitis whereas only approximately half of the patients with AKI in the 2nd study had sepsis because of various causes.

### Central Nervous System Dysfunction

Sepsis-associated encephalopathy (SAE) is an acute and sometimes reversible deterioration of mental status characterized by changes in consciousness, awareness, cognition, and behavior in people.<sup>143</sup> The pathophysiology of SAE is not completely understood. Initially, the blood–brain barrier is intact and this protects the brain from systemic inflammation. Inflammatory mediators (eg, IL-1 $\beta$ , TNF- $\alpha$ ) stimulate the afferent fibers of the vagus nerve, which acts as a conduit to the central nervous system. After stimulation of the vagus nerve, cerebral endothelial cells then are activated, resulting in breakdown of the blood–brain barrier.<sup>144,145</sup> Activation of cerebral endothelial cells also induces microcirculatory dysfunction and coagulopathy and changes in vascular tone leading to hemorrhagic and ischemic lesions.<sup>146</sup> In addition, reactive oxygen species are formed which compromise neuronal and microglial cell function and survival and eventually lead to apoptosis and edema. Finally, SAE is thought to decrease the vasodilatory response of the cerebrum leading to impairment of cerebral autoregulation of blood flow.<sup>145</sup> Brain histopathology from patients with septic shock is characterized by a variety

of lesions including cerebral edema, infarcts, microabscesses, intravascular thrombosis, and neuronal cell death.<sup>146</sup>

Sepsis-associated encephalopathy is the most common form of encephalopathy in people with an incidence of 8–70% of people with sepsis in the ICU.<sup>147</sup> However, the recognition of SAE often is hindered by the use of sedatives for mechanical ventilation. SAE is associated with a poor prognosis in people. In 1 report, the mortality rate of septic patients with an altered mental status was 49% compared to 26% of septic patients with no neurologic clinical signs.<sup>148</sup> The development of SAE in people with sepsis has long-term detrimental consequences including neurologic impairment, decreased cognitive scores in children, and psychologic disorders.<sup>149–151</sup> The incidence and long-term impact of this phenomenon in veterinary species is unknown.

### Adrenal Dysfunction

Critical illness-related corticosteroid insufficiency (CIRCI) is defined as inadequate corticosteroid activity relative to illness severity. CIRCI describes a reversible dysfunction of any aspect of the hypothalamic–pituitary–adrenal axis caused by proinflammatory mediators (eg, TNF- $\alpha$ ).<sup>152</sup> In addition, corticosteroid tissue resistance increases in acute inflammatory diseases such as sepsis. Thus, although adequate amounts of cortisol are produced, corticosteroid receptor binding is impaired.<sup>153</sup> CIRCI is a dynamic process that is characterized by basal serum cortisol concentrations that are often within or above the reference interval, but after adrenocorticotropin hormone (ACTH) administration there is dampened cortisol secretion.<sup>100</sup>

Critical illness-related corticosteroid insufficiency is believed to have an approximate overall prevalence of 30% in critically ill people and the prevalence increases to approximately 60% in people with septic shock.<sup>154</sup> Despite several research studies supporting the existence of and treatment for CIRCI,<sup>155–160</sup> there is also evidence of the contrary.<sup>161,162</sup> It is considered a controversial concept in human medicine and not widely accepted.<sup>163</sup>

There are a few veterinary studies regarding CIRCI, and the majority has found that critically ill animals have similar adrenal dysfunction to people.<sup>100,164–168</sup> In 1 study, 48% of dogs with sepsis had CIRCI, and dogs with a  $\Delta$ -cortisol (difference between cortisol measured pre- and post-ACTH stimulation) of  $<3$   $\mu\text{g/dL}$  were more likely to be hypotensive and less likely to survive.<sup>100</sup> There is only 1 case report each of a dog and cat with septic shock and evidence of CIRCI in which shock was reversed by the use of hydrocortisone or dexamethasone, respectively. Both animals experienced complete recovery.<sup>165,168</sup>

### Prognosis

In people with MODS, the number of dysfunctional organ systems correlates with mortality in the

ICU.<sup>18,169</sup> People with severe sepsis and multiple organ dysfunction are 2.2 times more likely to die than patients with severe sepsis and single organ dysfunction,<sup>170</sup> and people with  $\geq 4$  dysfunctional organs are 4 times more likely to die than those with single organ dysfunction.<sup>170</sup> One multicenter study found mortality rates corresponding with 1, 2, 3, and more than 4 dysfunctional organ systems were 21.2%, 44.3%, 64.5%, and 76.2%, respectively, in critically ill people.<sup>5</sup> Children with MODS have worse functional outcomes, higher mortality, and longer stays in the ICU than children who do not have MODS.<sup>171</sup> Mortality rates associated with MODS in people are influenced by comorbidities such as chronic kidney disease, cancer, and diabetes,<sup>5,172</sup> and cumulative comorbidities are associated with greater risk for organ dysfunction.<sup>173</sup>

The development of MODS and increasing number of organ systems affected also are associated with poorer outcome in veterinary medicine. In a recent study of dogs with abdominal sepsis, the overall survival rate was 79% compared to 40% in dogs with MODS.<sup>20</sup> In a separate study of dogs treated surgically for abdominal sepsis, dogs with MODS had a survival rate of only 30% compared to a 75% survival rate in dogs without MODS.<sup>6</sup> Survival was inversely proportional to the number of dysfunctional organ systems; reported survival rates were 46%, 24%, 8%, and 0% with 2, 3, 4, and 5 failed organs, respectively. Similar results were found in a report of MODS caused by canine babesiosis.<sup>174</sup> MODS secondary to trauma in dogs is less common than in sepsis, but mortality reached 100% in 1 retrospective study.<sup>7</sup>

## Conclusion

Multiple organ dysfunction syndrome is associated with high morbidity and mortality in both human beings and animals. Compared to human medicine, there is very little known regarding MODS in veterinary species outside of a laboratory setting. To better characterize MODS in clinical veterinary cases, the veterinary community needs to first develop consensus statements regarding the definition of MODS in animals that can then be used as the basis for prospective studies in this area.

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