Acute respiratory distress syndrome in dogs and cats: a review of clinical findings and pathophysiology

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Abstract

Objective: To review the clinical and pathophysiologic aspects of acute respiratory distress syndrome (ARDS) in dogs and cats.

Data sources: Data from human and veterinary literature were reviewed through Medline and CAB as well as manual search of references listed in articles pertaining to acute lung injury (ALI)/ARDS.

Human data synthesis: Since the term ARDS was first coined in 1967, there has been a abundance of literature pertaining to this devastating syndrome in human medicine. More complete understanding of the complex interactions between inflammatory cells, soluble mediators (e.g., tumor necrosis factor, interleukin (IL)-6, IL-8, platelet activating factor) and the clinical patient has provided for timely recognition and mechanistically based protective strategies decreasing morbidity and mortality in human patients with ARDS.

Veterinary data synthesis: Although little is known, ARDS is becoming a more commonly recognized sequela in small animals. Initial case reports and retrospective studies have provided basic clinical characterization of ARDS in dogs and cats. Additionally, information from experimental models has expanded our understanding of the inflammatory mechanisms involved. It appears that the inflammatory processes and pathologic changes associated with ARDS are similar in dogs, cats, and humans.

Conclusions: Unfortunately, current mortality rates for ARDS in small animals are close to 100%. As our capability to treat patients with advanced life-threatening disease increases, it is vital that we develop a familiarity with the pathogenesis of ARDS. Understanding the complex inflammatory interactions is essential for determining effective preventative and management strategies as well as designing novel therapies for veterinary patients.

Introduction

Acute lung injury (ALI) is a syndrome of pulmonary inflammation and edema resulting in acute respiratory failure. The clinical presentation varies in severity with the most severe manifestations termed acute respiratory distress syndrome (ARDS). The major difference between ALI and ARDS is the degree of hypoxemia as defined by the ratio of arterial oxygen tension to fractional inspired oxygen concentration (PaO2:FiO2).1 In a patient with appropriate risk factors and clinical findings (Table 1) a ratio of <300 or 200 mmHg differentiates ALI from ARDS, respectively.2

Risk factors

Since ALI/ARDS is a secondary inflammatory response to injury, multiple risk factors have been identified in dogs (Table 2). Inflammation that results from these conditions may originate from direct lung injury, or may be a part of a generalized inflammatory response. In dogs, ALI/ARDS is most commonly a sequel of bacterial pneumonia, aspiration pneumonia, sepsis, or shock.3 Although specific risk factors have not been identified in cats, severe sepsis has been associated with necropsy findings consistent with ALI/ARDS.4

Keywords: cytokines, immunology, non-cardiogenic pulmonary edema, respiratory pathology, respiratory tract inflammation
Clinical presentation

Clinical signs of ALI/ARDS may be delayed for 1–4 days after the inciting event triggers the pulmonary inflammatory response. Manifestations of ALI/ARDS may include progressive hypoxemia, tachypnea, respiratory distress, and cyanosis. Rarely, a productive cough may be present. Physical examination findings may include harsh lung sounds progressing to crackles, orthopnea, utilization of auxiliary respiratory muscles, and foamy pink expectorate in severe cases. Any animal with non-cardiogenic pulmonary edema and appropriate risk factors should be suspected of having ALI or ARDS.

Diagnosis

As a syndrome, diagnosis of ALI or ARDS is based on a combination of historical and clinical abnormalities. Criteria for the diagnosis of ALI/ARDS have been adapted from human medicine since the specific features of ALI/ARDS in veterinary patients have not been determined until publication in this issue (see Wilkins et al. p. 333). Acute onset of respiratory distress, presence of bilateral pulmonary infiltrates, absence of left atrial hypertension, appropriate risk factors, and a decreased PaO₂:FiO₂ ratio are consistent with ALI or ARDS (Table 2). Blood gas analysis and thoracic radiographs are typically the best indicators of ALI/ARDS. Owing to alterations in dynamic lung compliance, increased dead space, intrapulmonary shunting, amplified airway resistance and augmented pulmonary vascular resistance, blood gas abnormalities (including hypoxemia, hypercapnia, hypocapnia, respiratory alkalosis), and increased alveolar to arterial oxygen gradient are common with this syndrome. By definition, the ratio of PaO₂:FiO₂ should be <300 mmHg or 200 mmHg in patients with ALI or ARDS, respectively. Radiographic changes vary depending upon the stage and severity of the syndrome. Increased pulmonary interstitial and peribronchial markings to diffuse bilateral pulmonary alveolar infiltrates are detected (Figure 1) with ALI/ARDS. Radiographic evidence of cardiomegaly or distended pulmonary vessels suggest congestive heart failure or fluid overload, not ALI/ARDS. In some cases, echocardiography may be indicated to rule out cardiogenic causes of pulmonary edema.

Additional diagnostic testing such as a complete blood count and serum chemistry panel typically reflect nonspecific changes related to the underlying disease process rather than lung injury itself. Hypoalbuminemia occurred in 8 of 12 dogs in a retrospective study of canine ALI/ARDS, and has been correlated with an increased risk of developing ARDS in human patients with sepsis. Leukopenia is also a common finding in dogs with ALI/ARDS. Bronchoalveolar lavage fluid (BALF) analysis may indicate an increased protein concentration and suppurative in-

Table 1: Diagnostic criteria consistent with ALI or ARDS

<table>
<thead>
<tr>
<th>Appropriate risk factors (see Table 2)</th>
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<tbody>
<tr>
<td>Acute onset of respiratory signs</td>
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<tr>
<td>Bilateral pulmonary infiltrates</td>
</tr>
<tr>
<td>PaO₂: FiO₂ &lt;300 mmHg (ALI) or &lt;200 mmHg (ARDS)</td>
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<tr>
<td>No evidence of left atrial hypertension</td>
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Partial pressure of oxygen in the arterial blood to fraction of inspired oxygen ratio (PaO₂: FiO₂).

ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Table 2: Reported risk factors for development of ALI/ARDS in dogs

<table>
<thead>
<tr>
<th>Dogs</th>
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<tbody>
<tr>
<td>Primary respiratory disorders</td>
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<tr>
<td>Lung lobe torsion</td>
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<tr>
<td>Microbial pneumonia</td>
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<tr>
<td>Aspiration pneumonia</td>
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<tr>
<td>Smoke inhalation</td>
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<tr>
<td>Parasitic pneumonitis</td>
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<tr>
<td>Strangulation</td>
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<tr>
<td>Pulmonary contusions</td>
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<tr>
<td>Hyperoxia</td>
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<tr>
<td>Systemic disorders</td>
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<tr>
<td>Babesiosis</td>
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<tr>
<td>Paraquat poisoning</td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Shock</td>
</tr>
<tr>
<td>Gastric and splenic torsion</td>
</tr>
<tr>
<td>Bee envenomation</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
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<tr>
<td>Parvovirus</td>
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</table>

ALI, acute lung injury; ARDS, acute respiratory distress syndrome.
flammation.\textsuperscript{13–15} There are no published reports of ALI/ARDS in cats, and therefore specific clinical findings are speculative. In the future, more specific diagnostic tests may help diagnose ALI/ARDS and determine prognosis. For instance, lung angiotensin converting enzyme (ACE) and serum ACE have been evaluated as diagnostic and prognostic indicators, respectively, in a canine model of ALI/ARDS.\textsuperscript{16}

**Pathogenesis**

Regardless of the inciting trigger, the lung has a limited repertoire of responses to an insult. Therefore, the pathologic findings of ALI/ARDS are consistent despite varying etiologies. ALI/ARDS develops secondary to an inappropriate, overzealous inflammatory response that may last long after the inciting cause is removed. The pathophysiology is complex and mortality rates as high as 40–60\% have been reported in humans with ALI/ARDS.\textsuperscript{17} Reports of animals surviving ALI/ARDS are rare.\textsuperscript{18} As veterinary care becomes more advanced, there may be an increase in the number of patients with risk factors for ALI/ARDS. Considering these grave survival statistics, understanding the complex pathogenesis is essential to develop appropriate prevention and treatment strategies.

**Phases of ALI/ARDS**

Most human patients, like veterinary patients, that die of ALI/ARDS do so within the first 2 weeks following diagnosis.\textsuperscript{1,3} The evolving inflammatory condition is traditionally described based on morphologic changes in 3 overlapping phases: exudative, proliferative, and fibrotic.\textsuperscript{19–21} The ultimate outcomes for ALI/ARDS include persistence and progression, or recovery and resolution.\textsuperscript{22,23} For patients that have recovery and resolution of their pulmonary lesions, there is complete or nearly complete recovery of pulmonary function and quality of life.\textsuperscript{23,24}

**Exudative phase**

The exudative phase of lung injury begins with pulmonary vascular leakage and inflammatory cell infiltration.\textsuperscript{25,26} Loss of capillary integrity, alveolar epithelial damage, accumulation of protein-rich fluid, and development of pulmonary edema are characteristic features of the exudative phase in dogs and cats.\textsuperscript{5,27–29} The lung architecture becomes altered as type I alveolar pneumocytes, which are responsible for gas exchange, are irreversibly damaged.\textsuperscript{1} Because type I pneumocytes are unable to replicate, type II pneumocytes abandon their normal function of surfactant production to repair the denuded areas.\textsuperscript{21,30} Type I pneumocyte death and altered type II pneumocyte function leads to formation of hyaline membranes, deficiency of surfactant and collapse of alveoli.\textsuperscript{21,30–32} Vascular endothelial damage leads to local thrombosis. Grossly, the lungs are heavy, rigid, and fail to exude fluid on cut section due to the high protein content.\textsuperscript{5,6,20} Histologically, diffuse alveolar damage, eosinophilic hyaline membranes, marked congestion, edema, neutrophil infiltration, hemorrhage, and atelectasis are noted in dogs.\textsuperscript{5,6,14,26,33–35} Protein leakage, pulmonary edema, supplicative alveolitis, thickened alveolar septae, alveolar hemorrhagic necrosis, and thrombosis have been documented in models of feline ALI/ARDS.\textsuperscript{27,28,36,37} The exudative phase lasts for approximately 1 week after the onset of clinical signs in humans.\textsuperscript{20}

**Proliferative phase**

Organization of exudates and development of fibrosis characterize the proliferative phase. Type II pneumocytes proliferate in an effort to repair the denuded epithelial surfaces.\textsuperscript{21,30} Fibroblastic proliferation, initially in the pulmonary interstitium and later in the alveolar lumen, lead to narrowing and collapse of the airspaces and pulmonary hypertension.\textsuperscript{20} Histologically, the architecture of the lung becomes more deranged. The interstitial space becomes dilated and edematous, hyaline membranes progress and the alveolar lumen fills with fibrin and cell debris in dogs.\textsuperscript{11,38} There are no studies evaluating later phases of feline ALI/ARDS, although a similar pathogenesis to dogs and humans is possible.

**Fibrotic phase**

A fibrotic phase is the final morphologic stage of lung injury in ALI/ARDS before recovery. While the clinical manifestations of fibrosis are considered a late stage of ALI/ARDS, initiation of fibrosis actually begins much earlier in the syndrome. The magnitude of fibrosis is highly variable among human patients and may range from minimal to severe fibrosis.\textsuperscript{39}

The fibrotic phase involves collagen deposition in the alveolar, vascular, and interstitial beds. Total lung collagen may double in the first 2 weeks post-injury in humans.\textsuperscript{40} During the fibrotic phase microscopic cavities lined by epithelium containing fluid or other material, termed microcysts, develop in the pulmonary parenchyma. Grossly, the lungs may have a cobblestone character due to scarring. In humans with ALI/ARDS, fibrosis is a key predictor of survival.\textsuperscript{39,41} Little is known about this phase in clinical veterinary patients due to the high initial mortality rate. Experimentally, inflammatory cell infiltration, peribronchial fibrosis, destruction of alveolar structures, bronchiectasis, interstitial thickening, and obliteration of alveolar capillaries
by fibrous tissue is observed 40 days after induction of lung injury in dogs.48

Cellular mechanisms
The cellular and soluble mediator interactions responsible for lung injury in ALI/ARDS are complex and incompletely understood. However, a central role for macrophages, neutrophils, and a variety of cytokines is present.

Macrophages
Alveolar macrophages are the earliest effector cells of the pulmonary inflammatory response and are responsible for initiation of ALI/ARDS following an inciting event.17,20,36,42-44 Upon activation, alveolar macrophages undergo phenotypic changes.45 Cytokines and chemokines, including tumor necrosis factor (TNF-α) and interleukin (IL)-1β, are produced and reactive oxygen species (ROS) are released.45 Alveolar macrophage activation and elaboration of pro-inflammatory mediators to promote neutrophil migration into the pulmonary interstitium and alveolus, further contributing to lung inflammation and injury.46 Additionally, macrophages directly injure alveolar epithelial cells through induction of apoptosis.37

Neutrophils
Pulmonary neutrophil accumulation is seen in the early stages of ALI/ARDS histologically in dogs and cats and neutrophils predominate in the BAL fluid of dogs and humans.13-15,17,26 Similarly to activated macrophages, activated neutrophils release inflammatory mediators, and ROS. Such oxidants in turn lead to dysfunction and death of alveolar epithelial cells and decreased surfactant production.48

Although their importance is not questioned, the exact role of neutrophils in the pathogenesis of ALI/ARDS is under investigation. Originally, neutrophils were thought to act in concert with macrophages, the earliest effector cells of ALI/ARDS. Granulocyte depletion decreased vascular permeability and lessened formation of pulmonary edema in an ovine model of ALI.49 Furthermore, neutrophil influx and persistence of the initial neutrophilic inflammatory response is associated with a increased severity of lung injury and a higher mortality rate in humans.50 However, the incidence and severity of ALI/ARDS is not altered by either profound neutropenia or granulocyte colony stimulating factor induced neutrophilia in other models of ALI/ARDS.17,48 Certainly, neutrophils contribute to the inflammatory response in this syndrome. Whether neutrophils help macrophages to initiate ALI/ARDS or are simply responding to commands from macrophage populations has yet to be determined.

Soluble mediators

TNF-α and IL-1β: TNF-α and IL-1β are derived predominantly from activated macrophages and act via specific cell receptors. They trigger additional production of inflammatory mediators including cytokines, lipid mediators and ROS. TNF-α and IL-1β play an essential role in neutrophil recruitment and activation.58 IL-1β also stimulates inflammatory and fibroproliferative processes by altering fibroblast gene expression.51

Numerous studies have confirmed that TNF-α and IL-1β are the earliest soluble mediators in ALI/ARDS with increased concentrations 30-90 min post-injury.1,17,20,52,53 Clinically, TNF-α and IL-1β concentrations in bronchoalveolar fluid are significantly higher in human patients in the early but not late stages of ALI/ARDS.51,53 Additionally, increased concentration of membrane associated TNF-α on the surface of alveolar macrophages is found in human patients with ALI/ARDS and has been associated with induction of inflammatory cellular responses.54 TNF-α from human ALI/ARDS patient BALF has cytotoxic effects on microvascular endothelial cells suggesting that TNF-α directly damages lung tissue.53 TNF-α and IL-1β are increased in both serum and BALF in experimental models of canine ALI/ARDS.34,55 Interestingly, there is a significantly higher concentration of both mediators in dogs with ALI/ARDS triggered by direct pulmonary as opposed to systemic injury.34

TGF-β: Transforming growth factor-β (TGF-β) is a key mediator of tissue fibrosis and can be produced by virtually every cell type. TGF-β promotes the fibroproliferative response during the latter phase of ALI/ARDS. Although previously thought of as a late-stage mediator, TGF-β expression is markedly increased as early as 2 days after the induction of lung injury.56 This discovery led to recognition of additional roles for TGF-β. In the exudative phase of ALI/ARDS, TGF-β promotes pulmonary edema.57 TGF-β also acts as a chemoattractant for macrophages and neutrophils and stimulates macrophage production of TNF-α, IL-1β, and platelet activating factor (PAF).58

PAF: Macrophages, neutrophils, and endothelial cells produce PAF.59,60 In addition to activation of platelets, PAF is a potent pro-inflammatory mediator that acts also as a vasodilator and bronchoconstrictor.51 Much of the vascular endothelial effects of neutrophils are mediated through secretion of PAF. In experimental models, PAF alters vascular permeability resulting in pulmonary edema.62 Overexpression or disruption of the PAF receptor either increased or decreased the development of lung injury, edema, and respiratory failure in a mouse model respectively.53 Clinically, increased concentrations of PAF are found in BALF from...
humans in the early stages of ALI/ARDS, further supporting its role in lung injury.42

**IL-6:** A wide range of cells can produce the pro-inflammatory cytokine IL-6.51 IL-6 induces synthesis of acute phase proteins in ALI/ARDS. Serum IL-6 concentration is an excellent predictor of ALI/ARDS severity in human patients with conditions such as sepsis and pancreatitis.52 In experimentally induced ALI/ARDS in dogs, IL-6 is increased in both serum and BALF.34,55 Additionally, IL-6 is a critical mediator of fibroblast activation and proliferation and likely plays a role in the fibroproliferative phase of ALI/ARDS.51

**CXC chemokine ligand (CXCL)-8:** CXCL-8 (also known as IL-8) is a chemokine produced by many cells including fibroblasts, macrophages, lymphocytes, and endothelial cells. CXCL-8 stimulates neutrophil recruitment and activates neutrophils, causing granule, and leukotriene release, and stimulation of the respiratory burst.64,65 Serum and pulmonary CXCL-8 is significantly increased in canine models of ALI/ARDS.56,66 There is a significant association between alveolar CXCL-8 concentrations in at-risk human patients and ALI/ARDS development.64,67 Severity of pulmonary neutrophilia and mortality in human ALI/ARDS patients have been correlated with CXCL-8 and anti-CXCL-8: CXCL-8 complex concentrations.64,67

**Eicosanoids**

Eicosanoids are a group of hormones produced from arachadonic acid that include prostaglandins, thromboxanes, and leukotrienes. After stimulation, arachadonic acid is converted to either leukotrienes by lipoxygenase or to prostaglandins and thromboxanes by cyclooxygenase (COX). Products of the arachadonic acid cascade alter vascular permeability and tone, induce bronchoconstriction, and increase platelet aggregability. Arachadonic acid released by neutrophils has been associated with LPS-induced lung inflammation in rats.69 In canine models of ALI/ARDS, lung tissue concentrations of thromboxane are increased.70 Inhibition of COX-2 attenuates the deterioration of gas exchange by decreasing circulating and lung prostacyclin in canine models.70,71 In cats, leukotrienes play an important role in the pathogenesis of ALI/ARDS by promoting increased airway resistance, decreased lung compliance, increased pulmonary capillary permeability, and hypoxemia.27,36 However, some arachadonic acid-derived mediators, namely lipoxins, may be crucial for resolution of ALI/ARDS. Lipoxins are regulators of the recovery phase of inflammation and have potent anti-inflammatory properties enabling them to inhibit neutrophil activation and cytokine release. In a rodent model of ALI/ARDS, inhibition of COX-2 has been shown to inhibit resolution of ALI/ARDS by decreasing lipoxin production.72

**Anti-inflammatory mediators**

Although much attention is given to the pro-inflammatory mediators in ALI/ARDS, an anti-inflammatory response can also be detected following lung injury. An imbalance of pro-inflammatory and anti-inflammatory

<table>
<thead>
<tr>
<th>Dogs</th>
<th>Proposed mechanism</th>
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<tbody>
<tr>
<td>Pentoxifylline</td>
<td>Phosphodiesterase inhibitor, decreases production of inflammatory mediators and cellular infiltration</td>
</tr>
<tr>
<td>Tacrolimus (FK506)</td>
<td>Inhibits proinflammatory cytokine production</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Decreases surface tension in the alveoli</td>
</tr>
<tr>
<td>Oxazepol (OKY-046)</td>
<td>Thromboxane synthase inhibitor</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Cyclooxygenase inhibitor</td>
</tr>
<tr>
<td>Gabexate mesilate</td>
<td>Inhibits proinflammatory cytokine production</td>
</tr>
<tr>
<td>Aminoguanidine</td>
<td>Inhibits iNOS</td>
</tr>
<tr>
<td>S-methylisothiourea sulfate</td>
<td>Inhibits iNOS</td>
</tr>
<tr>
<td>N6-nitro-L-arginine methyl ester</td>
<td>NO synthesis inhibitor, prevents increased vascular permeability</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Cyclooxygenase inhibitor</td>
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<tr>
<th>Cats</th>
<th>Proposed mechanism</th>
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<tbody>
<tr>
<td>Diethylcarbamazine</td>
<td>Leukotriene synthase inhibitor</td>
</tr>
<tr>
<td>FPL 55712</td>
<td>Leukotriene antagonist</td>
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<tr>
<td>ICI 198,615</td>
<td>Leukotriene receptor antagonist</td>
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<tr>
<td>DPCPX</td>
<td>A1-adenoreceptor antagonist, anti-inflammatory</td>
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<tr>
<td>Bamiphylline</td>
<td>A1-adenoreceptor antagonist, anti-inflammatory</td>
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Table 3: Pharmacologic therapy evaluated in experimental canine and feline models of ALI/ARDS with positive outcomes8,14,27,28,32,33,36,70,79-81

Table 3

<table>
<thead>
<tr>
<th>Proposed mechanism</th>
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<tr>
<td>Phosphodiesterase inhibitor, decreases production of inflammatory mediators and cellular infiltration</td>
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ALI, acute lung injury; ARDS, acute respiratory distress syndrome; iNOS, inducible nitric oxide synthase; NO, nitric oxide.
mediators may be critical to the development of ALI/ARDS. IL-10 is an anti-inflammatory cytokine which inhibits the release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β). In humans with similar risk factors, those who develop ALI/ARDS have been found to have lower circulating concentrations of IL-10 than those who did not develop ALI/ARDS. Additionally, an increased ratio of pro-inflammatory to anti-inflammatory mediators corresponds with poor outcome in human patients with ALI/ARDS.

**Conclusions**

There are multiple risk factors associated with ALI/ARDS. While the inciting cause may vary, the resulting massive inflammatory cascade leads to devastating pulmonary damage. Currently, therapy focuses on aggressive supportive care. As we learn more about the pathophysiology of ALI/ARDS there is an increased focus on inflammatory cascade modulation and preventing development or progression of ALI/ARDS. Numerous medical therapies aimed at attenuating the inflammatory response have been evaluated in canine and feline models of ALI/ARDS (Table 3) with positive outcomes. However, many therapies that showed promise in experimental models of ALI/ARDS have been evaluated in humans with naturally occurring ALI/ARDS with little clinical success (Table 4).

The disjunction between experimental and clinical effects may be due to the complex nature of this syndrome. For instance, the failure of drugs targeting soluble mediators may be because the opportunity for inhibition has been missed when ALI/ARDS is clinically recognized. Because the inflammatory response is complicated, it is unlikely that inhibition of 1 or 2 soluble mediators will be a cure-all. Moreover, some initially pro-inflammatory mediators, like IL-1β, may promote repair of injured alveolar epithelium later in the syndrome, so inhibition may actually be harmful. Inhibition of COX-2 may present a similar challenge because it acts in a pro-inflammatory manner at the onset of ALI/ARDS and as a repair promoter during resolution of the syndrome. Successful immunomodulation for the management of ALI/ARDS will likely require combination therapy tailored to the unique needs of each patient. In the future, further understanding of the pathophysiology of ALI/ARDS may lead to advances in altering the inflammatory cascade and prevention of the syndrome.

**Self Quiz Questions**

Q1. What criteria must be fulfilled to diagnose ALI and ARDS?
A1. See Table 2.

Q2. What are the 3 morphologic phases of ARDS?
A2. Exudative, proliferative, and fibrotic.

Q3. What two inflammatory cell types are most important in the pathogenesis of ALI/ARDS?
A3. Macrophages and neutrophils.

Q4. Name 4 pro-inflammatory soluble mediators involved in the pathogenesis of ALI/ARDS.
A4. TNF-α, IL-1β, IL-6, CXCL-8, PAF, TGF-β, eicosanoids.
References


