State-of-the-Art Review

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

Amy E. DeClue, DVM, MS, DACVIM and Leah A. Cohn, DVM, PhD, DACVIM

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.

(J Vet Emerg Crit Care 2007; 17(4): 340–347) doi: 10.1111/j.1476-4431.2007.00247.x

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

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 (PaO_2:FiO_2).[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 sequela 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]

From the Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri, Columbia, MO.

Address correspondence and reprint requests to:
Dr. Amy E. DeClue, Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri, 900 E. Campus Drive, Columbia, MO 65211.
E-mail: decluea@Missouri.edu

Table 1: Diagnostic criteria consistent with ALI or ARDS[2]

Appropriate risk factors (see Table 2)
Acute onset of respiratory signs
Bilateral pulmonary infiltrates
PaO_2 : $FiO_2 < 300$ mmHg (ALI) or < 200 mmHg (ARDS)
No evidence of left atrial hypertension

Partial pressure of oxygen in the arterial blood to fraction of inspired oxygen ratio (PaO_2 : FiO_2).
ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Clinical presentation

Clinical signs of ALI/ARDS may be delayed for 1–4 days after the inciting event triggers the pulmonary inflammatory response.[3] Manifestations of ALI/ARDS may include progressive hypoxemia, tachypnea, respiratory distress, and cyanosis.[3,5,6] 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.[3] 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

Table 2: Reported risk factors for development of ALI/ARDS in dogs[3,5,6,9,18,74–76]

Dogs
Primary respiratory disorders
  Lung lobe torsion
  Microbial pneumonia
  Aspiration pneumonia
  Smoke inhalation
  Parasitic pneumonitis
  Strangulation
  Pulmonary contusions
  Hyperoxia
Systemic disorders
  Babesiosis
  Paraquat poisoning
  Pancreatitis
  Sepsis
  Shock
  Gastric and splenic torsion
  Bee envenomation
  Disseminated intravascular coagulation
  Parvovirus

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

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 PaO_2:FiO_2 ratio are consistent with ALI or ARDS (Table 2).[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.[7–10] By definition, the ratio of PaO_2:FiO_2 should be < 300 mmHg or 200 mmHg in patients with ALI or ARDS, respectively.[2] 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.[3,6,11] 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.[3,12] Leukopenia is also a common finding in dogs with ALI/ARDS.[3] Bronchoalveolar lavage fluid (BALF) analysis may indicate an increased protein concentration and suppurative in-
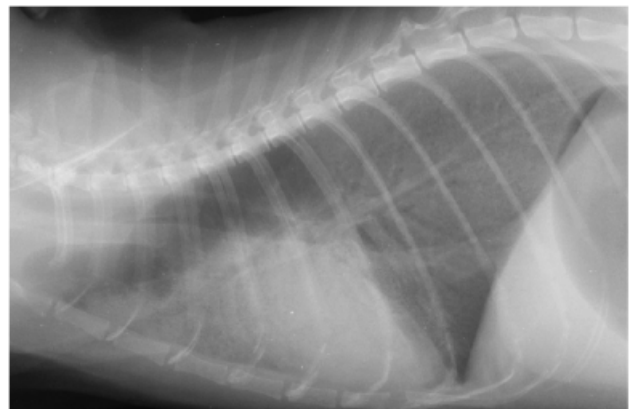
Figure 1: Lateral (a) and ventrodorsal (b) radiographs of the thorax from a cat with acute lung injury/acute respiratory distress syndrome. Note the classic diffuse, severe interstitial to alveolar pattern without signs of cardiac enlargement. Radiograph courtesy of Dr. Carol Reinero.

flammation.[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.[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.[17] Reports of animals surviving ALI/ARDS are rare.[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.[1,3] The evolving inflammatory condition is traditionally described based on morphologic changes in 3 overlapping phases: exudative, proliferative, and fibrotic.[19–21] The ultimate outcomes for ALI/ARDS include persistence and progression, or recovery and resolution.[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.[23,24]

Exudative phase

The exudative phase of lung injury begins with pulmonary vascular leakage and inflammatory cell infiltration.[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.[5,27–29] The lung architecture becomes altered as type I alveolar pneumocytes, which are responsible for gas exchange, are irreversibly damaged.[1] Because type I pneumocytes are unable to replicate, type II pneumocytes abandon their normal function of surfactant production to repair the denuded areas.[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.[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.[5,6,20] Histologically, diffuse alveolar damage, eosinophilic hyaline membranes, marked congestion, edema, neutrophil infiltration, hemorrhage, and atelectasis are noted in dogs.[5,6,14,26,33–35] Protein leakage, pulmonary edema, suppurative alveolitis, thickened alveolar septae, alveolar hemorrhagic necrosis, and thrombosis have been documented in models of feline ALI/ARDS.[27,28,36,37] The exudative phase lasts for approximately 1 week after the onset of clinical signs in humans.[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.[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.[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.[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.[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.[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.[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.[38]

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.[17,20,38,42–44] 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.[47]

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.[48] 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.[61] 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.[63] 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.[35,66] 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 lipooxygenase 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 3: Pharmacologic therapy evaluated in experimental canine and feline models of ALI/ARDS with positive outcomes[8,14,27,28,32,33,36,70,79–81]

	Proposed mechanism
Dogs	
Pentoxifylline	Phosphodiesterase inhibitor, decreases production of inflammatory mediators and cellular infiltration
Tacrolimus (FK506)	Inhibits proinflammatory cytokine production
Surfactant	Decreases surface tension in the alveoli
Ozagrel (OKY-046)	Thromboxane synthase inhibitor
Ibuprofen	Cyclooxygenase inhibitor
Gabexate mesilate	Inhibits proinflammatory cytokine production
Aminoguanidine	Inhibits iNOS
S-methylisothiourea sulfate	Inhibits iNOS
N^G-nitro-L-arginine methyl ester	NO synthesis inhibitor, prevents increased vascular permeability
Celecoxib	Cyclooxygenase inhibitor
Cats	
Diethylcarbamazine	Leukotriene synthase inhibitor
FPL 55712	Leukotriene antagonist
ICI 198,615	Leukotriene receptor antagonist
DPCPX	A_1-adenoreceptor antagonist, anti-inflammatory
Bamiphylline	A_1-adenoreceptor antagonist, anti-inflammatory

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; iNOS, inducible nitric oxide synthase; NO, nitric oxide.

Table 4: Pharmacologic therapy evaluated for ALI/ARDS with little or no effect on morbidity or mortality in human clinical trials[52,81–84]

Drug	Proposed mechanism
Albumin	Colloid support
Corticosteroids	Anti-inflammatory, prevents collagen deposition
Dazoxiben	Thromboxane synthase inhibitor
Furosemide	Diuretic
GM-CSF	Immunomodulation
Ibuprofen	Cyclooxygenase inhibitor
Idomethacin	Cyclooxygenase inhibitor
IL-10	Anti-inflammatory cytokine
Ketoconazole	Thromboxane and leukotriene inhibitor
Lisofylline	Inhibits release of TNF, IL-1 and IL-6, attenuates shock
N-acetylcysteine	Oxygen free radical scavenger
Pentoxifylline	Inhibits neutrophil chemotaxis and activation
Procysteine	Oxygen free radical scavenger
Prostaglandin E1	Decreases neutrophil activation, pulmonary vasodilator, blocks platelet aggregation
Sivelestat	Inhibition of neutrophil elastase
Surfactant	Decreases surface tension in the alveoli

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; TNF, tumor necrosis factor; IL, interleukin; GM-CSF, granulocyte-macrophage Colony-stimulating factor.

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).[73] 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.[74] Additionally, an increased ratio of pro-inflammatory to anti-inflammatory mediators corresponds with poor outcome in human patients with ALI/ARDS.[46]

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.[74] 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

1. Udobi K, Childs E, Touijer K. Acute respiratory distress syndrome. Am Fam Physician 2003; 67:315–322.

2. Bernard G, Artigas A, Brigham K, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149:818–824.

3. Parent C, King L, Walker L, et al. Clinical and clinicopathologic finding in dogs with acute respiratory distress syndrome: 19 cases (1985–1993). J Am Med Vet Assoc 1996; 208:1419–1427.

4. Brady C, Otto C, Winkle T, et al. Severe sepsis in cats: 29 cases (1986–1998). J Am Vet Med Assoc 2000; 217:531–535.

5. Darke P, Gibbs C, Kelly D, et al. Acute respiratory distress in the dog associated with paraquat poisoning. Vet Rec 1977; 100:275–277.

6. Lopez A, Lane I, Hanna P. Adult respiratory distress syndrome in a dog with necrotizing pancreatitis. Can Vet J 1995; 36:240–241.

7. Santos C, Ferrer M, Roca J, et al. Pulmonary gas exchange response to oxygen breathing in acute lung injury. Am J Respir Crit Care Med 2000; 161:26–31.

8. Koshika T, Ishizaka A, Nagatomi I, et al. Pretreatment with FK506 improves survival rate and gas exchange in canine model of acute lung injury. Am J Respir Crit Care Med 2001; 163:79–84.

9. Parent C, King L, Winkle TV, et al. Respiratory function and treatment in dogs with acute respiratory distress syndrome: 19 cases (1985–1993). J Am Med Vet Assoc 1996; 208:1428–1433.

10. Bigatello L, Davignon K, Stelfox H. Respiratory mechanics and ventilator waveforms in the patient with acute lung injury. Respir Care 2005; 50:235–245.

11. Hunter T. Acute respiratory distress syndrome in a 10-year-old dog. Can Vet J 2001; 42:727–729.

12. Mangialardi R, Martin G, Bernard G, et al. Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain, and death in patients with sepsis. Crit Care Med 2000; 28:3137–3145.

13. Suh G, Chung M, Park S, et al. Partial liquid ventilation with perfluorocarbon improves gas exchange and decreases inflammatory response in oleic acid-induced lung injury in beagles. J Korean Med Sci 1999; 14:613–622.

14. Luh S, Tsai C, Shau W, et al. Effects of gabexate mesilate (FOY) on ischemia-reperfusion-induced acute lung injury in dogs. J Surg Res 1999; 87:142–163.

15. Chen DL, Schuster DP. Positron emission tomography with [18F]fluorodeoxyglucose to evaluate neutrophil kinetics during acute lung injury. Am J Physiol Lung Cell Mol Physiol 2004; 286:L834–L840.

16. Castillo RD, Guerrero S, Escalante C, et al. Serum and pulmonary angiotensin converting enzyme as a marker of acute lung injury in an experimental model of adult respiratory distress syndrome. Ann Med Intern 1999; 16:229–233.

17. Ware L, Matthay M. The acute respiratory distress syndrome. N Engl J Med 2000; 342:1344–1349.

18. Walker T, Tidwell A, Rozanski E, et al. Imaging diagnosis: acute lung injury following massive bee envenomation in a dog. Vet Radiol Ultrasound 2005; 46:300–303.

19. Tamashefski J. Pulmonary pathology of the adult respiratory distress syndrome. Clin Chest Med 1990; 11:593–619.

20. Bellingan G. The pulmonary physician in critical care 6: the pathogenesis of ALI/ARDS. Thorax 2002; 57:540–546.

21. Anderson W, Thielen K. Correlative study of adult respiratory distress syndrome by light, scanning, and transmission electron microscopy. Ultrastruct Pathol 1992; 16:615–628.

22. Matthay M, Zimmerman G. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. Am J Respir Cell Mol Bio 2005; 33:319–327.

23. Garland A, Dawson N, Altmann I, et al. Outcomes up to 5 years after severe, acute respiratory failure. Chest 2004; 126:1897–1904.

24. Herridge M, Cheung A, Tansey C, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003; 248:683–693.

25. King L, Waddell L. Acute respiratory distress syndrome, In: Wingfield W, Raffe M. eds. The Veterinary ICU Book. Jackson Hole: Teton New Media; 2002, pp. 583–590.

26. Xiao S, Chunxue B, Qunying H, et al. Effect of continuous hemofiltration on hemodynamics, lung inflammation and pulmonary edema in a canine model of acute lung injury. Intensive Care Med 2003; 29:2034–2042.

27. Schutzer K, Larsson A, Risberg B. Leukotriene receptor antagonism prevents lung protein leakage and hypoxemia in a septic cat model. Eur Resp J 1994; 7:1131–1137.

28. Neely C, Jun J, Keith I. A1- adenosine receptor antagonists block endotoxin-induced lung injury. Am J Physiol 1997; 272:L353–L361.

29. Ye SQ, Simon BA, Maloney JP, et al. Pre-B-cell colony-enhancing factor as a potential novel biomarker in acute lung injury. Am J Respir Crit Care Med 2005; 171:361–370.

30. Wabg H, Shun C, Hsu S, et al. Fas/Fas ligand pathway is involved in the resolution of type II pneumocyte hyperplasia after acute lung injury: evidence from rat model. Crit Care Med 2002; 30:1528–1534.

31. Greene K, Wright J, Steinberg K, et al. Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med 1999; 160:1843–1850.

32. Novick RJ, Gilpin AA, Gehman KE, et al. Mitigation of injury in canine lung grafts by exogenous surfactant therapy. J Thorac Cardiovasc Surg 1997; 113:342–353.

33. Numata M, Suzuki S, Miyazawa N, et al. Inhibition of inducible nitric oxide synthase prevents LPS-induced acute lung injury in dogs. J Immunol 1998; 160:3031–3037.

34. Xie L, Liu Y, Zhao X, et al. Effects of prone position ventilation on inflammatory factors in blood and bronchial alveolar lavage fluid of acute respiratory distress syndrome dogs caused by pulmonary and extrapulmonary insults. Chin Med J 2004; 84: 1200–1204.

35. Liang H, Jiang C, Zhang X, et al. Modeling of acute respiratory distress syndrome in canine after inhalation of perfluoroisobutylene and preliminary study on mechanisms of injury. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi (Chinese J Ind Hygiene Occup Dis) 2004; 22:125–127.

36. Schutzer K, Haglund U, Flak A. Cardiopulmonary dysfunction in a feline septic shock model: possible role of leukotrienes. Circ Shock 1989; 29:13–25.

37. Schutzer K, Larsson A, Risberg B. Lung protein leakage in feline septic shock. Am Rev Resp Disease 1993; 147:1380–1385.

38. Suga K, Yuan Y, Ogasawara N, et al. Altered clearance of gadolinium diethylenetriaminepentaacetic acid aerosol from bleomycin-injured dog lungs: initial observations. Am J Respir Crit Care Med 2003; 167:1704–1710.

39. Martin C, Papazian L, Payan M, et al. Pulmonary fibrosis correlates with outcome in adult respiratory distress syndrome. A study in mechanically ventilated patients. Chest 1995; 107:196–200.

40. Raghu G, Striker L, Hudson L, et al. Extracellular matrix in normal and fibrotic human lungs. Am Rev Respir Dis 1985; 131:281–289.

41. Clark J, Milberg J, Steinberg K, et al. Type III procollagen peptide in the adult respiratory distress syndrome: association of increased peptide levels in bronchoalveolar lavage fluid with increased risk for death. Ann Intern Med 1995; 122:17–23.

42. Nakos G, Kitsiouli E. Bronchoalveolar lavage fluid characteristics of early intermediate and late phases of ARDS: alteration in leukocytes, proteins, PAF and surfactant components. Intensive Care Med 1998; 24:286–303.

43. Rosseau S, Hammerl P, Maus U, et al. Phenotypic characterization of alveolar monocyte recruitment in acute respiratory distress syndrome. Am J Physiol Lung Cell Mol Physiol 2000; 279:L25–L35.

44. Steinberg K, Milberg J, Martin T, et al. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. Am J Respir Crit Care Med 1994; 150:113–122.

45. Hashimoto N, Kawabe T, Imaizumi K, et al. CD40 plays a crucial role in lipopolysaccharide-induced acute lung injury. Am J Respir Cell Mol Biol 2004; 30:808–815.

46. Fan J, Ye R, Malik A. Transcriptional mechanisms of acute lung injury. Am J Physiol Lung Cell Mol Physiol 2001; 281:L1037–L1050.

47. Takemura Y, Iwasaki Y, Nagata K, et al. Influence of depletion of alveolar macrophages on apoptosis in Candida-induced acute lung injury. Exp Lung Res 2005; 31:307–321.

48. Shimabukuro D, Sawa T, Gropper M. Injury and repair in lung and airways. Crit Care Med 2003; 31:S524–S531.

49. Heflin A, Brigham K. Prevention by granulocyte depletion of increased vascular permeability of sheep lung following endotoxemia. J Clin Invest 1981; 68:1253–1260.

50. Baughman RP, Gunther KL, Rashkin MC, et al. Changes in the inflammatory response of the lung during acute respiratory distress syndrome: prognostic indicators. Am J Respir Crit Care Med 1996; 154:76–81.

51. Olman M, White K, Ware L, et al. Pulmonary edema fluid from patients with early lung injury stimulates fibroblast proliferation through IL-1b-induced IL-6 expression. J Immunol 2004; 172:2668–2677.

52. Bhatia M, Moochhala S. Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome. J Pathol 2004; 202:145–156.

53. Hamacher J, Lucas R, Lijnen R, et al. Tumor necrosis factor alpha and angiostatin are mediators of endothelial cytotoxicity in bronchoalveolar lavages of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2002; 166:651–656.

54. Armstrong L, Thickett D, Christie S, et al. Increased expression of functionally active membrane-associated tumor necrosis factor in acute respiratory syndrome. Am J Respir Cell Mol Biol 2000; 22:68–74.

55. Xie L, Liu Y, Zhao X, et al. Effects of lung protective ventilation on inhibiting inflammatory mediators released into plasma and bronchial alveolar lavage fluid in acute respiratory distress syndrome caused by pulmonary and extrapulmonary insults in dog. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue (Chinese Crit Care Med) 2004; 16:262–266.

56. Pittet J, Griffiths M, Geiser T, et al. TGF-[beta] is a critical mediator of acute lung injury. J Clin Invest 2001; 107:1537–1544.

57. Hybertson B, Jepson E, Allard J. Transforming growth factor beta contributes to lung leak in rats given interleukin-1 intratracheally. Exp Lung Res 2003; 29:362–373.

58. Dhainaut J, Charpentier J, Chiche J. Transforming growth factor-ß: a mediator of cell regulation in acute respiratory distress syndrome. Crit Care Med 2003; 31:S258–S264.

59. Betz S, Henson P. Production and release of platelet-activating factor (PAF): dissociation from degranulation and superoxide produciton in the human neutrophil. J Immunol 1980; 125:2756–2763.

60. Prescott S, Zimmerman G, Stafforini D, et al. Platelet-activating factor and related lipid mediators. Annu Rev Biochem 2000; 69:419–445.

61. Uhlig S, Goggel R, Engel S. Mechanisms of platelet-activating factor (PAF)-mediated responses in the lung. Pharmacol Rep 2005; 57(Suppl.):206–221.

62. Miotla J, Jeffery P, Hellewell P. Platelet activating factor plays a pivotal role in the induction of experimental lung injury. Am J Respir Cell Mol Biol 1998; 18:197–204.

63. Nagase T, Ishii S, Kume K. Platelet activating factor mediates acid induced lung injury in genetically engineered mice. J Clin Invest 1999; 104:1071–1076.

64. Kurdowska A, Noble J, Grant I, et al. Anti-interleukin-8 autoantibodies in patients at risk for acute respiratory distress syndrome. Crit Care Med 2002; 30:2335–2337.

65. Krupa A, Kato H, Matthay M, et al. Proinflammatory activity of anti-IL-8 autoantibody: IL-8 complexes in alveolar edema fluid from patients with acute lung injury. Am J Physiol Lung Cell Mol Physiol 2004; 286:L1105–L1113.

66. Miao C, Sun B, Jiang H, et al. Pharmacodynamics and pharmacokinetics of inhaled nitric oxide in dogs with septic acute respiratory distress syndrome. Acta Pharmacol Sin 2002; 23:278–284.

67. Aggarwal A, Baker C, Evans T, et al. G-CSF and IL-8 but not GM-CSF correlate with severity of pulmonary neutrophilia in acute respiratory distress syndrome. Eur Respir J 2000; 15:895–901.

68. Alba-Loureiro TC, Martins EF, Miyasaka CK, et al. Evidence that arachidonic acid derived from neutrophils and prostaglandin E2 are associated with the induction of acute lung inflammation by lipopolysaccharide of Escherichia coli. Inflamm Res 2004; 53: 658–663.

69. Gust R, Kozlowski J, Stephenson A, et al. Role of cyclooxygenase-2 in oleic acid-induced acute lung injury. Am J Respir Crit Care Med 1999; 160:1165–1170.

70. Leeman M, Beyl V, Biarent D, et al. Inhibition of cyclooxygenase and nitric oxide synthase in hypoxic vasoconstriction and oleic acid-induced lung injury. Am J Respir Crit Care Med 1999; 159:1383–1390.

71. Fukunaga K, Kohli P, Bonnans C, et al. Cyclooxygenase 2 plays a pivotal role in the resolution of acute lung injury. J Immunol 2005; 174:5033–5039.

72. Lo C, Fu M, Cryer H. Interleukin 10 inhibits alveolar macrophage production of inflammatory mediators involved in adult respiratory distress syndrome. J Surg Res 1998; 79:170–184.

73. Armstrong L, Milla A. Relative production of tumor necrosis factor alpha and interleukin 10 in adult respiratory distress syndrome. Thorax 1997; 52:442–446.

74. Geiser T AK, Jarreau PH, Ware LB, et al. Pulmonary edema fluid from patients with acute lung injury augments in vitro alveolar epithelial repair by an IL-1ß dependent mechanism. Am J Respir Crit Care Med 2001; 163:1384–1388.

75. Mohr A, Lobetti R, Lugt J. Acute pancreatitis: a newly recognized potential complication of canine babesiosis. J S Afr Vet Assc 2000; 71:232–239.

76. Neath P, Brockman D, King L. Lung lobe torsion in dogs: 22 cases (1981–1999). J Am Med Vet Assoc 2000; 217:1041–1044.

77. Orsher A, Kolata R. Acute respiratory distress syndrome: case report and literature review. J Am Anim Hosp Assoc 1982; 18:41–46.

78. Sprague R, Stephenson A, Mcmurdo L, et al. Nitric oxide opposes phorbol ester-induced increases in pulmonary microvascular permeability in dogs. J Pharmacol Exp Ther 1998; 284:443–448.

79. Wu W, Halebian P, Hariri R, et al. Differential effects of cyclooxygenase and thromboxane synthetase inhibition on ventilation-perfusion relationships in acid aspiration-induced acute lung injury. J Trauma 1992; 33:561–567.

80. Creamer K, McCloud L, Fisher L, et al. Pentoxifylline rescue preserves lung function in isolated canine lungs injured with phorbol myristate acetate. Chest 2001; 119:1893–1900.

81. Tamakuma S, Ogawa M, Aikawa N, et al. Relationship between neutrophil elastase and acute lung injury in humans. Pulm Pharmacol Ther 2004; 17:271–279.

82. Adhikari N, Burns K, Meade M. Pharmacologic therapies for adults with acute lung injury and acute respiratory distress syndrome. Cochrane Database Syst Rev 2004; 4:CD004477.

83. Bernard G. Acute respiratory distress syndrome: a historical perspective. Am J Respir Crit Care Med 2005; 172:798–806.

84. McIntyre R, Pulido E, Bensard D, et al. Thirty years of clinical trials in acute respiratory distress syndrome. Crit Care Med 2000; 28:3314–3331.