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Acute Lung Injury and Acute Respiratory Distress Syndrome in Foals

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Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are characterized by acute, uncontrolled interstitial and alveolar inflammation secondary to a pulmonary or systemic insult. Endothelial and epithelial damage increases alveolo-capillary permeability leading to protein-rich alveolar edema. Clinical manifestations include severe hypoxemia minimally responsive to oxygen therapy, decreased total lung compliance, and increased airway resistance. Foals present with acute onset of severe respiratory distress. In most cases the initial insult can be attributed to an underlying bacterial, or rarely, viral pneumonia. Laboratory findings include severe hypoxemia, hypo- or hypercapnia, leukocytosis, and hyperfibrinogenemia. Radiographic findings vary from heavy interstitial to coalescing alveolar patterns. Treatment consists of intranasal oxygen supplementation, anti-inflammatories, and antimicrobials if underlying bacterial infection is suspected. Based on limited available reports in foals, prognosis is guarded, but even severe cases can survive and return to athletic function.
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Acute lung injury (ALI) and the more severe form, acute respiratory distress syndrome (ARDS), are a syndrome of respiratory failure caused by noncardiogenic pulmonary edema, decreased pulmonary compliance, and ventilation-perfusion (V_A/Q) mismatch. It can occur secondary to a group of diverse diseases and incidents causing intra- or extrapulmonary injury. The syndrome has long been recognized and well described in human medicine. While recognition and awareness of ALI/ARDS in veterinary medicine is increasing, to date few clinical studies have been published in the peer-reviewed literature describing physical and laboratory findings as well as predisposing factors, treatment, and outcome. This article outlines the pathophysiologic events and their consequences for lung function as reported in human literature and summarizes what has been reported in equine literature describing typical case history, diagnostics, differential diagnoses, and treatment options.

Pathophysiology

ALI and ARDS are defined by the criteria established by the American-European Consensus Conference Committee (AECCC) in 1994[1] (Table 1). The definition includes acute onset, bilateral infiltrates on thoracic radiographs, a ratio of pulmonary arterial oxygen pressure (PaO_2) to the fraction of inspired oxygen (FiO_2) of 300 mm Hg or less for ALI and 200 mm Hg or less for ARDS and no clinical evidence of left arterial hypertension or a pulmonary arterial occlusion pressure of less than 18 mm Hg. Rather than a disease in itself, ALI/ARDS is the clinical expression of a group of diverse either intra- or extrapulmonary disease processes producing diffuse alveolar damage. The most common predisposing intrapulmonary insults are pneumonia, pulmonary contusion, aspiration of gastric contents, and smoke inhalation. Extrapulmonary diseases associated with ALI/ARDS include severe trauma, multiple transfusions, sepsis, and septic shock.[2] The initial insult provokes an inflammatory response aimed at clearing infection and repairing tissue damage.[3] The inflammation is tightly controlled and thus beneficial in most patients, resolving uneventfully during recovery. In some patients, however, the immune response becomes exaggerated and self-perpetuating, resulting in severe tissue damage.[3] An imbalance between pro- and anti-inflammatory mediators creates an autodestructive inflammatory response leading to activation of leukocytes, epithelial, and endothelial cells, increased migration and adhesion of leukocytes to the pulmonary vasculature, and releases of cytokines, vasoactive compounds, and reactive oxygen and nitrogen species.[4] Disruption of the endothelial-epithelial barrier leads to formation of interstitial pulmonary edema.[5] Once the pulmo-

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Table 1 Definition of Acute Lung Injury and Acute Respiratory Distress Syndrome

- Acute onset
- Bilateral infiltrates on chest radiographs
- PAWP* < 18 mm Hg or no clinical evidence of left arterial hypertension
- Acute lung injury: PaO_2:FiO_2† ≤ 300 mm Hg
- Acute respiratory distress syndrome: PaO_2:FiO_2 ≤ 200 mm Hg

*Pulmonary arterial wedge pressure.
†Parial arterial oxygen pressure to fraction of inspired oxygen ratio.

nary safety factors are exhausted, the alveolar barrier collapses suddenly and alveoli are flooded with protein-rich edema fluid.[2] Cross-talk and amplification between the inflammatory and the coagulation cascade creates a procoagulant environment in the tissue and promotes intra-alveolar and intravascular fibrin deposition.[6] Intra-alveolar fibrin interferes with gas exchange and may predispose the lung to fibrosis, while thrombi in the pulmonary microvasculature contribute to pulmonary dysfunction and V_A/Q mismatch.

Normal oxygenation of the blood depends on an intact alveolar unit comprised of alveolar epithelium, interstitial space, basement membrane and capillary endothelium, and matching of alveolar ventilation (V_A) with pulmonary perfusion (Q). To optimize gas exchange, ventilation of the alveolus must be matched with perfusion of the capillary bed surrounding it. In the normal lung, the ratio of ventilation to perfusion is approximately 1, indicating that most ventilated alveoli are adequately perfused and exchange of O_2 and CO_2 can take place. Ventilation-perfusion mismatch occurs when blood flow is distributed to nonventilated alveoli (low V_A/Q ratio = venous admixture or shunt) or well-ventilated areas of the lung are underperfused (high V_A/Q ratio = dead space ventilation). Pulmonary edema creates areas of low V_A/Q ratio, resulting in hypoxemia with a normal or decreased $Paco_2$ from compensatory increase in respiratory rate. As filling of the alveoli with proteinaceous fluid and debris increases, they cease to participate in ventilation and the condition becomes progressively less responsive to exogenous oxygen supplementation.[2] With high shunt fractions, PaO_2 becomes independent of FiO_2. Only if the shunt fraction increases significantly, $Paco_2$ begins to increase as well. Areas of high V_A/Q ratio cause hyoxemia and hypercapnia due to insufficient exchange of CO_2. They may occur with pulmonary emphysema, bullae formation, or in conditions characterized by decreased blood flow such as impaired cardiac output or pulmonary thrombembolism.

Resolution of pulmonary edema depends on the integrity of the alveolar epithelium. Fluid transport is facilitated by paracellular absorption following an osmotic gradient created by sodium channels in alveolar epithelial type I and II cells and transcellular transport via aquaporin-5 transport proteins expressed in type I cells. Removal of debris and preoteinaceous components relies on cellular clearance.[2] With minor damage to the alveolar epithelium, the edema fluid can be reabsorbed within 12 hours after onset of ALI. If large areas of epithelium are denuded, repair via accelerated epithelial cell replication, spreading, and migration is necessary before the edema fluid can be removed. Clinically, these processes correlate with marked improvement observed in some patients within a short time, while patients with extensive epithelial damage have prolonged respiratory impairment and gradual recovery.[2]

In equine medicine, early reports described cases of mainly fatal acute respiratory distress attributed to bronchointerstitial pneumonia.[7,8] The authors suspected an unidentified viral or toxic agent, but despite intensive search no common underlying agent could be identified. Predominant features included a fairly homogenous age group (foals 1–7 months of age), although some younger and older animals were included, a sudden onset of severe respiratory distress and a high mortality. Postmortem findings consisted of alveolar epithelial necrosis, focal alveolar hemorrhage, inflammatory cell infiltrates, alveoli filled with protein-rich edema fluid, and hyaline membranes and occasional microthrombi in the interstitial capillaries.[7,8] The first clinical report by Lakritz and coworkers described clinical, radiographic, and pathologic findings in these foals.[9] The authors suspected that not a single etiologic agent, but rather multiple agents leading to a common pulmonary response. Recently, the criteria established by the AECCC were applied to a group of foals presenting with acute respiratory distress.[10] These reports are the basis for the description of typical historical, clinical and diagnostic findings, and treatment options (Table 2).

History

Affected foals are predominantly between 1 and 9 months of age, although cases in younger foals have been reported.[7-10] No breed or sex predilection has been noted. There may be a

Table 2 Summary of History, Clinical Signs, Diagnostics, and Therapeutics for a Foal With ALI/ARDS

History	No abnormalities
	Previous respiratory disease
	Other systemic disease
Clinical Signs	Increased respiratory rate and respiratory effort
	Increased heart rate
	± Fever
	Injected or cyanotic mucous membranes
	Crackles and wheezes or absence of lung sounds on thoracic auscultation
Diagnosis	Acute onset of severe respiratory distress
	Heavy interstitial or alveolar pattern on thoracic radiographs
	PaO_2/FiO_2 < 300 mm Hg (PaO_2 < 63 mm Hg on room air)
	No signs or left sided cardiac failure
	Minimal response to oxygen supplementation
Treatment	Intranasal oxygen insufflation (10–30 L/min)
	Antimicrobials if indicated by primary disease process
	Steroidal anti-inflammatory drugs (e.g., prednisolone sodium succinate at 2.0 mg/kg/d IV divided in 2–4 doses)
	Intravenous fluid therapy and nutritional support if indicated