Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: The Dorothy Russell Havemeyer Working Group on ALI and ARDS in Veterinary Medicine

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Abstract

Background: As veterinary medicine has become more sophisticated, with greater numbers of veterinary patients receiving intensive care, more patients with an acute respiratory distress (ARDS)-like syndrome have been recognized.
Methods: A consensus definition meeting was held for the purpose of developing veterinary-specific definitions for acute lung injury (ALI) and ARDS.
Results/conclusions: Three clinically based definitions for acute lung injury and acute respiratory distress-like syndromes occurring in veterinary patients were described. Neonatal equine respiratory distress syndrome (NERDS) was defined separately due to the specific requirement for primary developmental surfactant dysfunction and lack of an inflammatory component. Five diagnostic criteria categories were established for Veterinary ALI/ARDS (Vet ALI/ARDS) with 4 required and a fifth highly recommended criteria. A strong consensus was reached that onset of respiratory distress must have been acute and that known risk factors must be present. Additional criteria included evidence of pulmonary capillary leak with no evidence of increased pulmonary capillary pressure, evidence of inefficient gas exchange and, finally, evidence of inflammation. Some features of ALI/ARDS in the neonatal horse were recognized as unique, therefore, equine neonatal ALI/ARDS (EqNALI/EqNARDS) was similarly defined but with a graded gas exchange inefficiency table to allow for normal developmental changes in gas exchange. Use of these definitions in planning prospective studies of these problems in veterinary patients should allow for more direct comparisons of studies and clinical trials, with a larger goal of improving outcome in veterinary patients.

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Introduction

A syndrome of acute respiratory distress in adults, closely resembling respiratory distress in infants, was first described in the human medical literature in 1967.[1] The 12 patients detailed in that initial article had an acute onset of tachypnea, hypoxemia, panlobular infiltrates on chest radiographs and a loss of lung compliance. In 1971, those same investigators coined the term adult respiratory distress syndrome (ARDS) to describe adult patients presenting with the above constellation of clinical signs.[2] Since that time, ARDS has been the

subject of many clinical trials and basic science studies aimed at improving the consistently dismal outcome in these patients.

The European–American Consensus Committee (EACC) on ARDS was formed specifically to develop a uniform definition of ARDS to aid clinical trial design and interpretation of results by providing a common, useful definition of acute lung injury (ALI) and ARDS.[3,4] The conference investigators agreed that ARDS is a severe form of ALI and recommended that the syndrome be termed Acute Respiratory Distress Syndrome rather that Adult Respiratory Distress Syndrome. ARDS and ALI were defined in humans by the EACC as follows: (1) acute onset; (2) bilateral infiltrates on chest radiographs; (3) hypoxemia; and (4) no evidence of left atrial hypertension (pulmonary artery occlusion pressure [PAOP] $< 18\,mmHg$). The degree of hypoxemia was deemed more severe in ARDS and defined as a PaO_2/FiO_2 ratio $\leq 200\,mmHg$ whereas a PaO_2/FiO_2 ratio $\leq 300\,mmHg$ is defined as ALI. Other clinical definitions of ALI/ARDS have since appeared, including the Lung Injury Score (LIS) and the Delphi system, based on similar diagnostic criteria.[5–7]

ALI/ARDS is an entity that occurs in a wide variety of clinical settings including, but not limited to sepsis, multiple/massive emergency transfusions (transfusion-related acute lung injury), near-drowning, smoke inhalation, trauma, pancreatitis, and aspiration of gastric contents. ALI and ARDS are characterized by noncardiogenic pulmonary edema, an increase in extravascular lung water due to primary pulmonary vascular endothelial injury or primary alveolar epithelial injury.

A PubMed literature search at the time of writing revealed a total of 12,409 citations for 'ARDS' and 12,680 citations for 'acute respiratory distress syndrome'. A search using 'acute lung injury' yielded 13,590 citations and 'ALI' revealed 9940 citations. While many of these papers used animal models (primarily dogs, pigs and sheep, for basic pathophysiologic research) very few manuscripts described clinical ARDS and ALI in veterinary medicine.[8] Clinical veterinary publications have been limited to case reports of pulmonary edema of noncardiogenic origin, and the majority are authored by small animal practitioners.[9–27] Many of the reports of non-cardiogenic pulmonary edema attribute the event to negative pressure pulmonary edema or endotoxemia.[22–28] Objective measurements of pulmonary edema (extravascular lung water [ELW], or extravascular thermal volume) are not commonly performed in the veterinary patient, although techniques for ELW measurement have been applied experimentally to dogs and horses.[29–33] Only one group has attempted the measurement of ELW in the awake, standing normal horse.[33]

As veterinary medicine has become more sophisticated, with greater numbers of veterinary patients receiving intensive care, more patients with an ARDS-like syndrome have been recognized. A review of ALI/ARDS in veterinary medicine recently called for clear definitions applicable to veterinary patients, using criteria both appropriate and applicable to veterinary clinical patients and recognizing species and developmental differences where they occur.[34] The larger purpose of the veterinary specific definition is to assist the development of basic scientific and prospective clinical trials, including multicenter studies, that are valid and readily comparable. Acute lung injury/ARDS studies using criteria defined for the veterinary population should allow for improved treatment and outcomes of veterinary patients affected by these syndromes, as has been the case in human medicine.

Materials and Methods

Following approval by the Dorothy Russell Havemeyer Foundation of a topic specific consensus meeting on veterinary definition for ALI and ARDS, a call for abstracts relating to ALI and ARDS in veterinary medicine was disseminated. Specifically, the call for abstracts was sent to veterinarians who are board certified by the American Colleges of Veterinary Internal Medicine and Veterinary Emergency and Critical Care, in addition to being posted on several associated internet list serves. The final study group included authors of submitted abstracts and individuals active in clinical or basic research relating to ALI and ARDS in veterinary medicine and specialists in ALI and ARDS research in human medicine, in addition to a representative from the sponsoring organization.

Each workshop participant presented a 30-minute abstract relating to either basic or clinical research in ALI and ARDS. A summary of the preceding day's abstracts was presented at the start of each day, with the final day of the meeting focused on formulating specific definition(s). The group reviewed several current clinical definitions of ALI/ARDS and other relevant materials, including definitions based on developmental differences.[2–7,35] Following this preliminary discussion the participants determined that there was an initial need for 3 ALI/ARDS veterinary working definitions: Neonatal equine respiratory distress syndrome (NERDS), veterinary ALI and ARDS (VetALI/VetARDS) and equine neonatal ALI/ARDS (EqNALI/EqNARDS).

Results and Discussion

Abstracts

A total of 10 abstracts and 2 summaries were presented over the first 2 days with the third and final day reserved for summary, discussion, and definition development. Three papers specifically presented clinical cases/case series representing 62 total foals (47 neonatal foals and 15 foals older than 30 days but <1 year of age).[a,b,c] For all 3 studies the EACC definition was used, but with some variation. Modifications of the EACC definition for the studies included: calculating the PaO_2/FiO_2 ratio on room air, using only lateral thoracic radiographs to determine the presence of diffusely distributed lung pathology, and determining normal left heart function on the basis of clinical lack of evidence of dysfunction. Two papers discussed postmortem histopathologic lesions and the finding of severe pulmonary disease rather than diffuse alveolar damage in many of the cases. Clearly defined postmortem tissue sampling protocols that take into consideration the relationship of the clinically defined syndrome with gross and histopathology findings could not yet be established in veterinary species because: the studies were retrospective in nature, the heterogeneous distribution of pathologic processes within the lung, and the variability that depends on the stage of development or repair. Defining gross and histopathological findings for ALI/ARDS is deserving of a prospective clinical study.

Three papers presented findings on various aspects of cyclical recruitment of the lung in ALI/ARDS in a rabbit lung lavage model of ALI. The first described cyclical recruitment of atelectatic lung with mechanical ventilation, recognized by PaO_2 oscillations, and its potential role in the development of ventilator-associated ALI (VALI).[36] The study group demonstrated that increased levels of positive end-expiratory pressure (PEEP) reduced end-expiratory collapse and, subsequently, cyclical recruitment. A novel finding was that the same effect on cyclical recruitment was achieved by increasing respiratory rate alone, clarifying the importance of the dynamic behavior of atelectasis and the role of time on tissue responsiveness to any applied pressure change. A second study from this group outlined the role of cyclical recruitment as a mediator of inflammation in acute lung injury and potentially the development of VALI.[d] This work again demonstrated the heterogeneity of distribution and severity of injury to the lung with ALI, in addition to suggesting that cyclical recruitment led to greater inflammation than did mere overdistention of alveoli. Finally, as a clinical application, the group presented data evaluating 'bedside' monitoring techniques for recognition of cyclical recruitment in ventilated patients.[e]

The effect of inhaled recombinant activated Protein C (hrAPC) in a pig model of ARDS induced by intravenous injection of lipopolysaccharide (LPS) was reported by one group, where hrAPC appeared to ameliorate some of the LPS-induced pulmonary injury.[f] The use of echocardiography as an alternative to pulmonary arterial catheterization (PAC) for evaluating left heart function in the diagnosis and management of ALI/ARDS was presented in one abstract[g] and, finally, an overview of ALI and ARDS in human medicine was presented.

Development of definitions

After thorough discussion of the current methods of defining ALI and ARDS in human medicine (EACC, LIS and Delphi Score) the participants determined that the requirements that were common to all definitions included: *an acute onset*, the *presence of risk factors*, a measure of *abnormal gas exchange*, and evidence of *respiratory capillary leak* not associated with increased capillary pressure and evidence of *inflammation*. The group agreed that some species and age specific definitions would be required and that data are currently lacking to fully develop all definitions at this time. The following definitions were discussed and developed:

NERDS: A syndrome of severe respiratory distress occurring over the first 24 hours following birth has been recognized in neonatal foals since the 1960s.[37–39] This equine neonatal syndrome is presumed to be similar to infant respiratory distress syndrome (IRDS), also known as simply 'RDS' or 'hyaline membrane disease', occurring primarily in very low birth weight premature human infants.[40–43] In human medicine, IRDS is a distinct syndrome that is clinically and developmentally distinguished from ALI and ARDS, and from pediatric ALI/ARDS. IRDS is a primary surfactant deficiency related to gestation length and readiness for birth of the fetus. In human infants, surfactant is produced by the alveoli during the final one-third of gestation. Treatment of babies born at <30 weeks of gestation with exogenous inhaled surfactant prophylactically, rather than as a rescue therapy, is now considered a standard of care in human medicine.[44] Respiratory distress usually begins at, or soon after, delivery and tends to worsen over time. Affected infants demonstrate tachypnea, nasal flaring, intercostal and sternal retractions, and expiratory grunting. Low or very-low birth weight preterm infants who lack pulmonary surfactant may fail to initiate ventilation in the delivery room and rapidly become hypoxic and apneic. Chest radiography shows diffuse atelectasis that appears in the non-mechanically ventilated baby as reduced lung volume, with homogeneous haziness or the 'ground glass' appearance of lung fields, and air bronchograms. Positive

Table 1: Definition of NERDS: Neonatal Equine Respiratory Distress Syndrome

Etiology: Primary surfactant deficiency due to failure of final fetal pulmonary surfactant metabolism maturation. Diagnosis requires meeting all criteria listed below:

1. Persistent hypoxemia, progressive hypercapnia
   a. Hypoxemia defined as $PaO_2 < 60$ mmHg taken with foal in lateral recumbency while breathing room air
2. Appropriate risk factors present: (1 or more of 3)
   a. Very early gestational age: less than 290 days of gestation OR less than 88% of average of dam's previous gestation lengths
   b. Induction of parturition
   c. Caesarian section
3. Failure to develop normal immediate postpartum respiratory patterns: development/persistence of paradoxical breathing over first several hours of life, persistent tachypnea
4. At 24 hours of age or less 'ground glass' appearance of lateral radiograph(s) of lungs taken either standing or in lateral recumbency
5. Absence of evidence of fetal inflammatory response syndrome (FIRS) at birth
   a. Normal white blood cell count, differential and fibrinogen concentration for gestational age
6. Congenital cardiac disease ruled out as a cause of hypoxemia

pressure ventilation can reverse the radiographic findings of atelectasis. Infant respiratory distress syndrome is diagnosed when a premature infant has respiratory distress and a characteristic chest radiograph. The most common differential diagnosis is group B streptococcal pneumonia.[45]

In the foal, lung maturation continues after birth as it does in the human, and surfactant production has begun by 88% of gestation length, or around day 290 for most foals.[38,39] One recent study suggested that surfactant maturation is not complete in the newborn term foal based on increased surface tension compared to adult horses, which is consistent with continued lung maturation following birth.[46] Because surfactant replacement therapy may be beneficial in these cases, and the importance of distinguishing NERDS cases from foals with other respiratory problems such as meconium aspiration syndrome, persistent pulmonary hypertension of the neonate or ALI/ARDS associated with sepsis, a separate definition for NERDS is necessary and is presented in Table 1.

VetALI/VetARDS: A syndrome resembling ALI and ARDS in human medicine has been recognized in veterinary species, most commonly described in small animals (dogs and cats) and foals although single reports exist in many species.[9–27] All veterinary descriptions to date have relied on variations of the EACC human consensus definition. All conference participants agreed there were insufficient data at this time to develop species-specific definitions but that a general definition for mammalian veterinary species could be developed. One general and one species/age specific definition were developed. The species/age specific definition applies to equine neonates presenting with ALI/ARDS-like symptoms but without the primary surfactant deficiency required for a diagnosis of NERDS.

Five criteria categories were established for VetALI/VetARDS, with 4 required criteria and a fifth criteria that is highly recommended although considered optional at this time (Table 2). A strong consensus was reached that onset of respiratory distress must have been acute and that known risk factors must be present. The current proposed list of risk factors (Table 3) is based both on clinical observation of veterinary patients and known risk factors for human ALI/ARDS.

The criteria defining the mechanism of pulmonary capillary leak departed from the limited human definition (PAOP < 18 mmHg), by allowing any diagnostic tool that may be applied to rule out causes of leak not due to increased capillary pressure. Radiography is commonly employed and readily available to most veterinary practitioners and the presence of diffuse bilateral infiltrates remains part of the EACC definition of ALI/ARDS. Recognizing that radiographic techniques in some veterinary species do not allow practical use of ventrodorsal or dorsoventral (VD or DV) thoracic radiography, the veterinary definition stipulates bilateral/diffuse infiltrates present in more than 1 quadrant or lobe, allowing for lateral thoracic radiographs in species such as the horse. Additionally, the veterinary definition permits evidence of capillary leak to be described in the following ways: the presence of a bilateral dependent gradient density with computed tomography (CT); the presence of proteinaceous fluid within the conducting airways; and increased extravascular lung water in species where techniques measuring extravascular lung water have been validated.

All evidence of pulmonary capillary leak must be accompanied by some evidence that left heart function is acceptable and that capillary leak is not secondary to increased pulmonary vein/left atrial pressures. For species in which pulmonary vascular pressures have been extensively studied, such as the horse, pulmonary artery catheterization with a pulmonary artery occlu-

Table 2: Definition of VetALI/VetARDS: Veterinary Acute Lung Injury and Acute Respiratory Distress Syndrome

Must meet at least one each of the first 4 criteria; 5 is a recommended but optional measure

1. Acute onset ($<$72 hours) of tachypnea and labored breathing at rest
2. Known risk factors (see Table 3)
3. Evidence of pulmonary capillary leak without increased pulmonary capillary pressure*: (any one or more of the following):
    a. Bilateral/diffuse infiltrates on thoracic radiographs (more than 1 quadrant/lobe)
    b. Bilateral dependent density gradient on CT
    c. Proteinaceous fluid within the conducting airways
    d. Increased extravascular lung water
4. Evidence of inefficient gas exchange (any one or more of the following):
    a. Hypoxemia *without* PEEP or CPAP and *known* FiO$_2$
        i. PaO$_2$/FiO$_2$ ratio
            1. $\leq$ 300 mmHg for VetALI
            2. $\leq$ 200 mmHg for VetARDS
        ii. Increased alveolar-arterial oxygen gradient
        iii. Venous admixture (noncardiac shunt)
    b. Increased 'dead-space' ventilation
5. Evidence of diffuse pulmonary inflammation
    a. Transtracheal wash/bronchoalveolar lavage sample neutrophilia
    b. Transtracheal wash/bronchoalveolar lavage biomarkers of inflammation
    c. Molecular imaging (PET)

*No evidence of cardiogenic edema (one or more of the following):
    PAOP $<$ 18 mmHg (adult horse).
    No clinical or diagnostic evidence supporting left heart failure, including echocardiography.

CT, computed tomography; PEEP, postive end expiratory pressure; CPAP, continuous positive airway pressure; FiO$_2$, fraction inspired oxygen; PET, positron emission tomography; PAOP, pulmonary artery occlusion pressure.

Table 3: Risk Factors for Veterinary Acute Lung Injury and Acute Respiratory Distress Syndrome (VetALI/VetARDS)

1. Inflammation
2. Infection
3. Sepsis
4. Systemic inflammatory response syndrome (SIRS)
5. Severe trauma
    a. Long bone fracture
    b. Head injury
    c. Pulmonary contusion
6. Multiple transfusions
7. Smoke inhalation
8. Near-drowning
9. Aspiration of stomach contents
10. Drugs and toxins

VetALI/VetARDS, veterinary acute lung injury and acute respiratory distress syndrome.

sion pressure $<$18 mmHg is acceptable, but absence of clinical signs suggestive of left-sided heart failure is considered sufficient.[47,48] However, the conference participants uniformly encouraged development of less invasive means of documenting appropriate left heart function including, but not limited to, echocardiography.

Ineffective or inefficient gas exchange lies at the heart of any ALI/ARDS definition for any age or species, and hypoxemia is a hallmark of ALI/ARDS. With the exception of neonatal foals, where developmental differences are well known, acceptable evidence for ineffective gas exchange include any one or more of the following: hypoxemia *without* PEEP or continuous positive airway pressure and *known* (not estimated) FiO$_2$ (i.e., room air, mechanical ventilation with known FiO$_2$, or oxygen cage with known FiO$_2$); a PaO$_2$/FiO$_2$ ratio $\leq$ 300 mmHg for VetALI and $\leq$ 200 mmHg for VetARDS; increased alveolar-arterial oxygen gradient; or large venous admixture (non-cardiac shunt). Increased 'dead-space' ventilation may also be considered as evidence of inefficient gas exchange if cardiac function/output is normal and minute volume is appropriate.[49]

The development of ALI/ARDS involves the pro-inflammatory cascade and the working group added a fifth criteria category of evidence of pulmonary inflammation as an ideal but, due to current diagnostic constraints, optional criteria at this time. The group recognizes the potential complication of primary respiratory causes of ALI/ARDS as a source of inflammation but encourages future investigation of potential markers of inflammation specific for ALI/ARDS. Currently, transtracheal wash/bronchoalveolar lavage cytologic samples demonstrating neutrophilia and transtracheal wash/bronchoalveolar lavage biomarkers of inflammation are considered evidence of pulmonary inflammation. Molecular imaging techniques such as Positron Emission Tomography (PET) may prove useful in the future.

Table 4: Definition of EqNALI/EqNARDS: Equine Neonatal Acute Lung Injury/Respiratory Distress Syndrome

Postnatal age	Normal PaO_2 (mmHg)	Normal PaO_2/FiO_2 ratio	NALI PaO_2/FiO_2 cutoff	NARDS PaO_2/FiO_2 cutoff
60 minutes	60.9 ± 2.7	>300 mmHg	<175 mmHg	<115 mmHg
12 hours	73.5 ± 3.0	>350 mmHg	<200 mmHg	<140 mmHg
24 hours	67.6 ± 4.4	>350 mmHg	<200 mmHg	<140 mmHg
48 hours	74.9 ± 3.3	>350 mmHg	<200 mmHg	<140 mmHg
4 days	81.2 ± 3.1	>400 mmHg	<250 mmHg	<160 mmHg
7 days	90.0 ± 3.1	>430 mmHg	<280 mmHg	<190 mmHg

As for VetALI/VetARDS but adhering to the following age-dependent adaptation of the PaO_2/FiO_2 ratio in term foals in lateral recumbency breathing room air ($FiO_2 = 0.21$) based on age-dependent normal values for PaO_2 under similar conditions.

FiO_2, fraction inspired oxygen; NALI, neonatal acute lung injury; NARDS, neonatal acute respiratory distress syndromes.

EqNALI/EqNARDS: A specific definition for ALI/ARDS occurring in the neonatal (defined as <1 week of age) foal was developed to recognize the well-documented changing gas exchange efficiency that occurs developmentally in these animals over the first week of life. Similar age-specific definitions have been proposed for the human neonatal and pediatric patient population to recognize these differences from the adult population.[50] Diagnosis of EqNALI/EqNARDS is essentially identical to that of VetALI/VetARDS except that an age-specific progressive scale of the PaO_2/FiO_2 ratio abnormality is utilized to document hypoxemia (Table 4). The table is based on blood gas values for foals breathing room air and in lateral recumbency, a position known to decrease PaO_2 values in normal foals by up to 10 mmHg.[51–54]

Conclusions

Three definitions based on clinically relevant criteria for acute lung injury and acute respiratory distress-like syndromes occurring in veterinary patients have been described. Use of a common definition/inclusion criteria in planning prospective studies of respiratory injury/respiratory distress in critically ill veterinary patients will allow direct comparisons of studies and clinical trials, and meet the larger goal of improving outcome in veterinary patients with these disease syndromes. Further refinement of these definitions will be necessary as more species and age specific information is obtained.

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