AIP: What We Know, and What We Are Learning We Don't Know

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SCFA Feedlot Management School

Overview

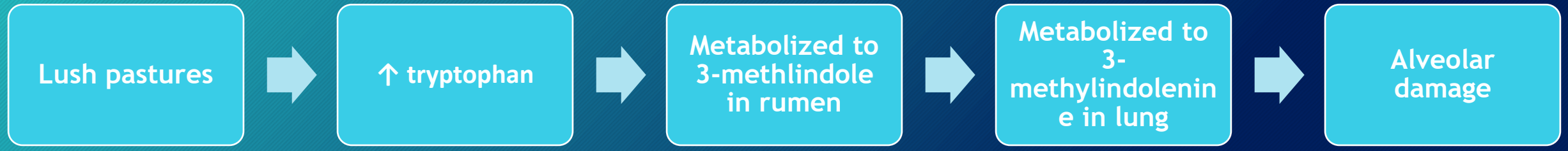
1. Review of AIP - History
2. Clinical Presentation
3. Pathology
4. Known causes
5. Speculated causes
6. Acute Respiratory Distress Syndrome
7. Moving forward …

History

- Term introduced by Blood in 1962
- Bovine respiratory disorder with some or all of the following:
  - Congestion
  - Edema
  - Hyaline membranes
  - Interstitial emphysema
  - Alveolar epithelial hyperplasia
  - Fibrosis and cellular infiltration of inter alveolar septa
- Acute and chronic forms described
- AIP of pastured cattle (fog fever, perilla mint toxicosis, etc.)
- AIP of feedlot cattle

AIP – Cattle on Pasture

- "Fog Fever" – Acute Bovine Pulmonary Edema and Emphysema



- Other causes
  - Perilla mint ketones
  - Moldy sweet potatoes → 4-Ipomeanol
  - Hypersensitivities

Clinical Presentation

- Sudden onset of labored breathing
- Head and neck extended
- Open mouth breathing +/- frothing, expiratory grunt
- +/- fever
- Often with basewide stance
- Sway backed
- May crowd water tanks

Animal and Environmental Demographics

- “Classic” demographics
  - Female, late feeding period, +/- MGA, late summer, dusty environment
- From the older literature (Curtis 1979)
  - Between 6 and 24 months of age, initial BRD but recovered, off feed, then developed severe respiratory dyspnea in the recovery period over 6-12 hours
- Other demographics
  - Local feedyards in Saskatchewan, verbal communication
  - No sex predilection, middle feeding period, March to April, sometimes into May, sometimes respond to treatment

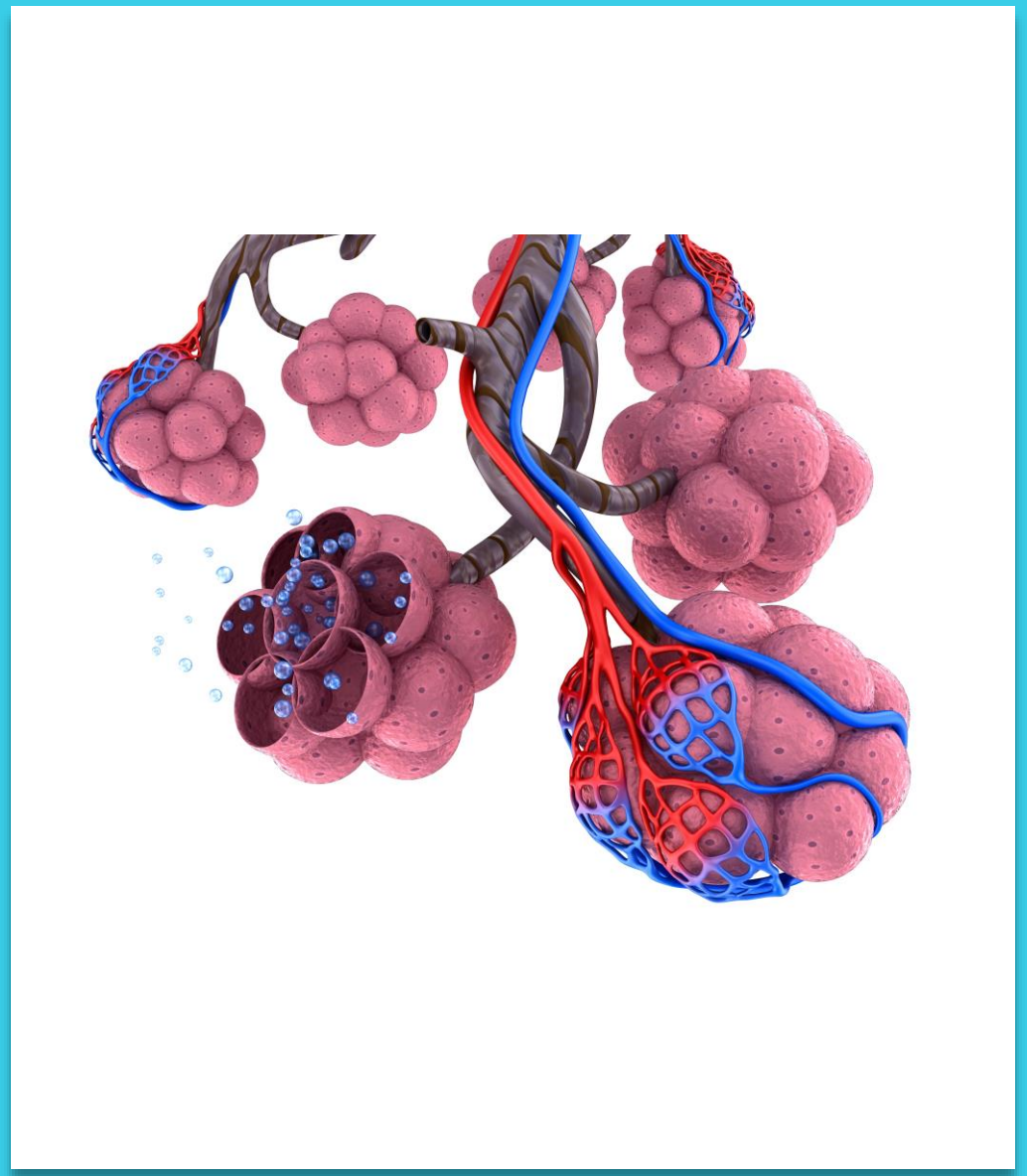
Necropsy

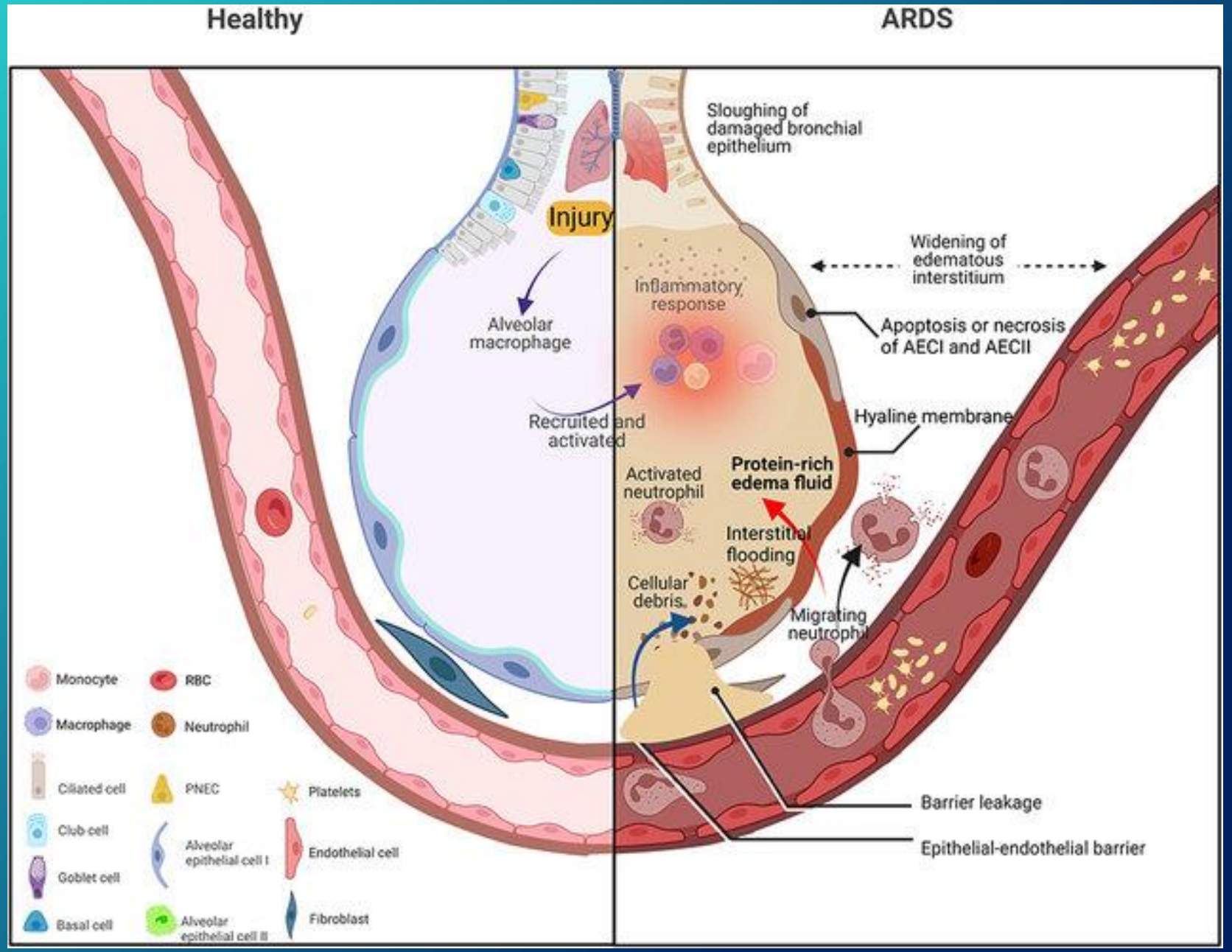
- Lungs that fail to collapse
- Lungs are firm and rubbery
- “Patchwork” appearance to lungs
- Emphysematous bullae
- Interstitial emphysema
- Edema
- +/- hemorrhage

Eugene Janzen

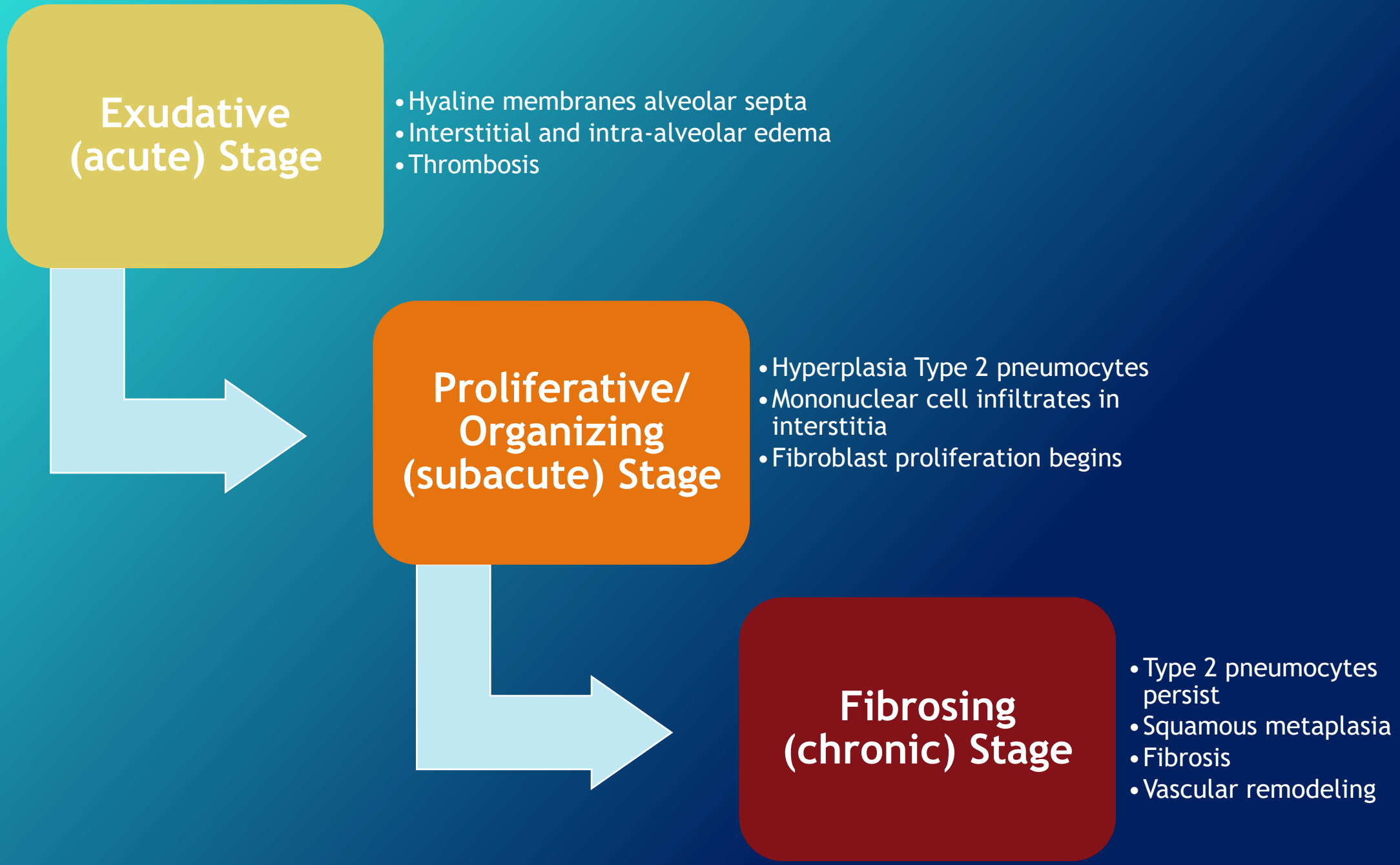
Under the Microscope – Diffuse Alveolar Damage

- Diffuse Alveolar Damage – Acute exudative phase
  - Damage to alveoli or endothelial cells
  - Alveoli flooded → alveolar edema
  - Alveolar macrophages release proinflammatory cytokines
  - Neutrophils recruited → damage alveoli
  - Hyaline membranes form – cellular debris, plasma proteins, surfactants
  - Fibrin thrombi in pulmonary vessels



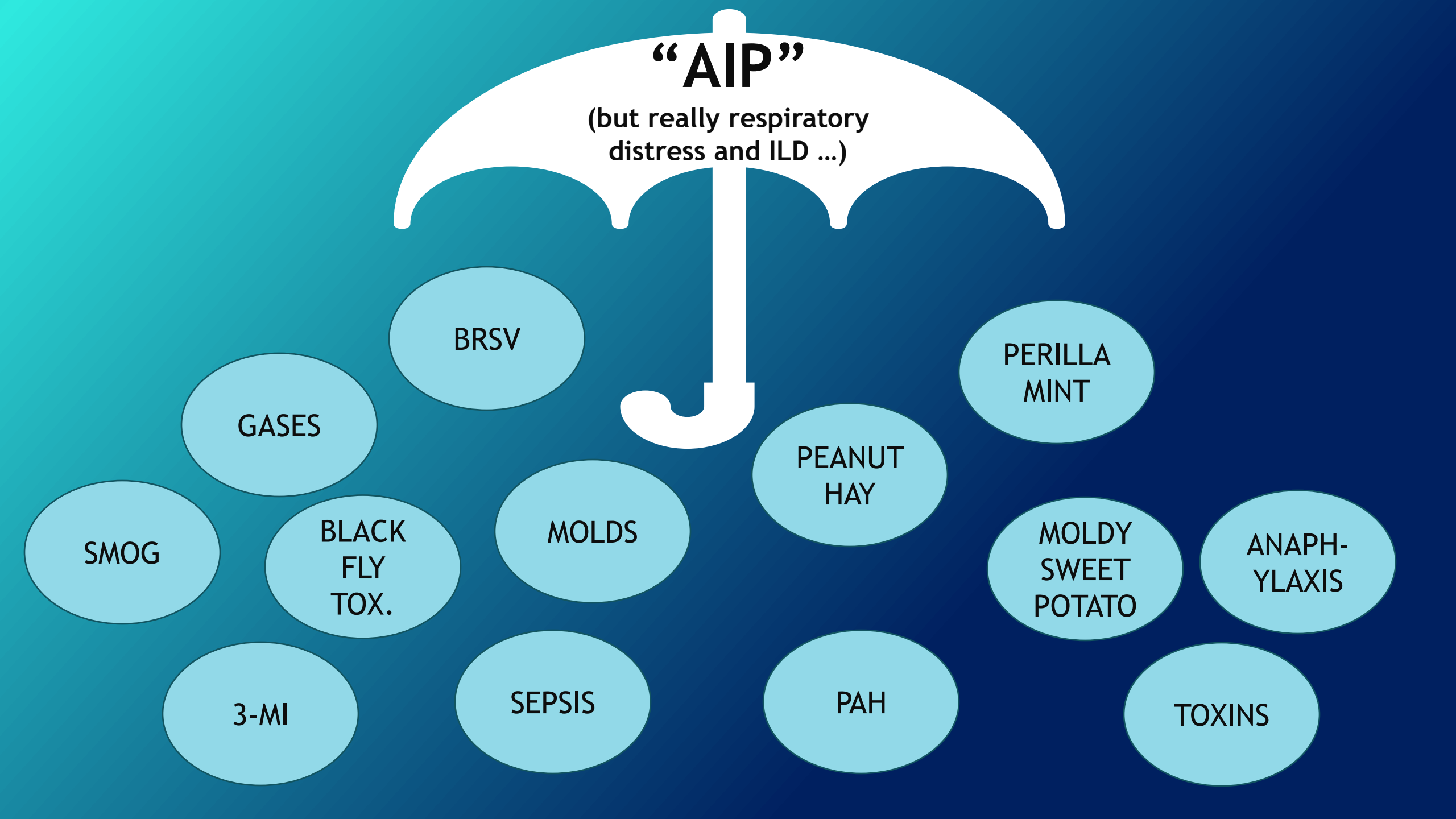


1. Cao C, Zhang L, Liu F, et al. Therapeutic Benefits of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome: Potential Mechanisms and Challenges. *J Inflamm Res* 2022;15:5235-5246.


Exudative (acute) Stage
• Hyaline membranes alveolar septa
• Interstitial and intra-alveolar edema
• Thrombosis
Proliferative/ Organizing (subacute) Stage
• Hyperplasia Type 2 pneumocytes
• Mononuclear cell infiltrates in interstitia
• Fibroblast proliferation begins
Fibrosing (chronic) Stage
• Type 2 pneumocytes persist
• Squamous metaplasia
• Fibrosis
• Vascular remodeling

Known Causes and Diseases with Similar Lesions

- ABPE - 3-methylindole damage associated with lush pastures
- BRSV
  - Bovine Respiratory Syncytial Virus
- Ingestion of Perilla mint - ketones
- *Ingestion of plants contaminated with Fusarium spp.*
  - Moldy sweet potato – 4-Ipomeanol
  - Peanut hay
- Ingestion of *Brassica spp.*
- Inhalation of noxious gases
  - Smoke
  - Welding gases (Zinc oxide)
  - Smog
  - Nitrogen dioxide (Silo Filler's Disease)
- Lung worms (*Dictyocaulus spp.*)
- Black fly (*Simulium spp.*) outbreaks – Simulitoxicosis
- Hypersensitivities
  - Anaphylaxis
  - Mold exposure (*Microsporum spp.*, *Saccharopolyspora spp.*)
  - Milk allergy


"AIP"
(but really respiratory distress and ILD …)
BRSV
GASES
SMOG
BLACK FLY TOX.
MOLDS
PEANUT HAY
PERILLA MINT
MOLDY SWEET POTATO
ANAPH-YLAXIS
3-MI
SEPSIS
PAH
TOXINS

Proposed Causes and Associations – Feedlot

- BRSV
  - Ruled out – virus not associated with disease
- 3-MI
  - Alberta study found an association - AIP vs control (Ayroud 2000)
  - Western US study found association – AIP and BP vs control (Loneragan 2001)
- Female?
  - Association
- Melangestrol acetate (MGA)
- Late summer - weather
  - US
  - Canada – March and April?
- Dust
  - Mechanical
  - Aerosolized endotoxin?

None of these proposed etiologies have been proven as definitive causes

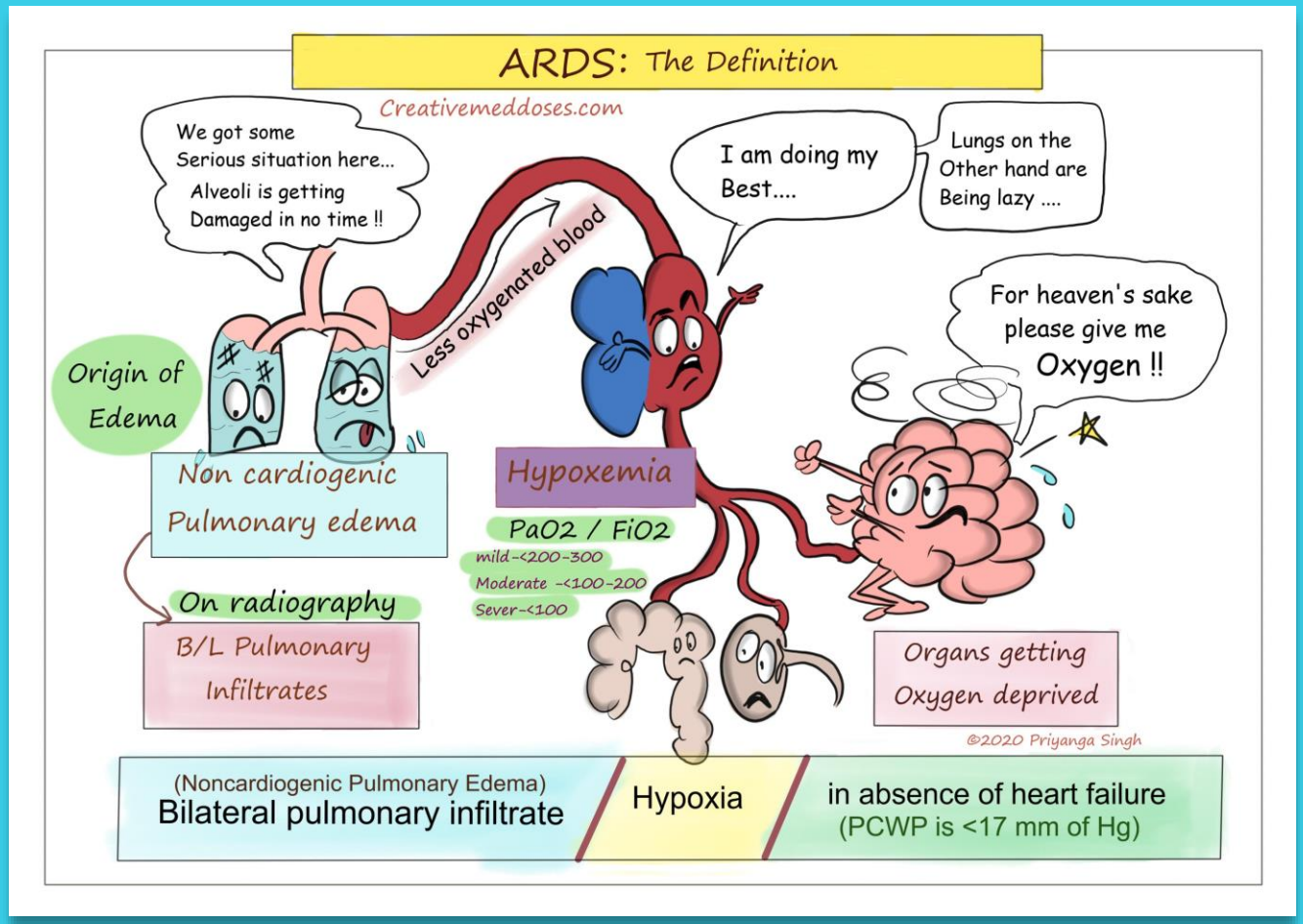
The clinical and pathologic manifestations of what we call AIP isn’t so much a single disease as it is a way that lungs react to insult

We are using a pathologic description “Atypical/Acute Interstitial Pneumonia” to describe a clinical disease’s presentation

Acute Respiratory Distress Syndrome

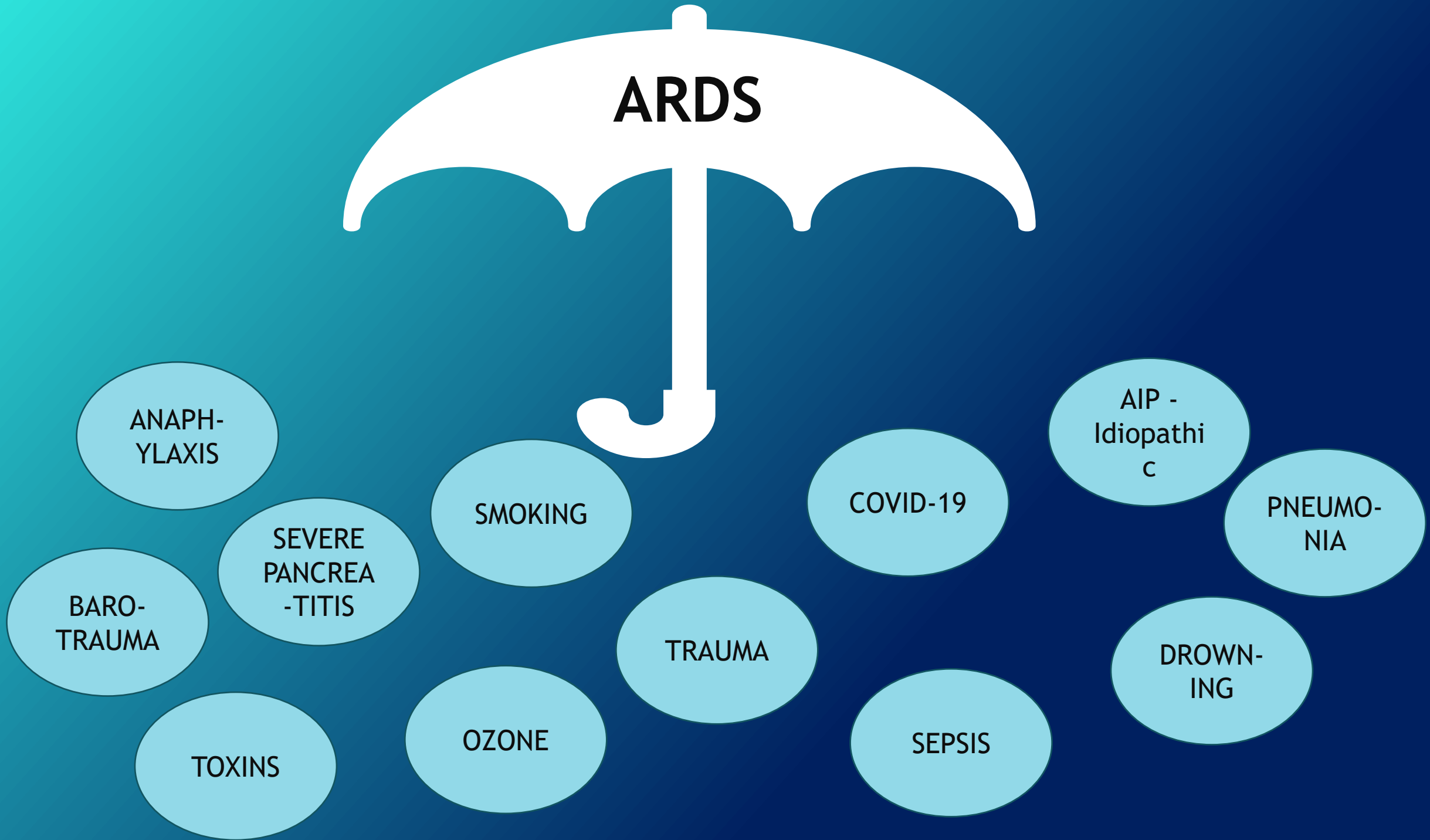
Acute Respiratory Distress Syndrome (ARDS)

- Initially defined in 1967
- Characterized by:
  - Acute dyspnea
  - Acute hypoxemia
  - Non-cardiogenic pulmonary edema
  - Reduced lung compliance
- Formalized definitions in 1992, 2012 – Berlin definition
- High-mortality – 30-40%



ARDS – Known Causes

- Dozens of etiologies
  - 60 or more
- Pneumonia
  - COVID-19
- Sepsis
- Severe Pancreatitis
- Exposure to pollution, toxic gases
- Acute Interstitial Pneumonia (AIP)/Hammann-Rich Syndrome
  - This term only used for idiopathic cases


ARDS
ANAPH-
YLAXIS
SMOKING
COVID-19
AIP -
Idiopathi
c
PNEUMO-
NIA
SEVERE
PANCREA
-TITIS
BARO-
TRAUMA
TRAUMA
DROWN-
ING
OZONE
SEPSIS
TOXINS

ARDS in Veterinary Medicine

VetARDS	• Veterinary ARDS • Must meet at least one each of 4 criteria
NERDS	• Neonatal Equine Respiratory Distress Syndrome
EqNARDS	• Equine Neonatal Respiratory Distress Syndrome

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,

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.

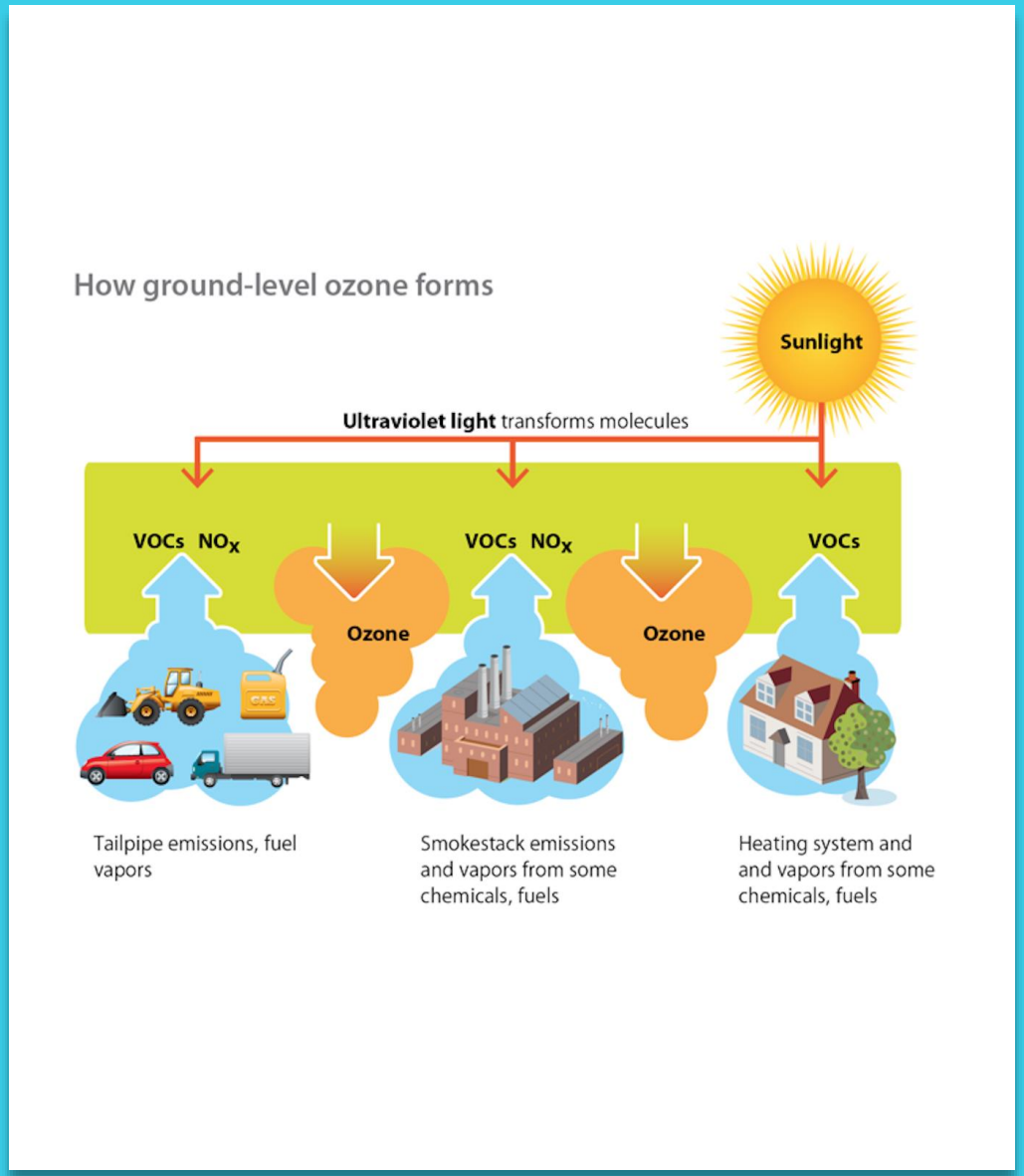
Bovine Acute Respiratory Distress Syndrome (BARDS)

- No criteria have been established for cattle
- Should criteria focus on those that we can actually measure/identify in the field?
- Could this allow us to create a more precise case definition to rule in/rule out the disease?
- Would this make us think about “AIP” as more of a syndrome rather than a specific disease?
- Would thinking of “AIP” as a syndrome help us to think more broadly about the disease and consider multiple possible etiologies in feedlot medicine?

What can we learn from ARDS that might give us some causes to investigate in feedlot medicine?

Ideas for areas of investigation from ARDS

- Ozone
  - Humans – incidence of ARDS increases with increased ozone exposure
  - Animal models – acute ozone exposure → acute lung injury → death
  - Feline – ARDS was observed in kittens exposed to ozone-generating air purifier
- Toxins
  - Feed – fungal toxins
- Diet
  - Changes in gut microbiome → changes in bacterial products



Questions or comments?