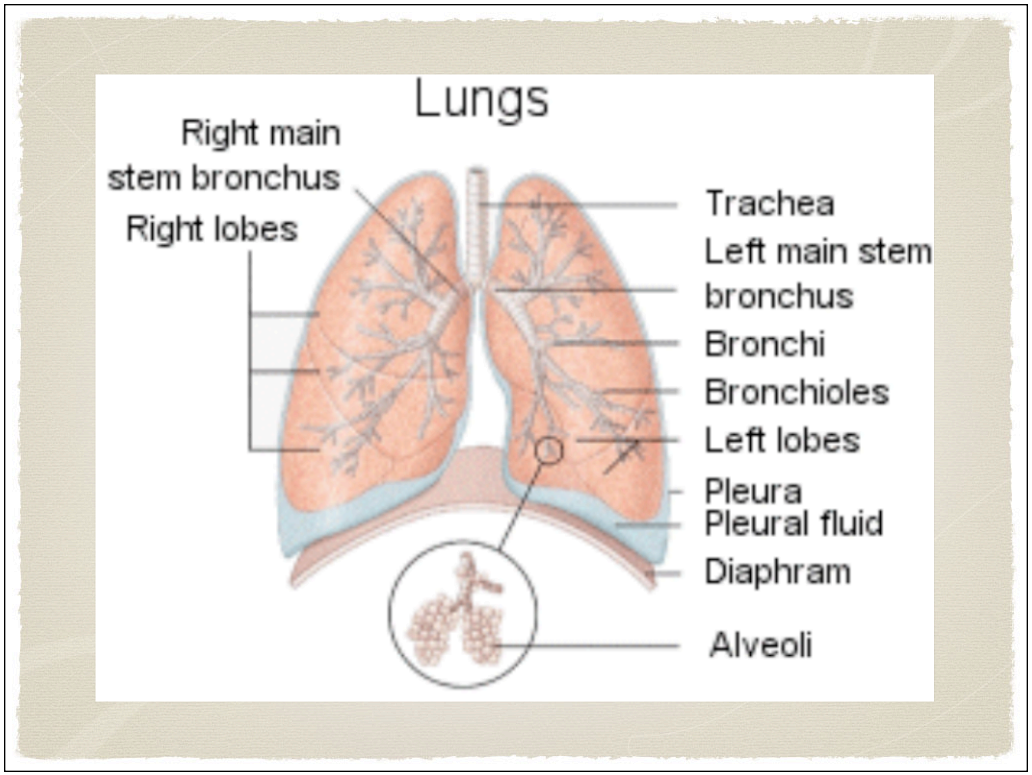
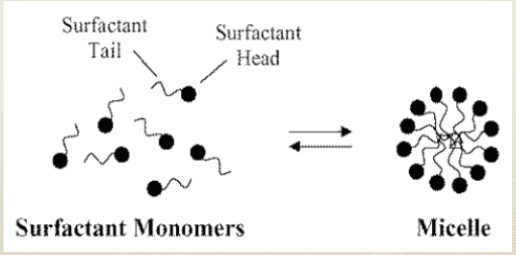
PATHOPHYSIOLOGY


Lungs
Right main stem bronchus
Right lobes
Trachea
Left main stem bronchus
Bronchi
Bronchioles
Left lobes
Pleura
Pleural fluid
Diaphram
Alveoli

Surfactant

- Detergent in the fluid of the lungs
- Secreted by type II alveolar cells
- Composed of phospholipids
- Decreases surface tension



Pathophysiology

- All disorders that result in ARDS acutely injure the alveolocapillary membrane and cause severe pulmonary edema.
- Can occur directly (insult to the lungs) or indirectly (acute systemic inflammatory response)

Patho Text

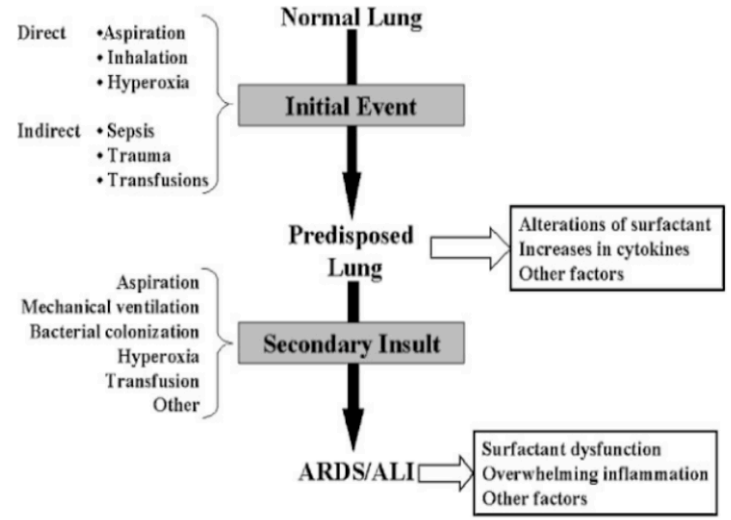
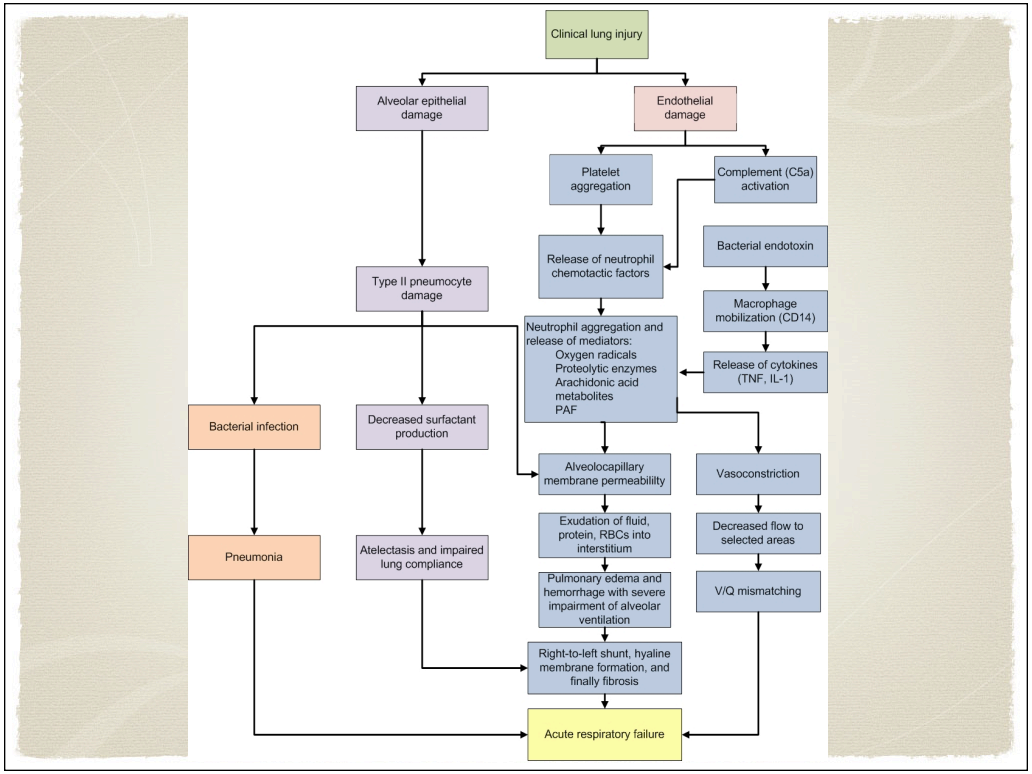
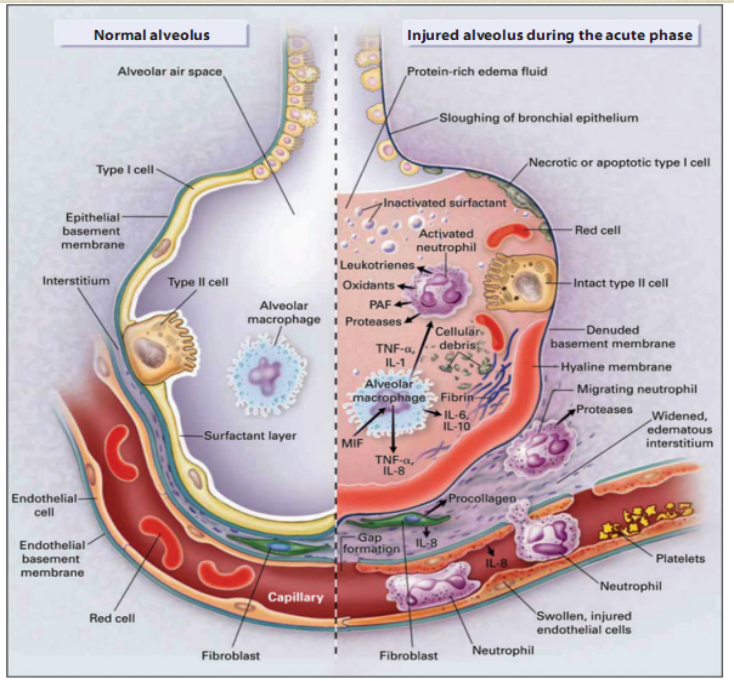


Figure 1 Paradigm representing the pathophysiology of ARDS. Multiple insults may occur, each contributing to the host's inflammatory response. If this response becomes overwhelming, progressive lung dysfunction may occur. Alterations in the endogenous surfactant system at various stages of this paradigm contribute to the development of ARDS (see text).

Cell Types and Inflammatory Mediators that Play a Key Role in Lung Injury

- Neutrophils
- Macrophages
- Complement
- Endotoxin
- Interleukin-1
- Tumor Necrosis Factor


Clinical lung injury
Alveolar epithelial damage
Endothelial damage
Platelet aggregation
Complement (C5a) activation
Release of neutrophil chemotactic factors
Bacterial endotoxin
Type II pneumocyte damage
Macrophage mobilization (CD14)
Neutrophil aggregation and release of mediators:
Oxygen radicals
Proteolytic enzymes
Arachidonic acid metabolites
PAF
Release of cytokines (TNF, IL-1)
Bacterial infection
Decreased surfactant production
Alveolocapillary membrane permeability
Vasoconstriction
Exudation of fluid, protein, RBCs into interstitium
Decreased flow to selected areas
Pneumonia
Atelectasis and impaired lung compliance
Pulmonary edema and hemorrhage with severe impairment of alveolar ventilation
V/Q mismatching
Right-to-left shunt, hyaline membrane formation, and finally fibrosis
Acute respiratory failure


Normal alveolus
Alveolar air space
Type I cell
Epithelial basement membrane
Interstitium
Type II cell
Alveolar macrophage
Surfactant layer
Endothelial cell
Endothelial basement membrane
Red cell
Capillary
Fibroblast
Injured alveolus during the acute phase
Protein-rich edema fluid
Sloughing of bronchial epithelium
Necrotic or apoptotic type I cell
Inactivated surfactant
Activated neutrophil
Red cell
Leukotrienes
Oxidants
PAF
Proteases
Intact type II cell
Cellular debris
TNF-α, IL-1
Denuded basement membrane
Hyaline membrane
Alveolar macrophage
Fibrin
Migrating neutrophil
Proteases
IL-6, IL-10
MIF
TNF-α, IL-8
Widened, edematous interstitium
Procollagen
Gap formation
IL-8
IL-8
Platelets
Neutrophil
Swollen, injured endothelial cells
Fibroblast
Neutrophil

Stages of ARDS

- Diffuse alveolar damage (DAD)
- Exudative (1-7 days)
- Proliferative (3-10 days)
- Fibrotic (>1-2 weeks)

Exudative Phase

- Capillary congestion
- Alveolar epithelial cell necrosis
- Interstitial and intra-alveolar edema and hemorrhage
- Neutrophils in the capillaries
- Alveolar ducts are dilated
- Alveoli are collapsed
- Fibrin thrombi may be present
- Most characteristic finding during this phase is the formation of hyaline membranes in alveolar ducts and air spaces.
- Lungs closely resemble the liver: dark red, airless, heavy, and stiff

Proliferative Phase

- Type II pneumocytes
  - Proliferate
  - Differentiate into Type 1 cells
  - Reline alveolar walls
- Fibroblast proliferation
  - Interstitial/alveolar fibrosis
- Ingestion of hyaline membranes by macrophage

Fibrotic Phase

- Lung recovers
- Resolution of
  - inflammation
  - excess cellularity
  - fibrosis settles
- Oxygenation improves
- Lung function may continue to improve for as long as 6 to 12 months after onset of failure
- There are different levels of pulmonary fibrotic changes between individuals who suffer from ARDS

Results of Edema

- Causes alveolar and capillary space to thicken
- Alveoli contain less gas
- Intrapulmonary shunting occurs
- As condition worsens:
  - Alveoli may collapse or fill completely with fluid
  - Deoxygenated blood leaving lungs
  - Difficulty breathing
  - Less oxygen to organs
  - MODS

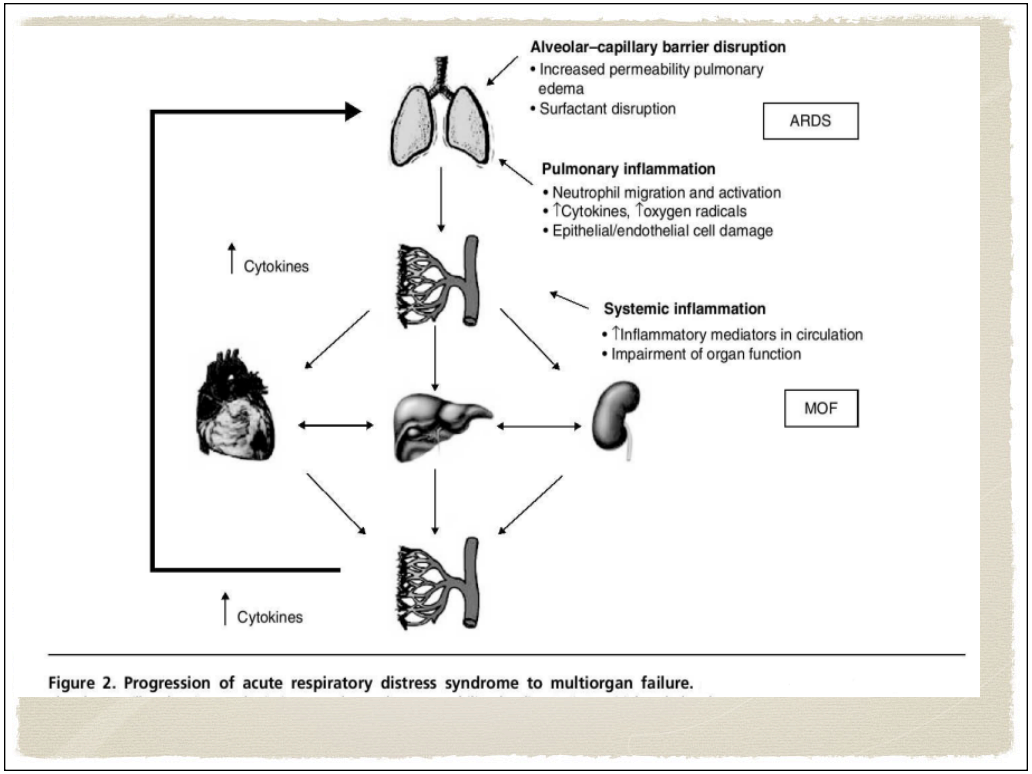
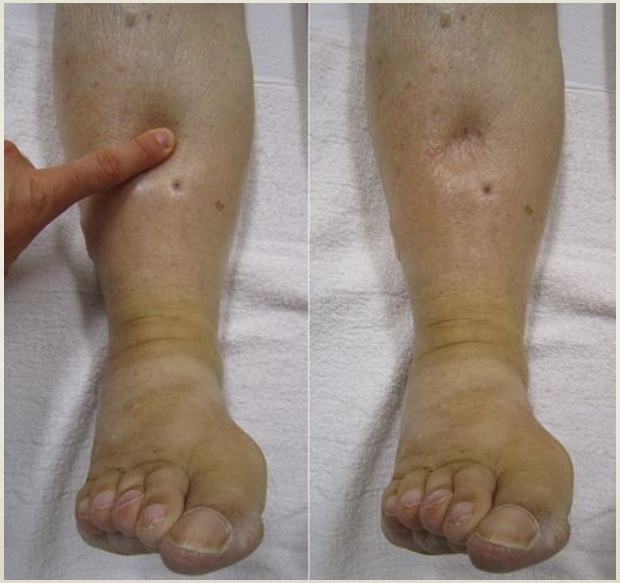


Figure 2. Progression of acute respiratory distress syndrome to multiorgan failure.

Pitting Edema



Pitting Classifications of Edema

- 1+ is if the pitting lasts 0 to 15 sec
- 2+ is if the pitting lasts 16 to 30sec
- 3+ is if the pitting lasts 31 to 60sec
- 4+ is if the pitting lasts >60sec

TREATMENT

Types of Treatments

- Ventilators
- Positioning
- Corticosteroids
- Surfactant
- Nitric Oxide
- Other
- Treatments aren't used to cure, but are used as supportive measures.

Ventilators

- Main treatment for ARDS combined with oxygen therapy
- Supports the patient's breathing and helps ensure their cells are being oxygenated
- Only proven treatment to significantly decrease mortality in ARDS

Types of Ventilators

- Negative-pressure ventilators
- Positive-pressure ventilators

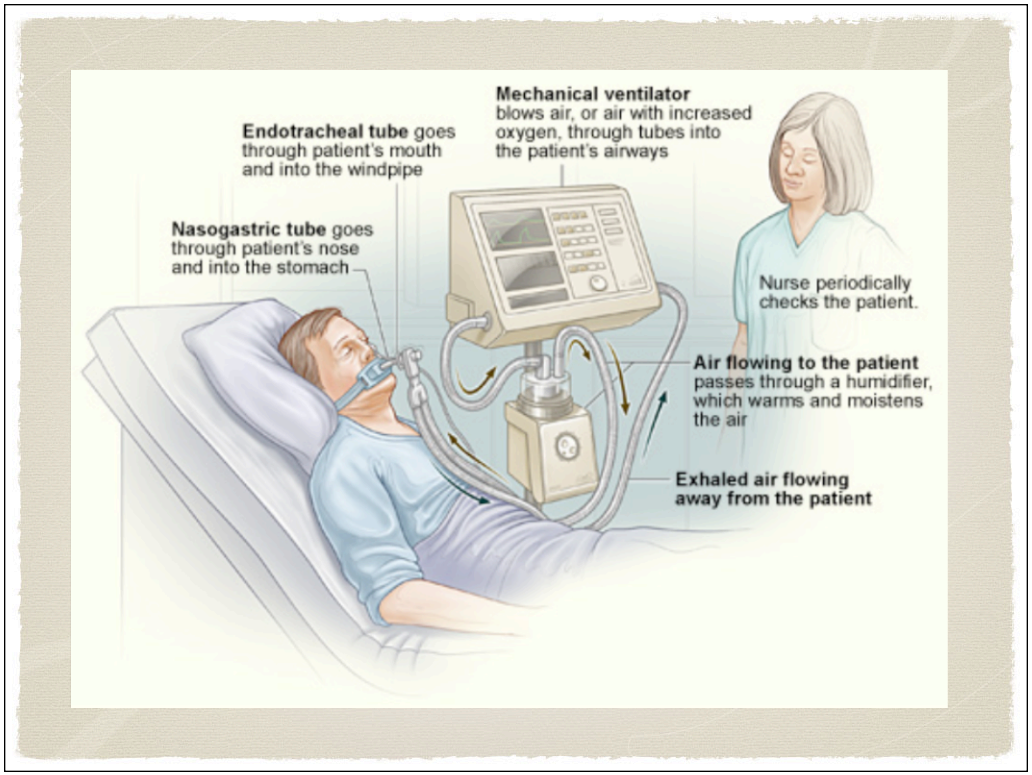
Negative-pressure Ventilation

- Involves enclosing either the whole body or the body from the neck down in order to imitate the physiological mechanisms used by the body to breathe
- Ex: iron lung- causes the lungs to inhale when the pressure inside the chamber is greater than that in the lungs and to exhale when the pressure is lower than that in the lungs.

Polio

Positive-pressure Ventilation

- Positive-pressure ventilation pushes air into the lungs to create a pressure difference that facilitates breathing.
- This type of ventilation is the type of mechanical ventilation that is used in treating most pulmonary disease and is used to treat ARDS.
- Often called PEEP (Positive End Expiratory Pressure)


Mechanical ventilator
blows air, or air with increased oxygen, through tubes into the patient's airways
Endotracheal tube goes through patient's mouth and into the windpipe
Nasogastric tube goes through patient's nose and into the stomach
Nurse periodically checks the patient.
Air flowing to the patient passes through a humidifier, which warms and moistens the air
Exhaled air flowing away from the patient

4 Modes of Ventilation

- Control
- Assist/control
- Synchronized intermittent mandatory ventilation
- Continuous positive airway pressure

Control Mode

- Ventilator controls the patient's breathing completely
- The machine triggers when breaths will be taken by the patient

Assist/Control Mode

- Allows patients to stimulate their own breaths.
- When a patient attempts to breathe the ventilator is triggered to assist with the breathing
- The ventilator can still be set with an amount of set breaths to ensure the patient is breathing sufficiently

Synchronized Intermittent Mandatory Ventilation Mode

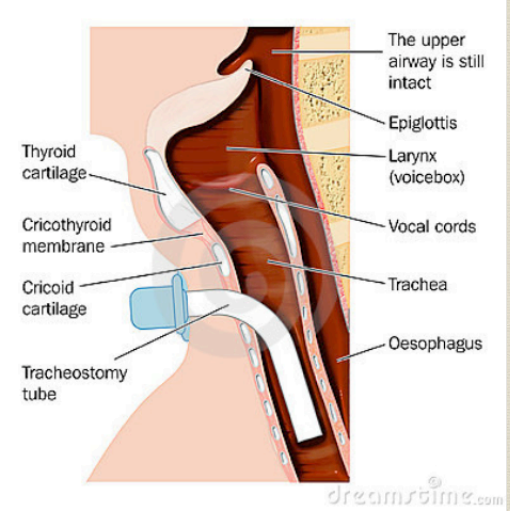
- Useful in helping a patient regain lung and breathing strength.
- Assists in breathing for a certain amount of breaths and then allows the patient to breathe without assistance for a set number of breaths.

Continuous Positive Airway Pressure (CPAP) Mode

- Does not provide any breathing assistance, but it controls the amount of oxygen and keeps track of the patients breathing
- Alarms go off if there is something wrong with the patient's breathing.

Ventilators

- Tube can be placed in:
  - Mouth
  - Nose
  - Trachea



Changes in Ventilation

- In 2000 The National Institutes of Health Sponsored ARDS Network funded a study dealing with the tidal volume used in ventilation.
- Found that a lower tidal volume 6 ml/kg was associated with significantly lower mortality rates when compared with the traditional tidal volume of 12 ml/kg. Lower tidal volume is now the standard treatment.
- Results in lower ventilation related lung injuries and problems.

Problems associated with Ventilation

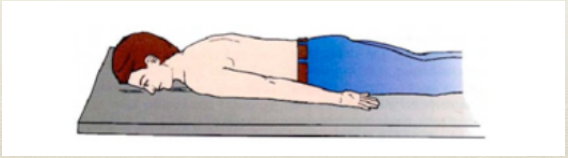
- Macroscopic damage
- Multiple organ dysfunction
- Pulmonary Edema
- Diffuse ventilator-induced lung injury
- Increased inflammation
- Production of cytokines that leak into systemic circulation.
- Patient may require weaning off of the ventilator
- May cause pneumonia

Combination Therapies with Ventilators

- Fluid conservation strategy with patient's with ARDS when no longer in shock is associated with reduced time on ventilators
- Sedatives and pain medications to help keep the patient in a calm and relaxed state while on ventilators

Prone Positioning

- Supine is the position that most patients are typically kept in.
- Studies have shown that by placing an ARDS patient in the prone position for about 7 hours each day for a period of time, they have improved oxygenation because of improved gas exchange
- Has not been proven to increase survival rates.



Pharmacotherapy

- Many medications have been tested to see if they provide any benefit in treating ARDS
- Most have no significant benefit
- There is a huge interest in finding a medication that can be helpful in treating ARDS since there are not a lot of options for treatment.

Pharmacotherapy	Mechanism of Action
Prostaglandin E1	Pulmonary vasodilator; decreases neutrophil activation; decreases platelet aggregation
N-acetylcysteine and procysteine	Antioxidant (scavenger of free radical oxygen species)
Corticosteroids	Multiple anti-inflammatory pathways; prevents collagen deposition
Surfactant	Restores normal mechanical properties of alveoli (surface tension, alveolar opening)
Dazoxiben	Anti-inflammatory agent and pulmonary vasodilator (inhibits thromboxane synthase)
Acyclovir	Treats herpes simplex virus, which can be found in lower respiratory tract of patients with lung injury
Indomethacin	Anti-inflammatory agent (decreases thromboxane production by inhibiting cyclooxygenase)
Pentoxifylline	Prevents neutrophil chemotaxis and activation (phosphodiesterase inhibitor)
Neutrohil elastase inhibitor	Inhibits pro-inflammatory and tissue destroying protease
Interleukin-10	Immunomodulator (anti-inflammatory cytokine)
Ketoconazole	Multiple anti-inflammatory pathways (inhibits thromboxane synthase, 5-lipoxygenase, alveolar macrophages)

Corticosteroids

- Not recommended for preventative ARDS treatment
- Associated with an increase in mortality
- Use may have a potential benefit if used in long term ARDS.
- May decrease mortality or decrease ventilation time.

Exogenous Surfactant Replacement

- Function to decrease surface tension
- May also have antioxidant and anti-inflammatory effects
- Success in treating neonatal respiratory distress syndrome (nRDS)
- Unsure in Adults
- Those who have ARDS as a result of pneumonia or aspiration have seen positive results with surfactant and are associated with decreased mortality rates.

Nitric Oxide

- Function: causes vasodilatation and relaxes smooth muscle so it has a potential to increase oxygenation
- In studies it increased amount of oxygenation, but did not decrease overall mortality
- Harmful effects:
    - Toxic in high amounts
    - Can inactivate proteins like surfactant
- More research needs to be done to determine its use.