UMC Utrecht

Acute inhalational exposure (Inhalatieletsels na toxische blootstelling)

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Disclosure

(potential) conflict of interest	**no**
Relevant relation with companies	Names of companies involved
• Sponsoring • Honorarium or consulting fee • Shareholder • Other relations?	• • • •

Triage following (acute) inhalational exposure

The following subjects will be discussed

- specific aspects concerning inhalational exposure to toxic agents
- how to distinguish between toxic lung injury caused by water soluble and almost water insoluble agents
- evaluation of the exposed patient
- the management of toxic lung injury

Triage following (acute) inhalational exposure

relevant aspects concerning exposure

Severity of injury depends on:

- exposure time
- concentration of the substance in air
- toxic potency of the substance
- exercise (respiratory minute volume, tidal volume, respiratory frequency)
- size of particle or droplet
- water solubility of the compound
- individual susceptibility

Triage following (acute) inhalational exposure

respiratory minute volume

Exercise will increase exposure to toxic agents by increase of respiratory minute volume (= tidal volume x respiratory frequency)

Exercise	Respiratory minute volume (l/min)
no	7-12
slight	10-26
moderate	26-44
heavy	44-64
extreme	>64

Triage following (acute) inhalational exposure

water solubility

Kind of agent determines the sort of lung injury

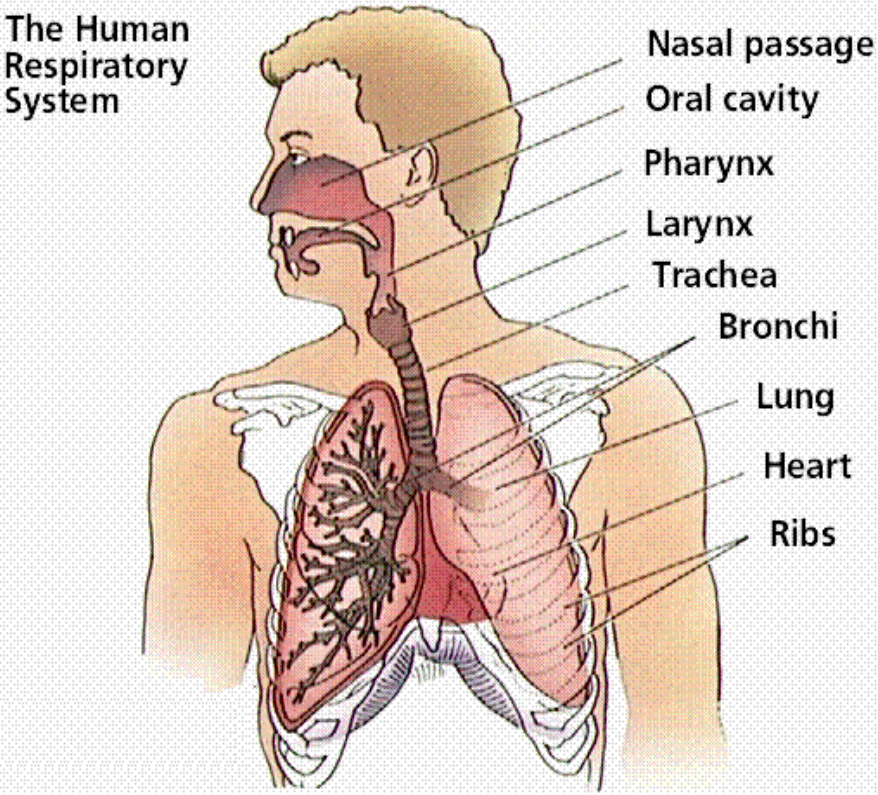
- type I — compounds dissolving easily in water cause primarily effects in the upper part of the airways

- type II — compounds dissolving hardly in water cause primarily effects deep in the lung in the alveolar region

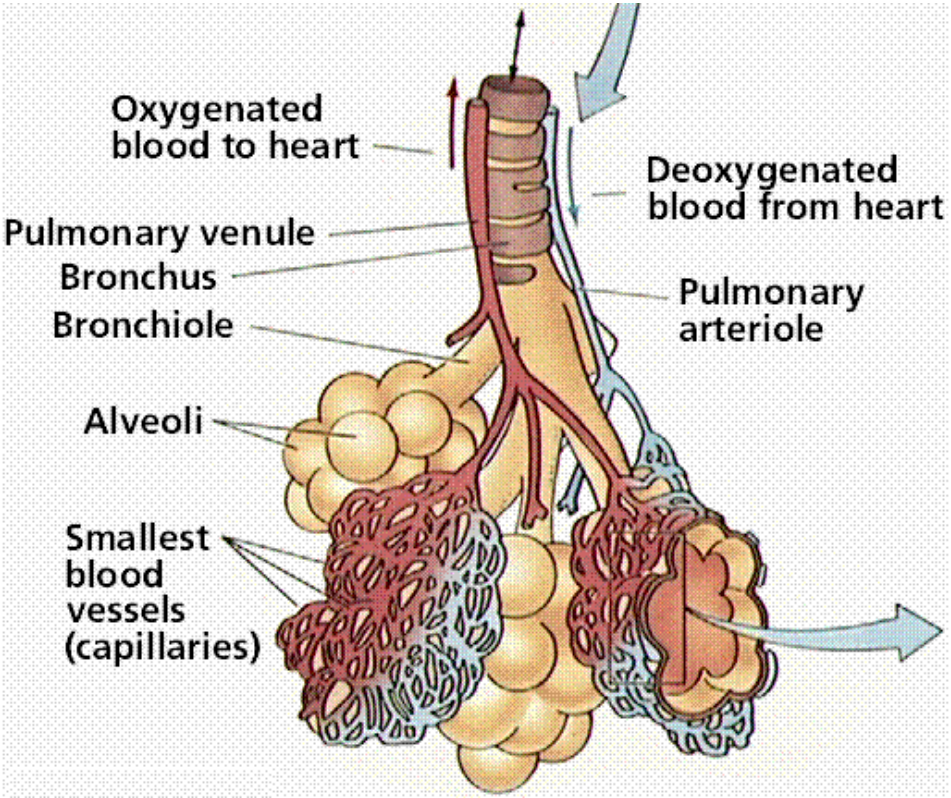
- type III — compounds easily absorbed in the lung without causing relevant lung tissue damage (primarily effects elsewhere in the body, carbon monoxide, cyanide, xylene, toluene)

Triage following (acute) inhalational exposure

airways (particle size, water solubility)



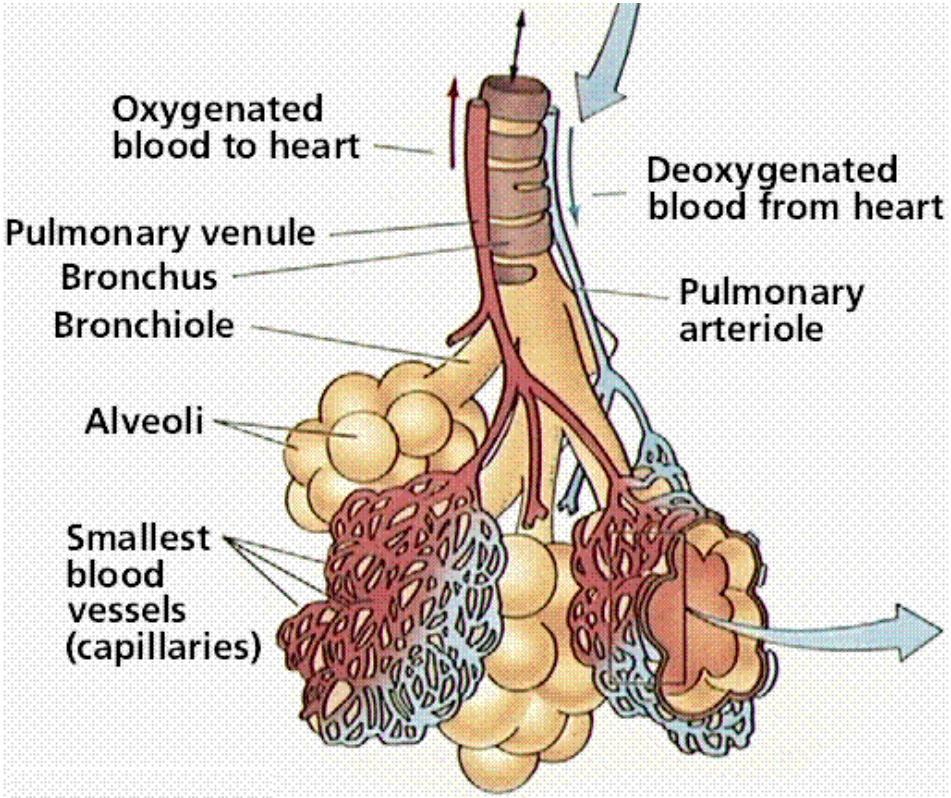
- 'ineffective' part of tidal volume
(= circa 150 ml, dead space ventilation)
- almost continuous air movement
- mucosa covered with mucus

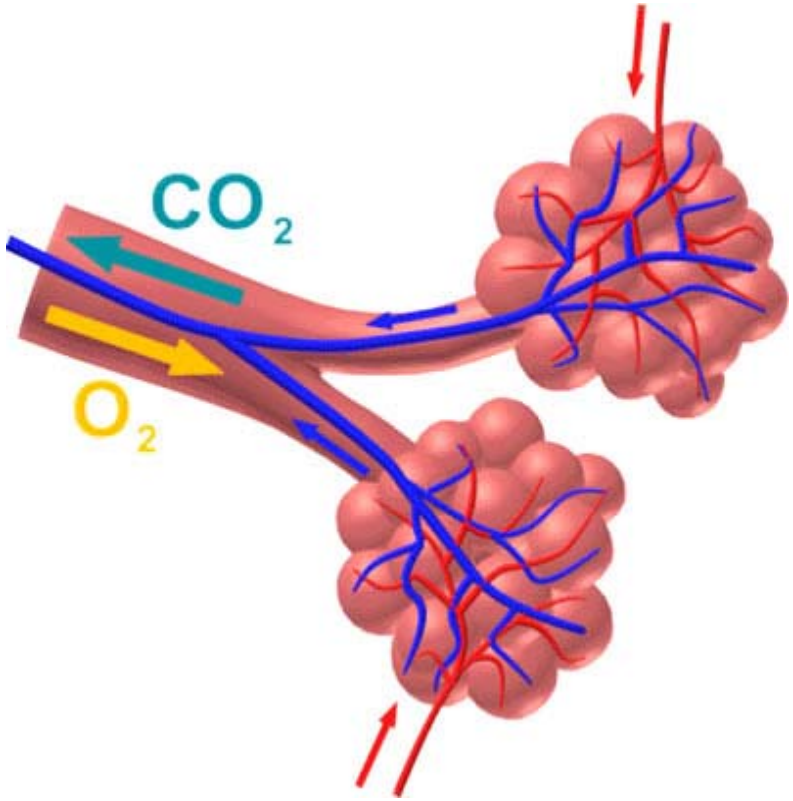


- 'effective' part of tidal volume
- alveolar ventilation
- short period no air movement

Triage following (acute) inhalational exposure

airways (particle size, water solubility)





- ‘effective’ part of tidal volume
- alveolar ventilation
- short period no air movement

Triage following (acute) inhalational exposure

Type I water solubility

Compounds dissolving easily in water

Examples:

- Cl_2, NH_3, HCl vapour
- acrylonitrile
- lacrimators (tear gas)
- smoke inducing agents
  - sulfur trioxide-chlorosulfonic acid (50% and 50%)
  - zinc chloride, titanium tetrachloride and stannic chloride react with water and produce HCl droplets

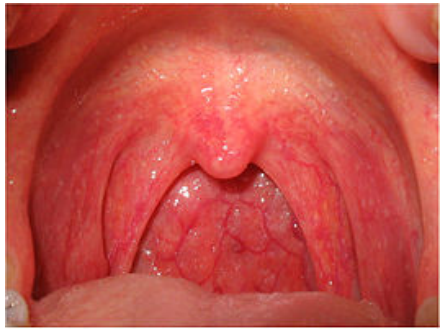
Triage following (acute) inhalational exposure

Type I symptoms

Immediate symptoms (eyes, nose, throat, airways)

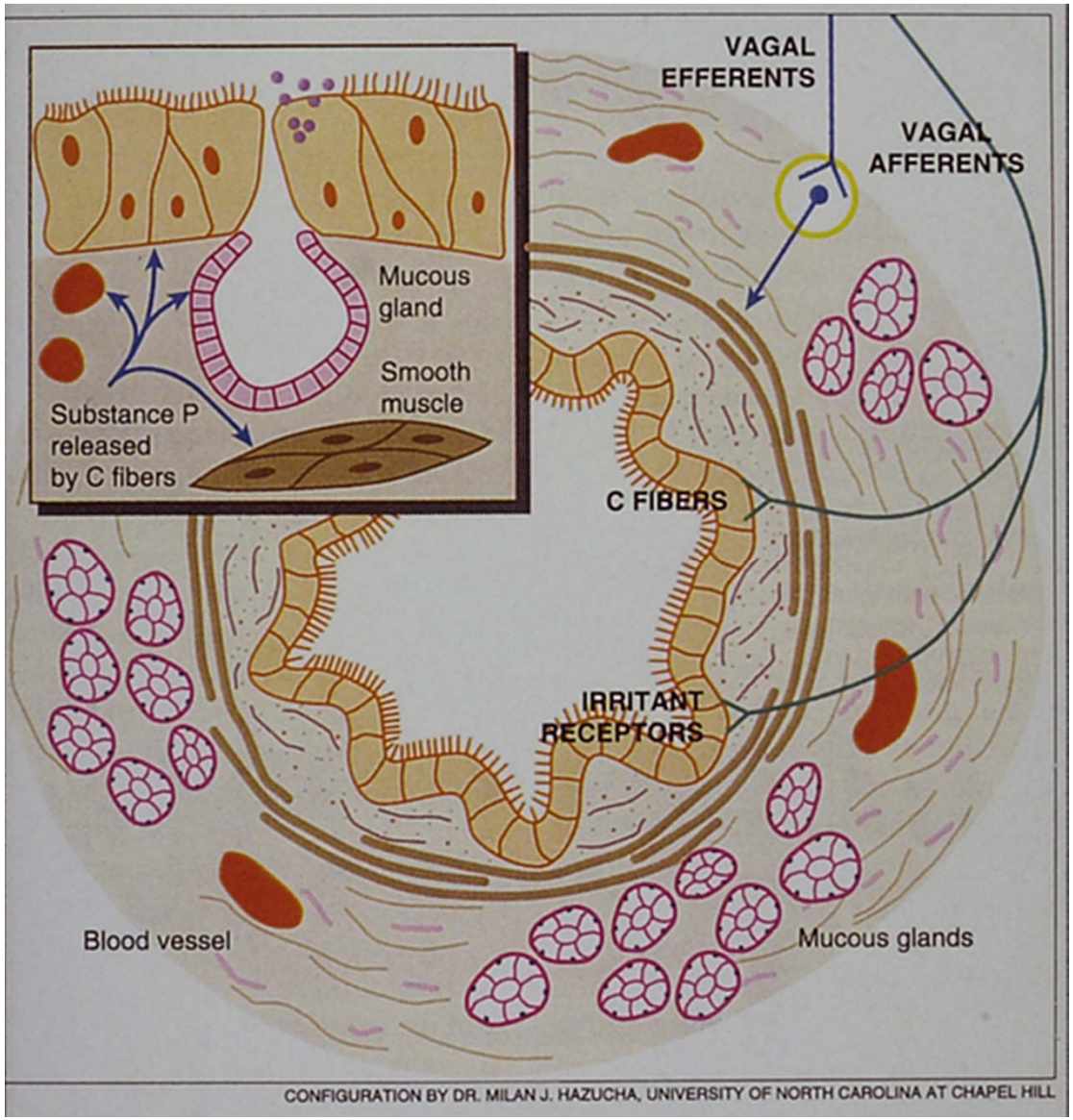
some examples:

- conjunctival irritation
- nasal discharge
- retrosternal pain while breathing
- laryngeal edema (stridor)
- bronchospasms
- hemoptysis
- lung oedema.....?



Triage following (acute) inhalational exposure

Type I airway resistance



Diameter of the bronchus is regulated by:

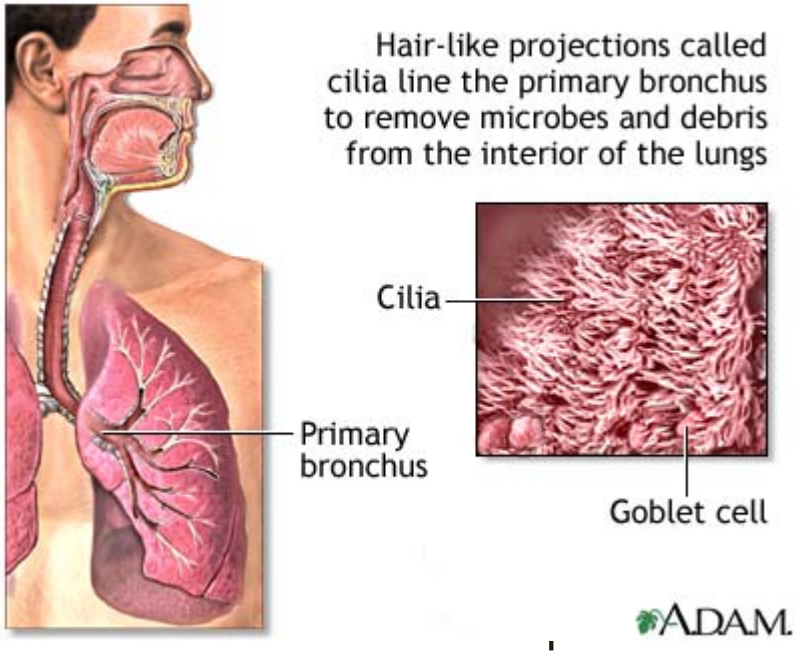
a. the vagal nerve

b. auto-regulation by unknown mediators, substance P, produced by local cells causing bronchodilation

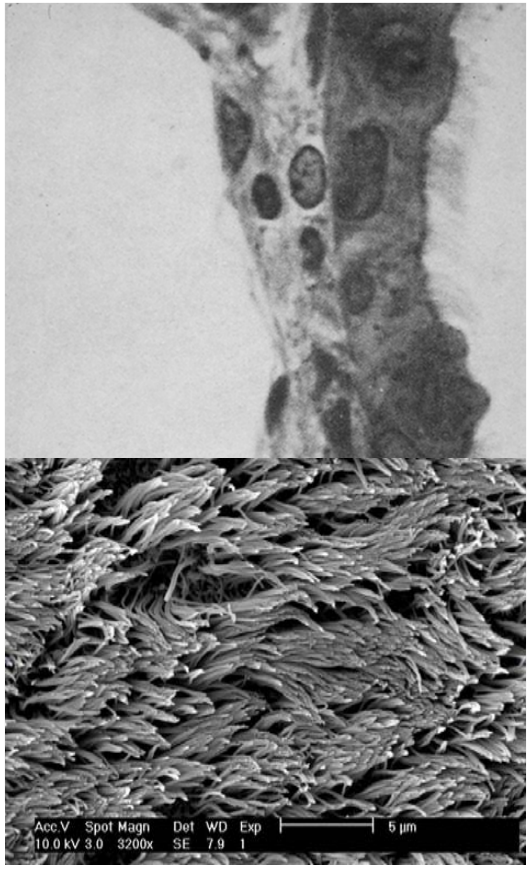
exposure to toxic agents may disturb these regulation mechanisms causing bronchospasms

Triage following (acute) inhalational exposure

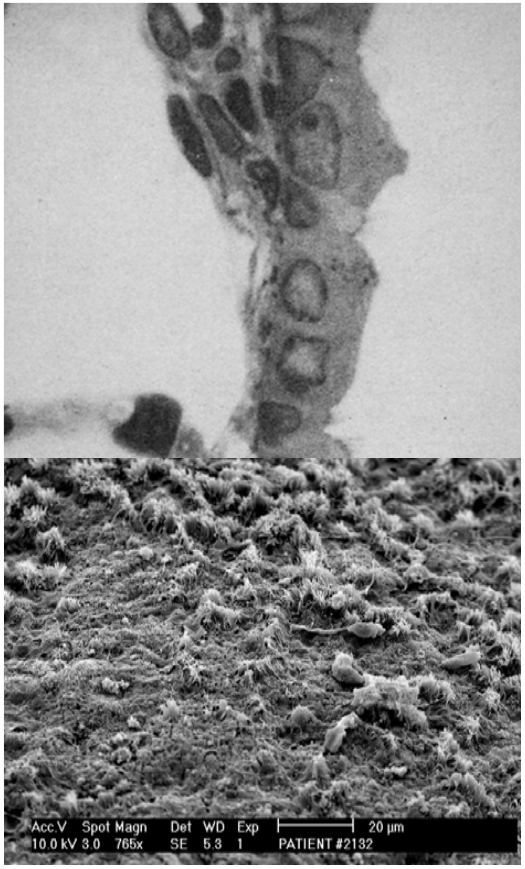
Type I airway resistance



Cilia are important for transport of sputum, particles and/or bacteria to the pharynx



Normal bronchiolar epithelium cells covered with cilia



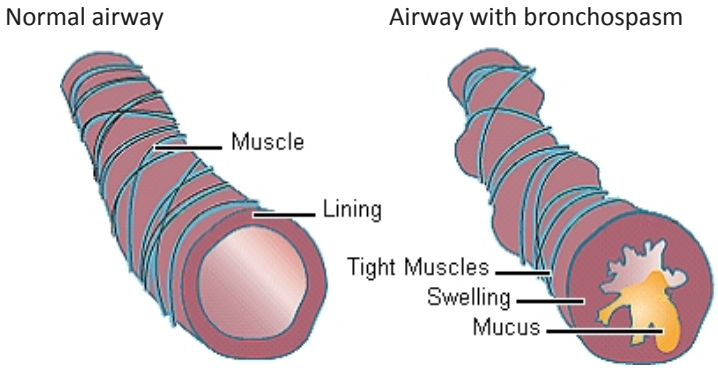
Cilia disappeared following toxic exposure

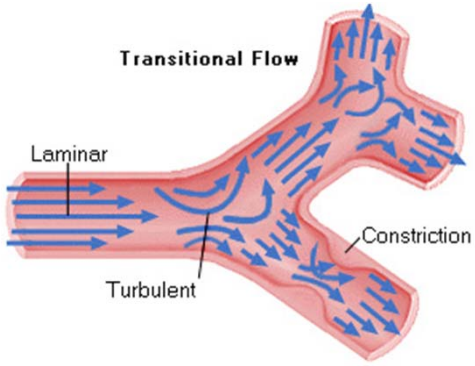
Triage following (acute) inhalational exposure

Type I airway resistance

Increased airway resistance in the large airways is caused by:

- local epithelial edema
- increased sputum production
- decreased sputum clearance
  because of damaged cilia transport
- bronchospasm induced by:
  - irritation of the airway cells → vagal nerve stimulation
  - disturbance of down regulation mechanism by mediators which decrease bronchospasms
- disturbance of lamellar airflow causing turbulence





Triage following (acute) inhalational exposure

Type I management

Immediate clinical effects of upper airways (caused by e.g. Cl_2, NH_3, HCl-vapor)

Triage is simple because severity of symptoms are indicative for the severity of exposure

When after exposure no symptoms are present:

- Hardly increase of symptoms occur
- Observation is not necessary
- No additional diagnostic procedures are needed, such as blood gas analyses, X-thorax, etc.

Triage following (acute) inhalational exposure

Type I management

Symptoms present:

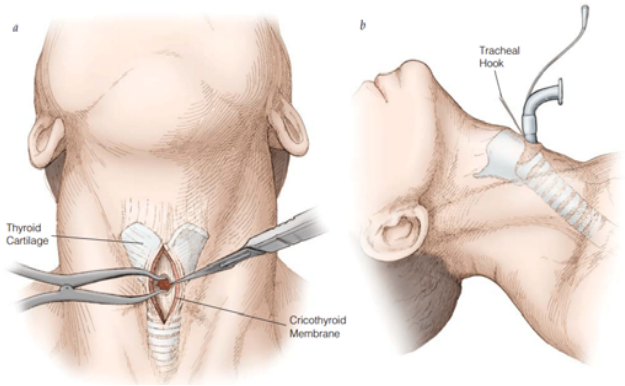
- put the patient in a sitting position
- keep the patient calm
- oxygen treatment
- broncho-dilators preferably via an electrically powered nebulizer

Triage following (acute) inhalational exposure

Type I management

Symptoms present

- prophylactic antibiotics to prevent bacterial overgrow is questionable because the outcome does not improve
- corticosteroids (oxygenation ±, inflammation -, outcome -)?
- tracheostomy or coniotomy
- mechanical ventilation



Triage following (acute) inhalational exposure

water solubility

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Triage following (acute) inhalational exposure

Type II water solubility

Compounds involved (dissolving hardly in water)

some examples

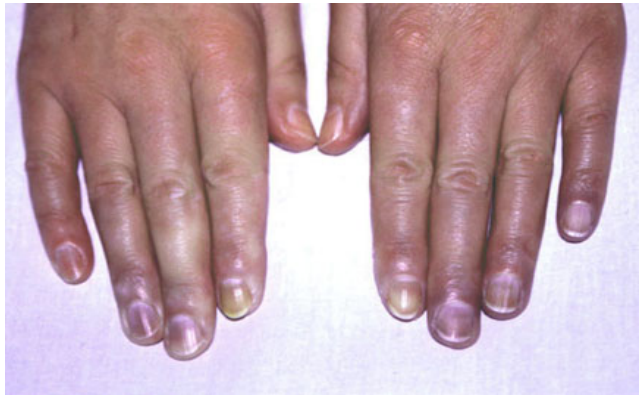
- Nitrogen dioxide (NO_2)
- Ozone (O_3)
- Phosgene (CCl_2O)
- “Mustard gas”
- Methyl bromide

Triage following (acute) inhalational exposure

Type II symptoms

Clinical symptoms manifest later

- dyspnea
- cyanosis
- slight or no bronchospasms
- acute Lung Injury (ALI)
- acute Respiratory Distress Syndrome (ARDS)



Triage following (acute) inhalational exposure

Type II mediators

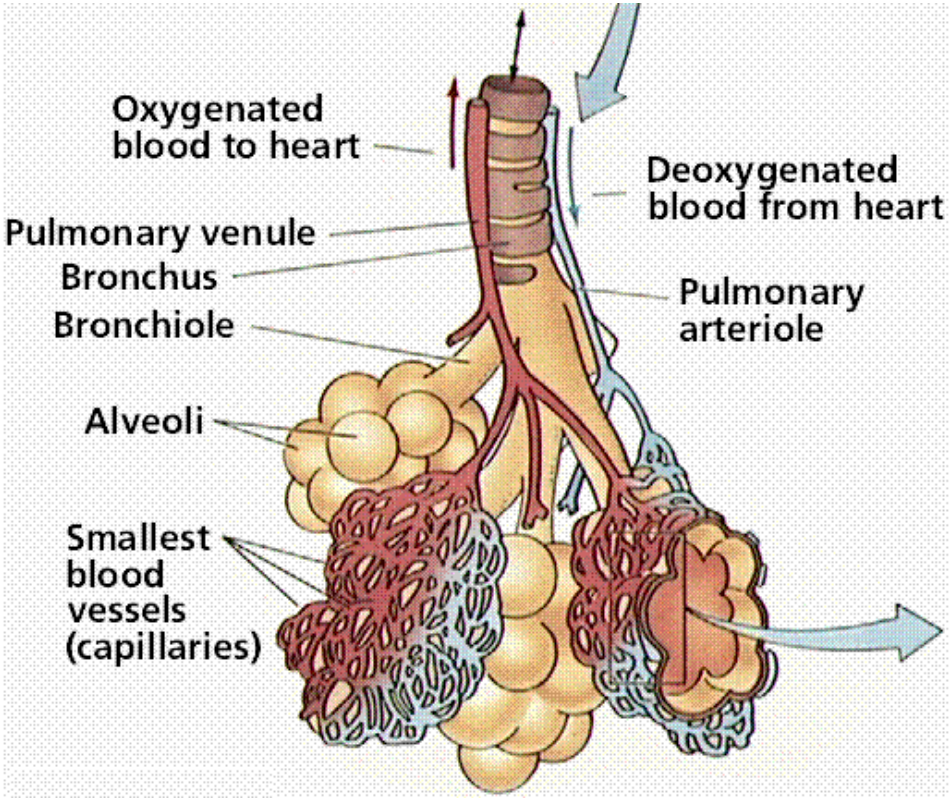
Following type II lung injury biological mediators are released causing ALI / ARDS

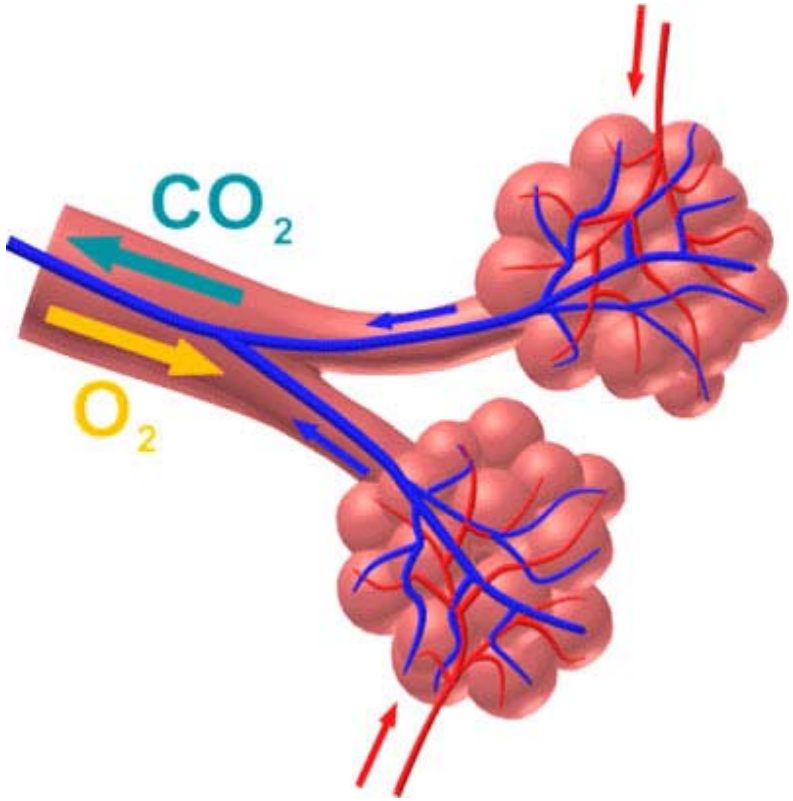
Potential pro-inflammatory mediators	Potential anti-inflammatory mediators
TNF-α IL-1β, IL-8, IL-6 Leucotrienes Platelet Activation Factor	IL-10 IL-1 receptor antagonist sTNFR1 sTNFR2 IL-6 Prostaglandin-E1

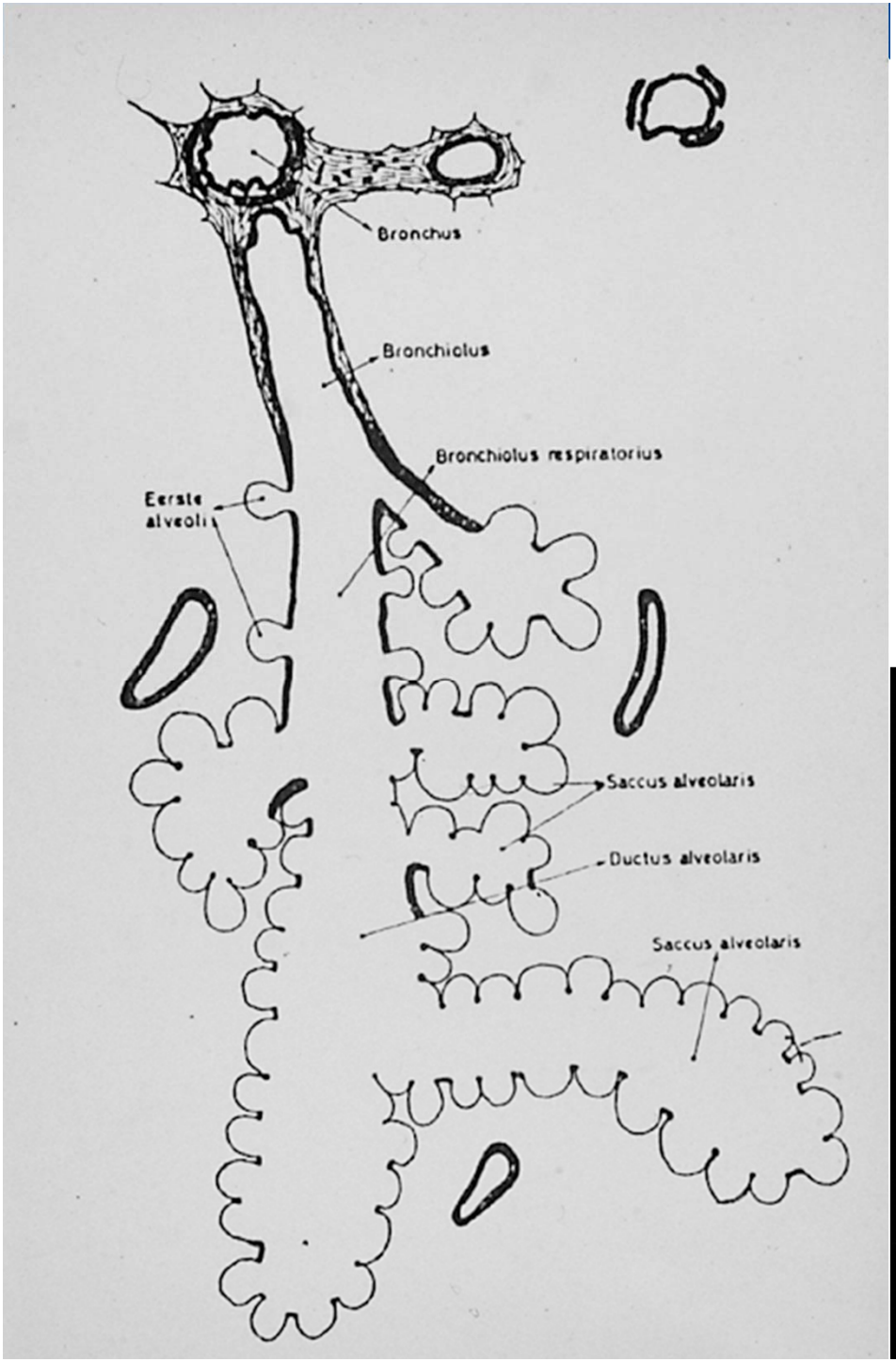
Frank JA et al. Chest 2006;130;1906-1914

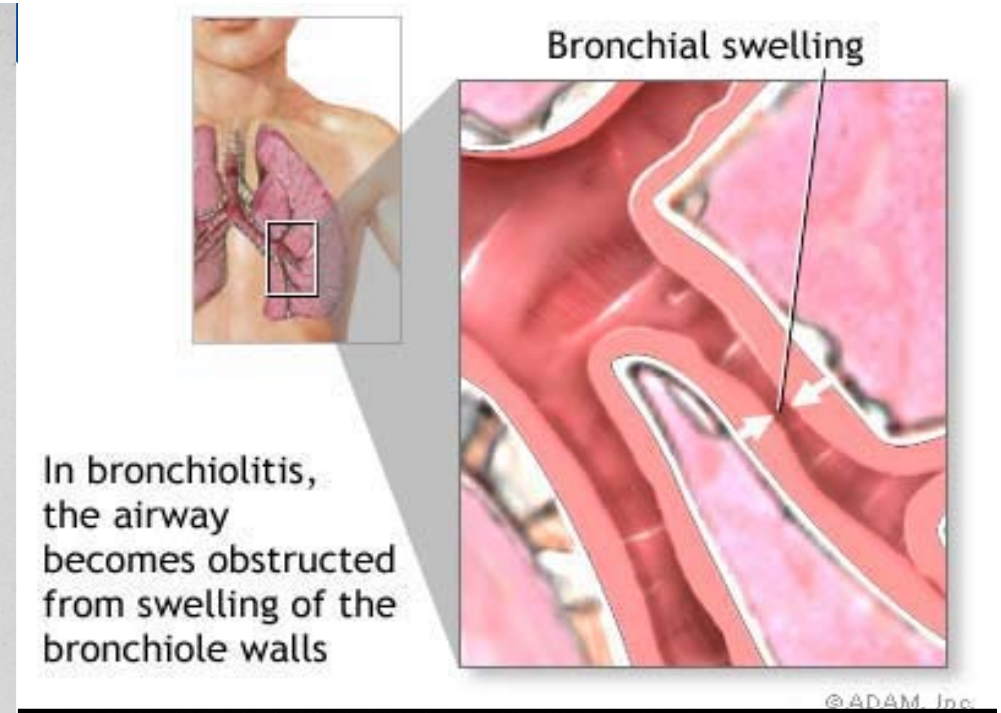
Triage following (acute) inhalational exposure

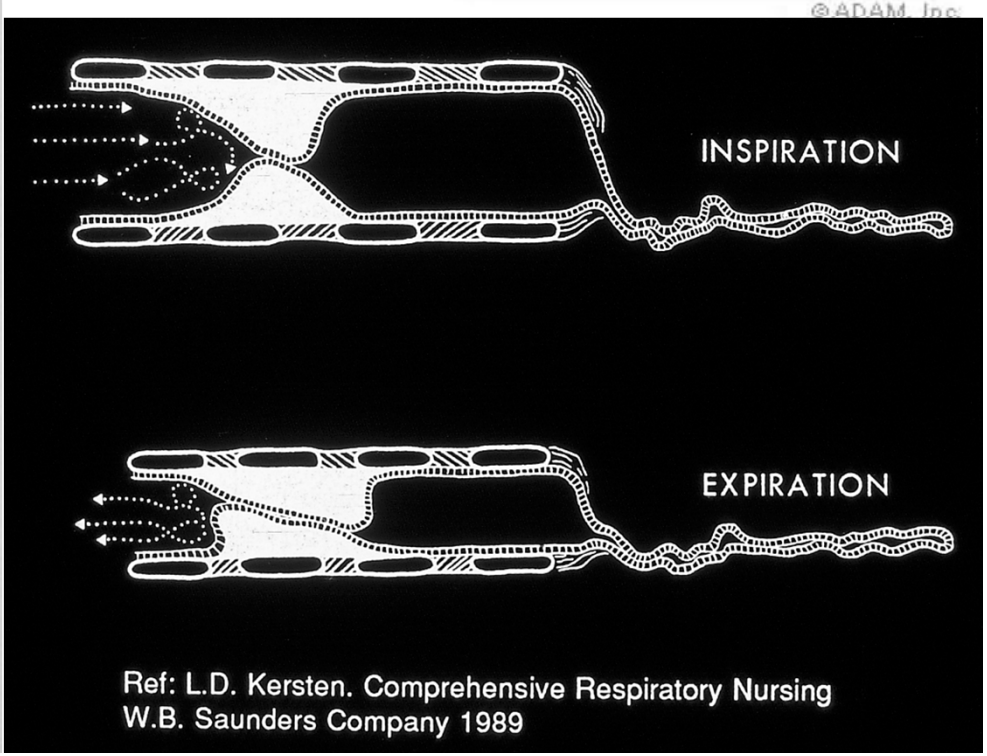
Type II injury at alveolar region

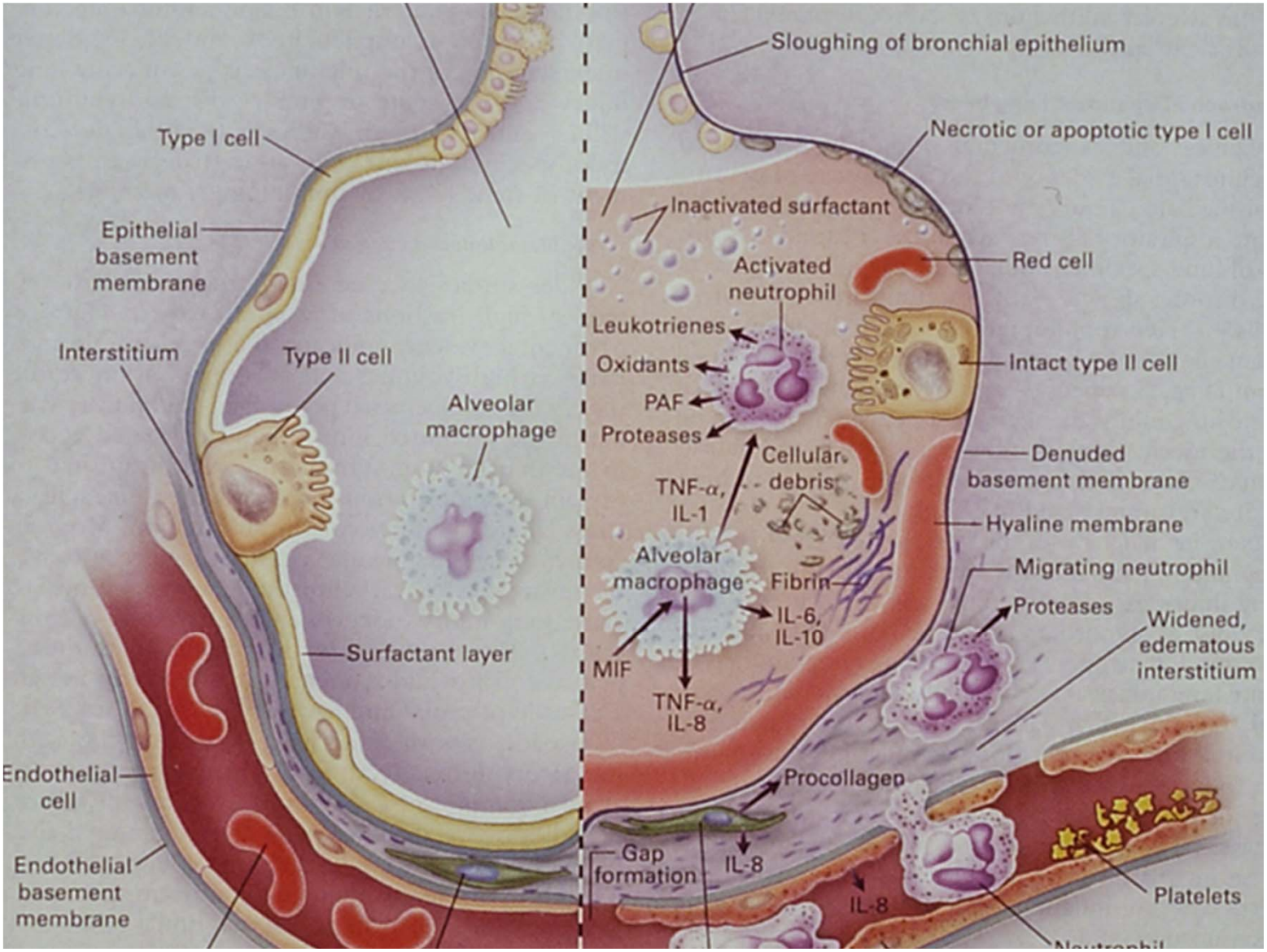





Bronchus
Bronchiolus
Bronchiolus respiratorius
Eerste alveoli
Saccus alveolaris
Ductus alveolaris
Saccus alveolaris


Bronchial swelling
In bronchiolitis, the airway becomes obstructed from swelling of the bronchiole walls
©ADAM, Inc.

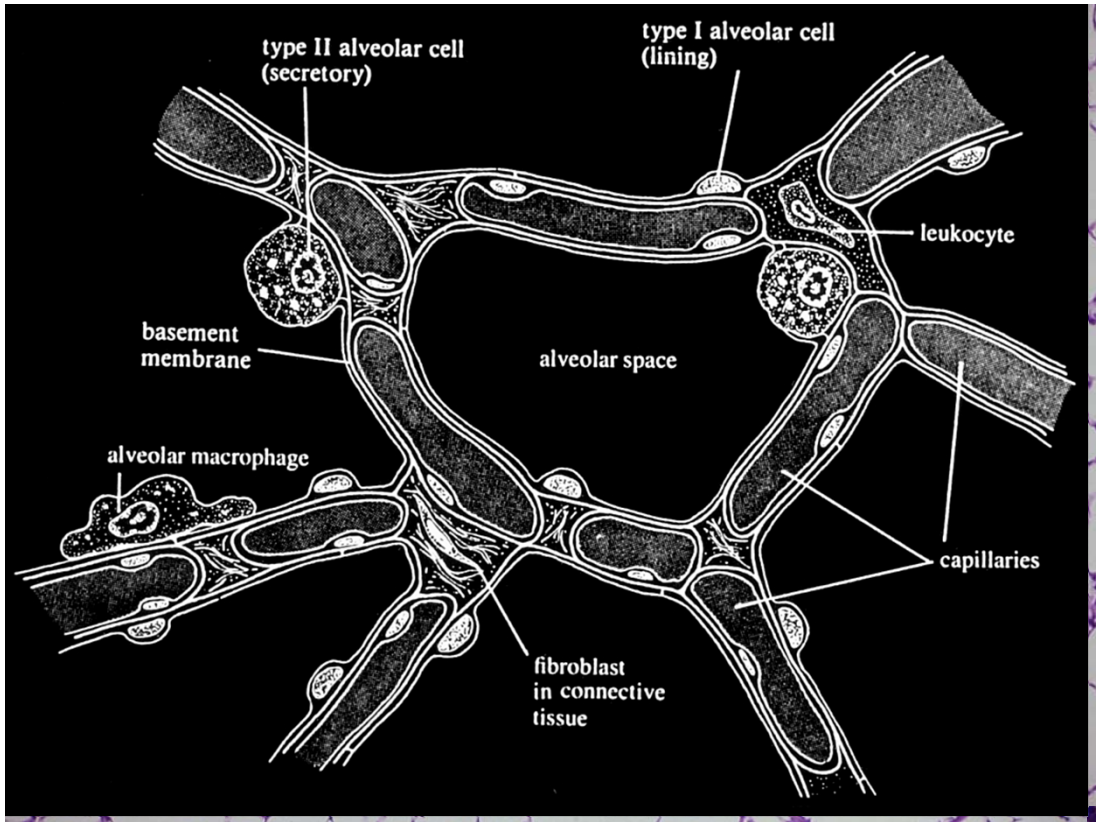

INSPIRATION
EXPIRATION
Ref: L.D. Kersten. Comprehensive Respiratory Nursing
W.B. Saunders Company 1989

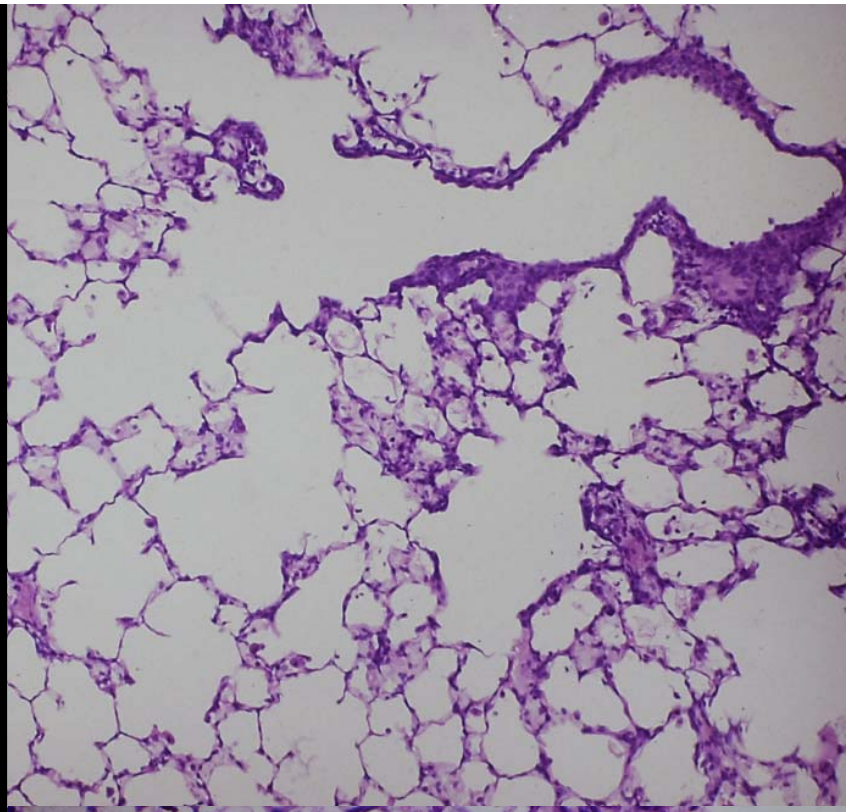


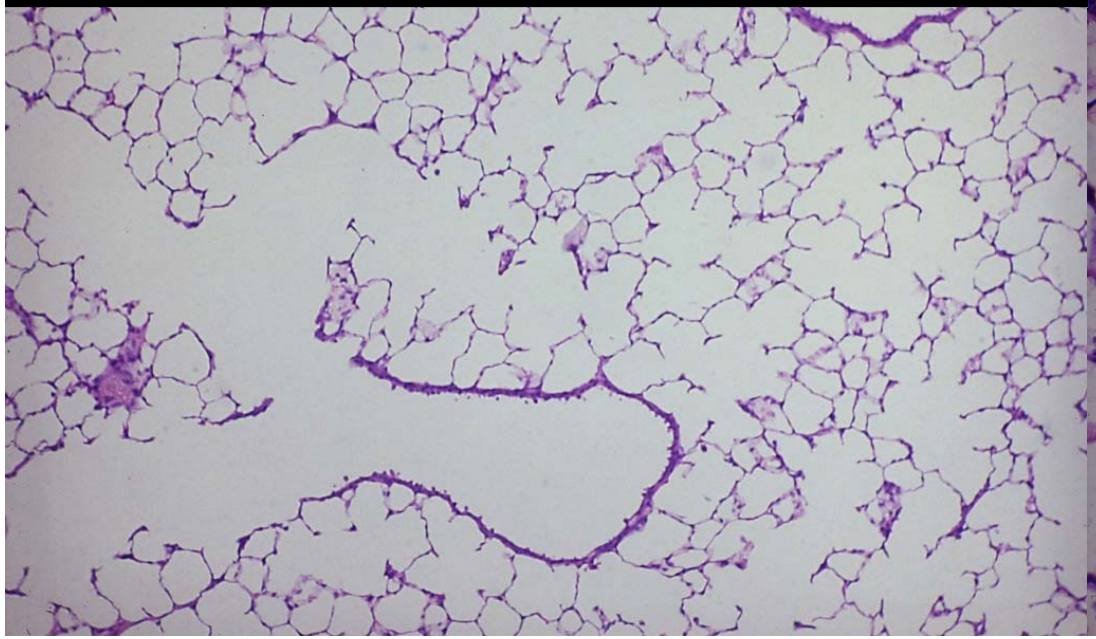
N Eng J Med 2000; 342:1334-1349

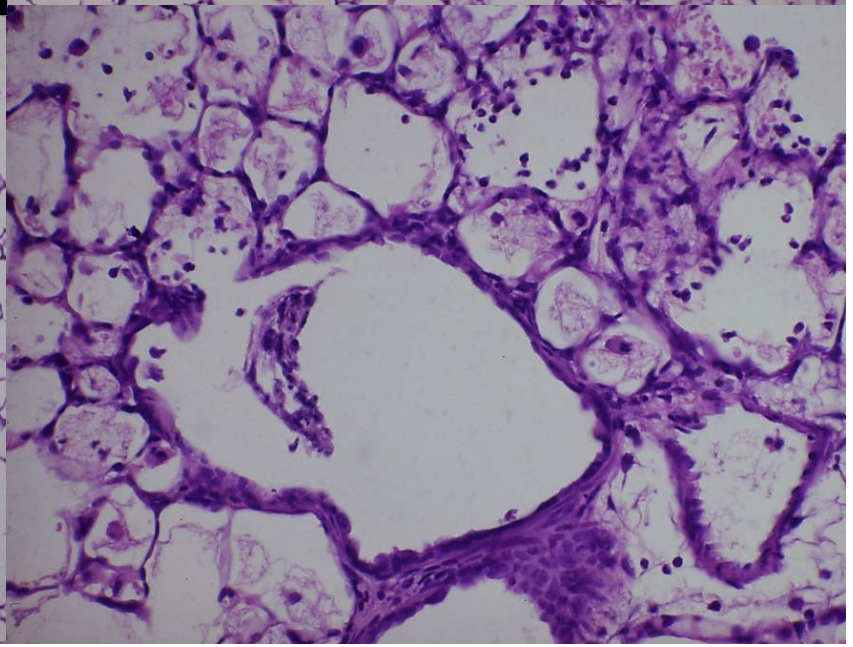
Injury phase

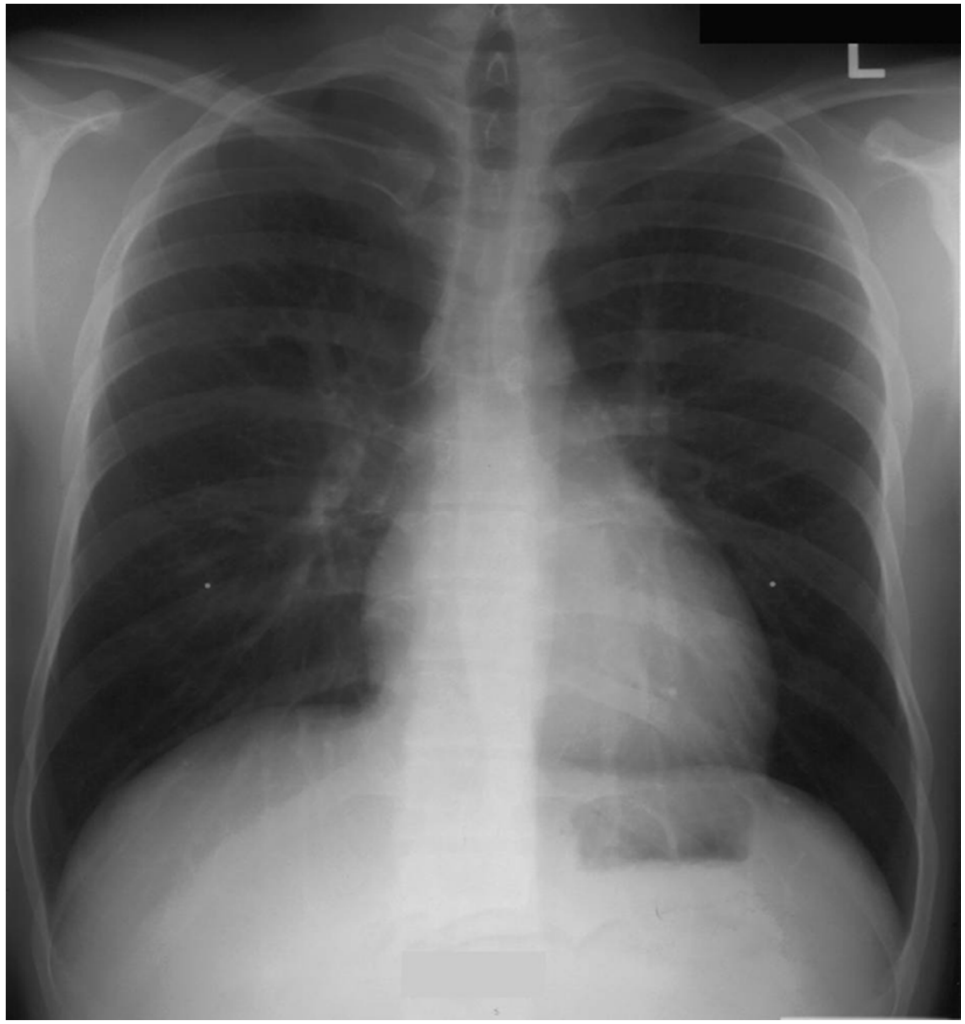
Type II and Clara cells are important for re-epithelialization


type II alveolar cell
(secretory)
type I alveolar cell
(lining)
leukocyte
basement
membrane
alveolar space
alveolar macrophage
capillaries
fibroblast
in connective
tissue

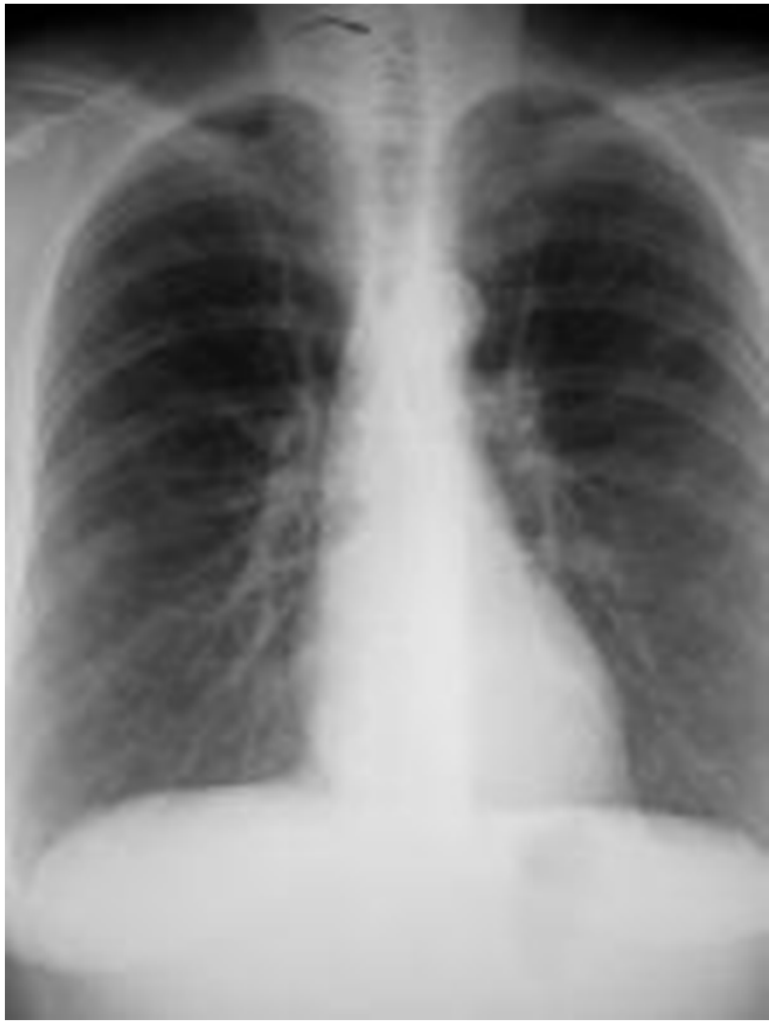




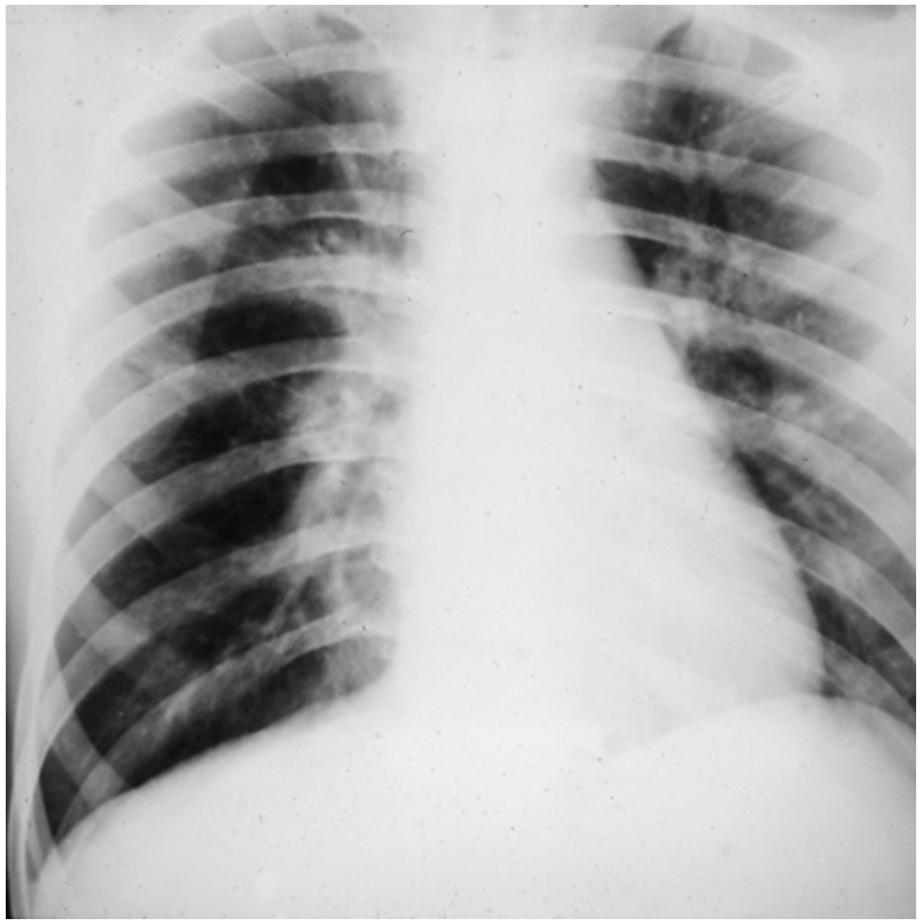




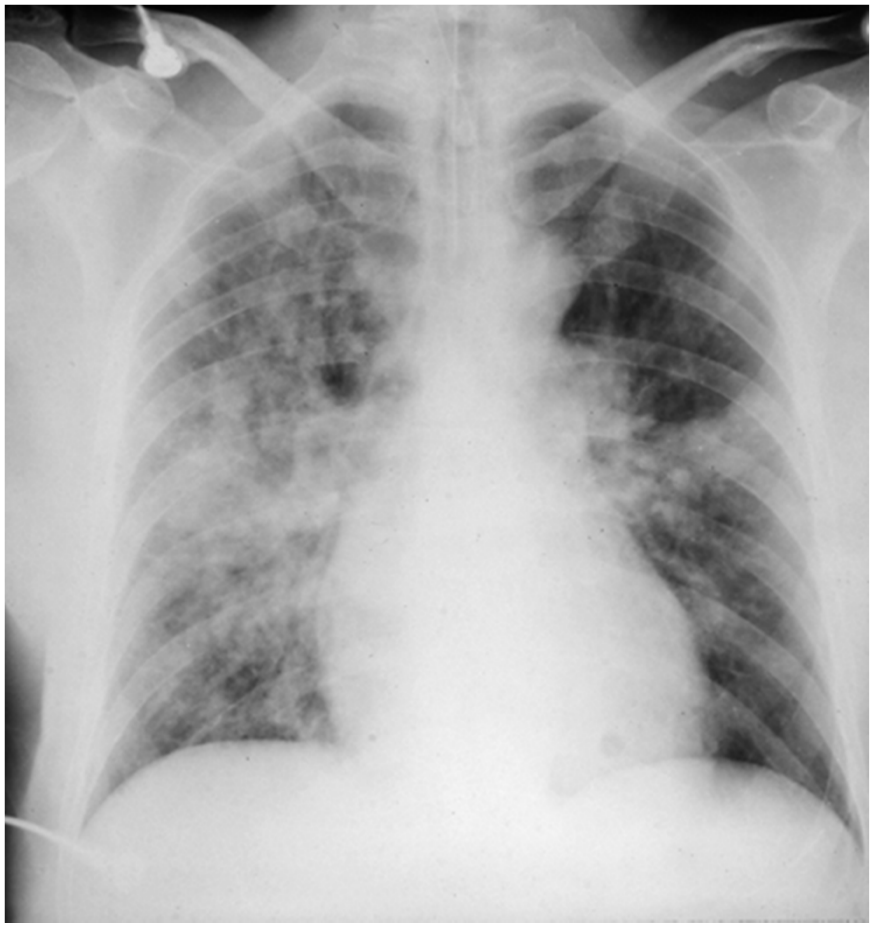
Normal X-thorax



Subtle interstitial edema

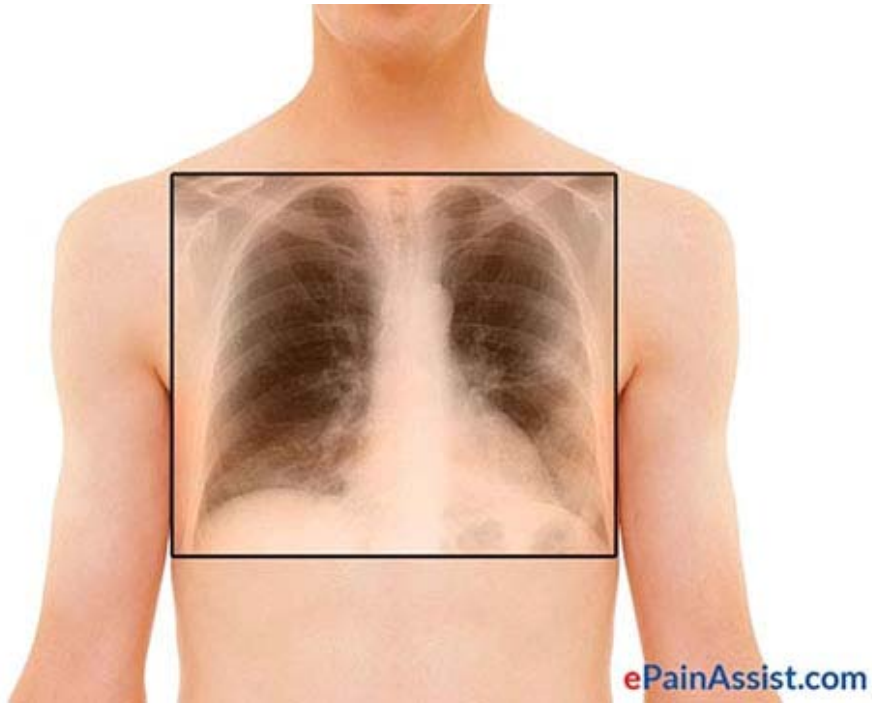


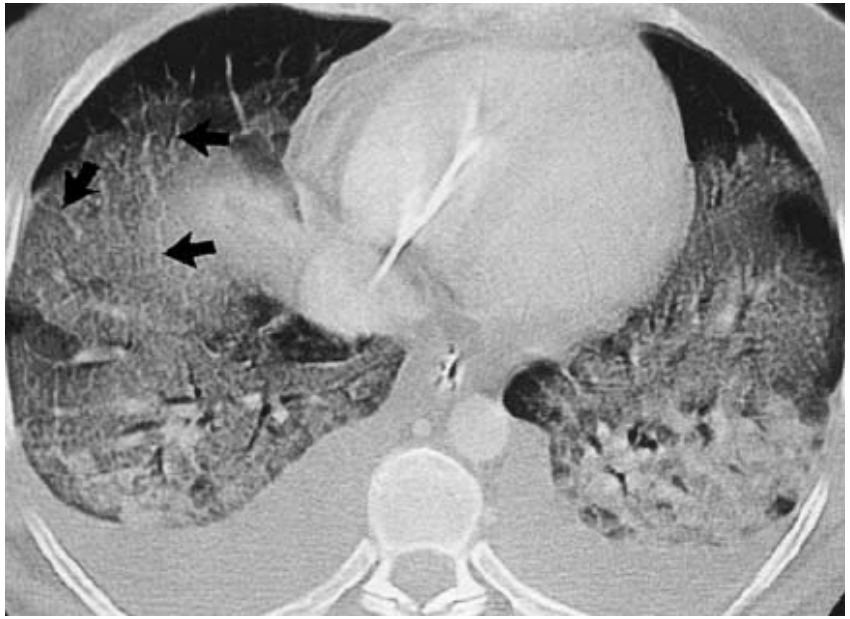
Interstitial lung edema



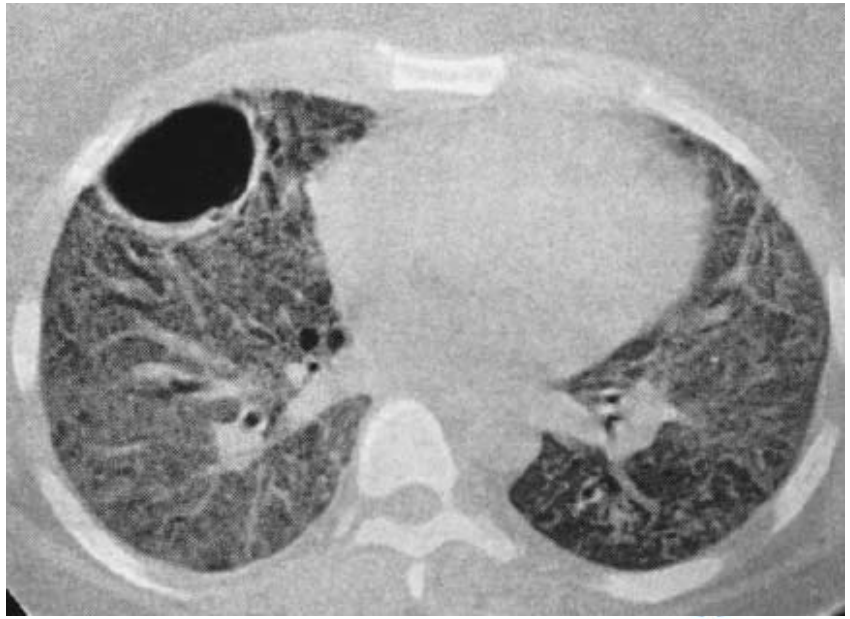
Interstitial lung and alveolar edema

Bronchiolitis Obliterans Organizing Pneumonia (BOOP disease)





Acute phase

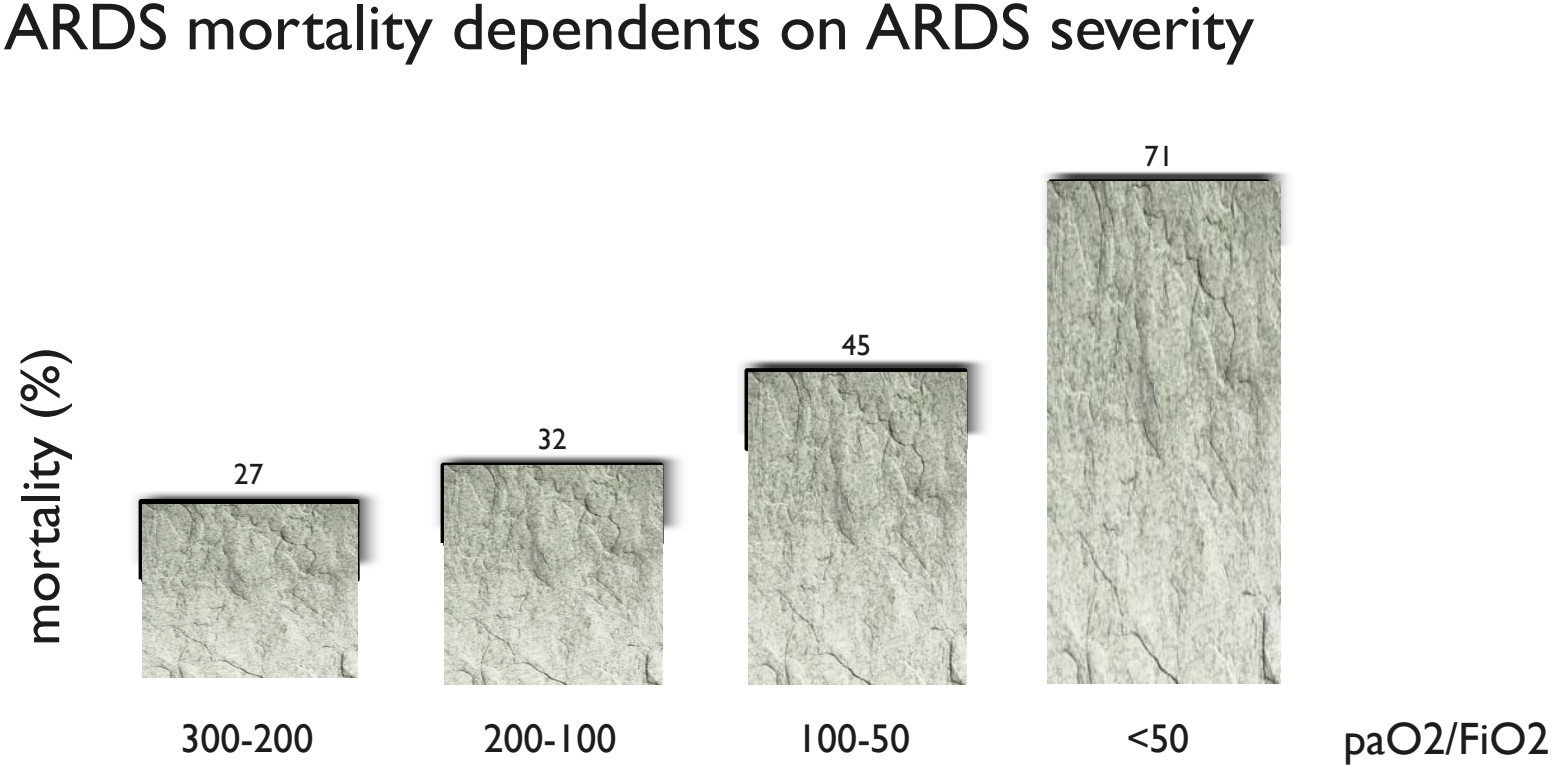


Fibrosing phase

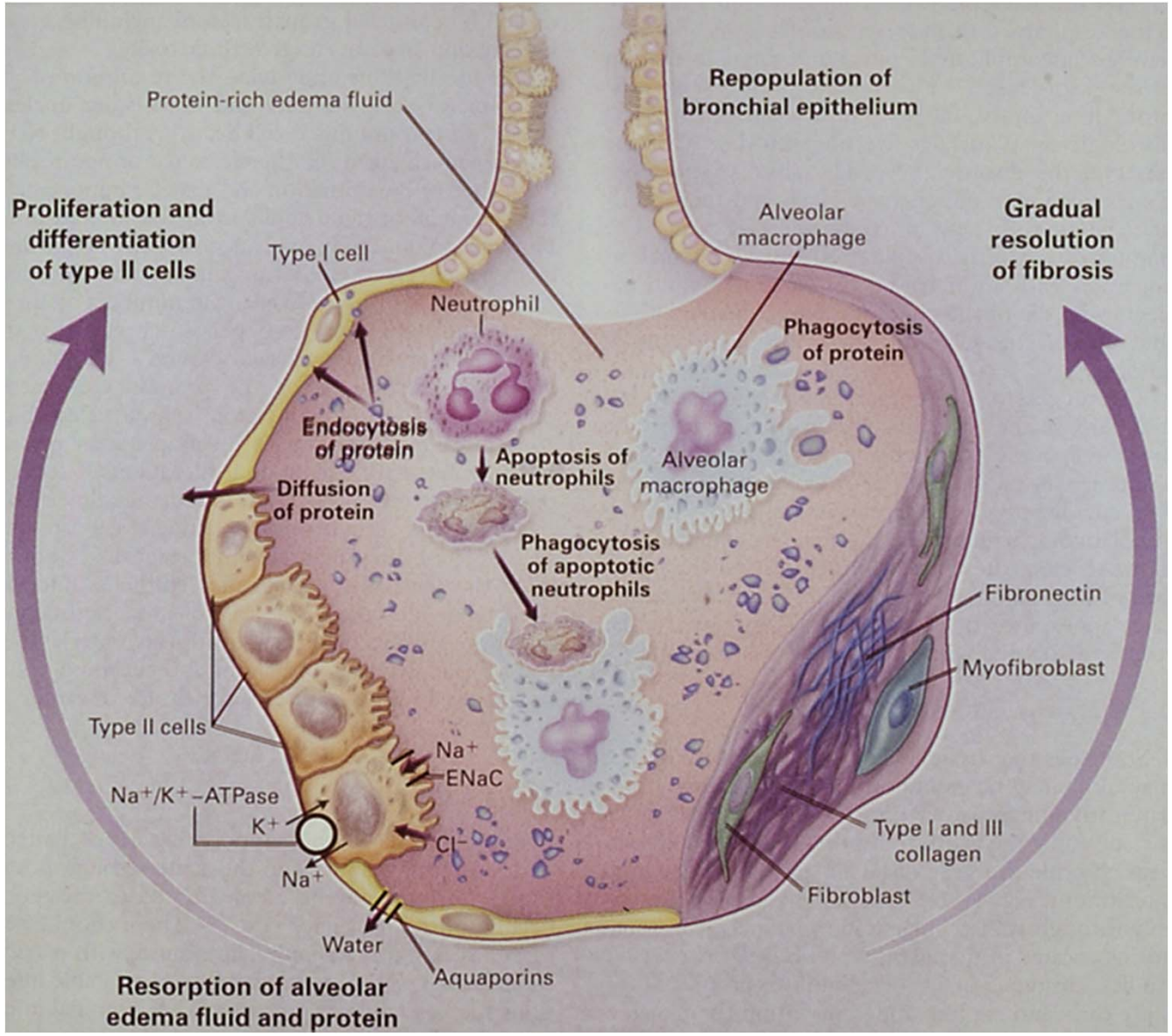
Ware et al. NEJM 2000;342:1334-49

Triage following (acute) inhalational exposure

Type II mediators



www.elso.med.umich.edu



N Eng J Med 2000; 342:1334-1349

Repair phase

Triage following (acute) inhalational exposure

Type II management

In type II compounds symptoms manifest later;

thus directly after exposure the severity of intoxication is unclear

Consequently

- triage is difficult
- observation period is needed to evaluate the severity of exposure (at least 6 h)
- further diagnostic procedures are needed, such as
  - blood gas analysis
  - Chest X-ray

Triage following (acute) inhalational exposure

Type II management

Diagnostic procedures circa 6 hours after exposure

- blood gas analysis may indicate the severity of exposure

PaO_2 =, $PaCO_2$ ↓	mild damage	(subclinical)
PaO_2 ↓, $PaCO_2$ ↓↓	moderate damage	(clinical symptoms)
PaO_2 ↓↓, $PaCO_2$ ↑	severe damage	(severe clinical symp.)

- chest X-ray (interstitial/alveolar lung edema? ARDS?)

Triage following (acute) inhalational exposure

Type II management

Therapy

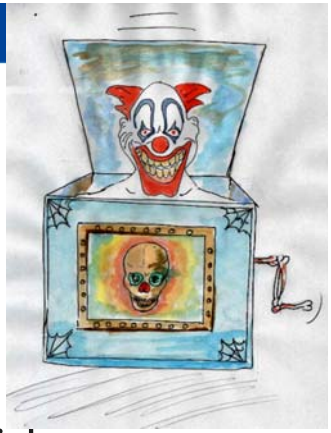
- put the patient in a sitting position
- keep the patient calm
- oxygen supply
- (bronchodilators…?)
- prophylactic antibiotics disputable?
- corticosteroids (60th and 70th, inflammation-, outcome-?

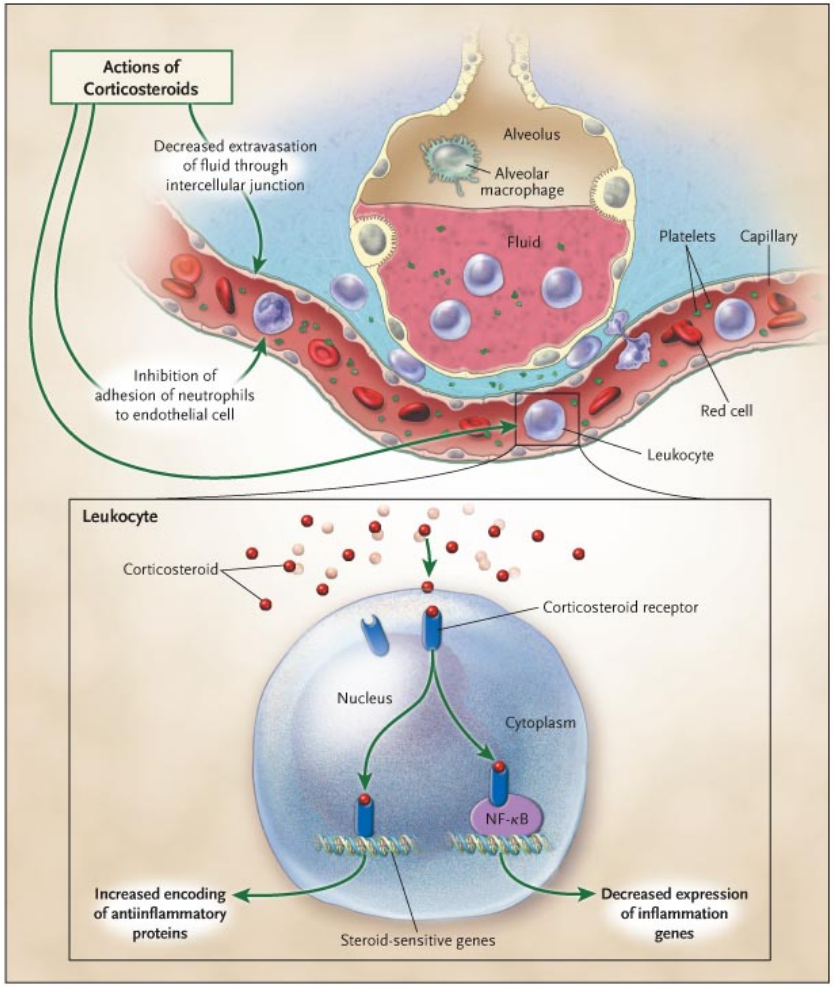
de Lange DW, Meulenbelt J. Do corticosteroids have a role in preventing or reducing acute toxic lung injury caused by inhalation of chemical agents? Clin Toxicol . 2011 Feb;49(2):61-71. (Review)

- are there other therapeutic options?
- symptomatic treatment
- mechanical ventilation
- extracorporeal membrane oxygenation

Triage following (acute) inhalational exposure

Type II management (corticosteroids)



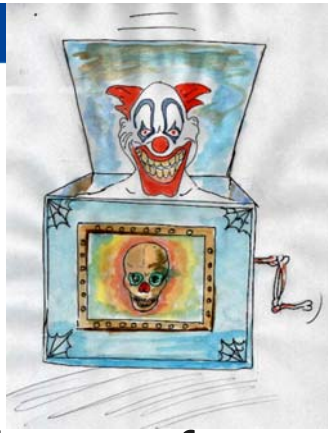


Potency of corticosteroids:

- Reduce the extravasation of plasma through intercellular junctions of capillaries
- Inhibit the adhesion and migration of leucocytes across the capillary wall
- Switch off genes encoding fro pro-inflammatory proteins
- Switch on genes encoding for anti-inflammatory proteins

Triage following (acute) inhalational exposure

Type II management (corticosteroids)



- No effect of high corticosteroid dose in early phase of acute ARDS

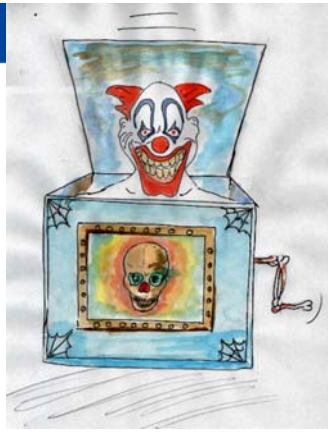
  (Bernard GR et al. N Eng J Med 1987; 317:1565-70. {n=99})
  (Conner BD, Bernard GR. Acute Respiratory Distress Syndrome : Potential Pharmacological Interventions. In: Clinics in Chest Medicine vol 21; September 2000)

- Also no effect of high corticosteroid dose on ARDS in early phase of sepsis and septic shock, whilte it is associated with an increased mortality in patients with a creatinine level above 2 mg/dL

  (Luce JM. Corticosteroids in ARDS. In: Critical Care Clinics vol 18. January 2002)

Triage following (acute) inhalational exposure

Type II management (corticosteroids)



- Effect of high corticosteroids dose in not resolved ARDS, 7 days after onset of the ARDS, might be useful

  (Meduri et al. JAMA 1998; 280:159-65 {n=24 included; n=8 in placebo, 4 crossed-over after 10 days of treatment to the other treatment group, thus only four patients originally included in placebo group where evaluated, five of the original placebo group died; n=16 in non-placebo, only survivors})

- Corticosteroids did not improve outcome. Starting > 2 weeks after the onset of ARDS corticosteroids may increase the risk of death

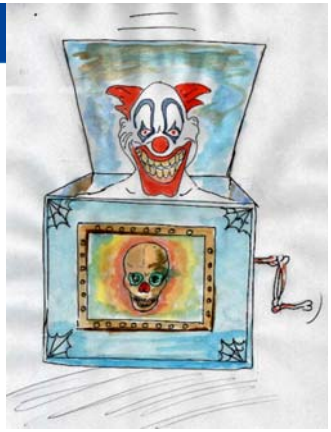
  (ARDS Network, 25 US hospitals, N Eng J Med 2006;354:671-84 {n=180 included})

- Corticosteroids are not useful in type II intoxications. In type I intoxications corticosteroids may temporally improve arterial oxygen concentration in the first hours, although this effect is not observed in severe intoxications.

  (de Lange DW, Meulenbelt J. Do corticosteroids have a role in preventing or reducing acute toxic lung injury caused by inhalation of chemical agents? Clin Toxicol (Phila). 2011 Feb;49(2):61-71. Review)

Triage following (acute) inhalational exposure

Type II management (corticosteroids)



Disadvantages of high corticosteroids dose in the early repair phase in animal studies are:

- initial inhibition of collagen production, although after ending corticosteroid therapy, an increase of collagen production and decrease in degradation of synthesized collagen is observed causing large pulmonary deposition of collagen
- (Kehrer JP, 1985)

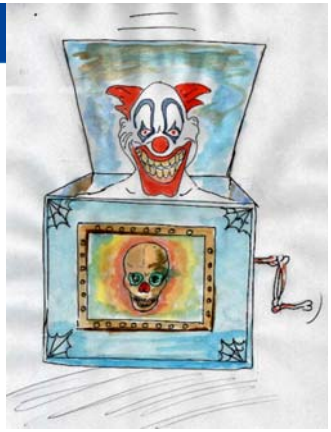
- the inhibition of alveolar type II cells division is crucial
  (Meulenbelt J et al, 1994, Kehrer et al, 1984)

- as is the inhibition of differentiation of alveolar type II cell into alveolar type I cell

  (Smith LJ et al, 1981, Kehrer et al, 1984)

Triage following (acute) inhalational exposure

Type II management (corticosteroids)



Disadvantages of high corticosteroids dose in the early repair phase in animal studies are:

- initial inhibition of collagen production, although after ending corticosteroid therapy, an increase of collagen production and decrease in degradation of synthesized collagen is observed causing large pulmonary deposition of collagen (Kehrer JP, 1985)

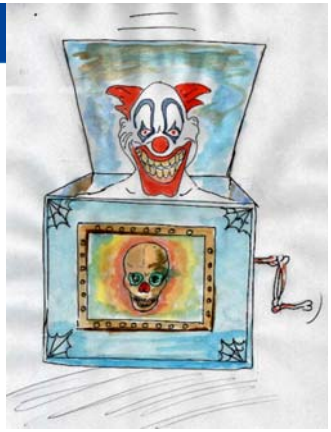
- the inhibition of alveolar type II cells division is crucial
  (Meulenbelt J et al, 1994, Kehrer et al, 1984)

- as is the inhibition of differentiation of alveolar type II cell into alveolar type I cell

  (Smith LJ et al, 1981, Kehrer et al, 1984)

Triage following (acute) inhalational exposure

Type II management (corticosteroids)



Disadvantages of high corticosteroids dose after 7 days in not resolved ARDS in human studies are:

- increased incidence of sepsis
- impaired wound healing
- disturbance of glucose metabolism
- prolonged neuromuscular weakness

(ARDS Clinical trials network. N Eng J Med 2006:354:1671-84

Suter PM. N Eng J Med 2006:1739-41 (editorial))

Triage following (acute) inhalational exposure

Type II management

None of the following therapies were successful

- Arachidonic acid metabolites influencing medicines (Ibuprofen, Dazoxibin, Ketoconazole, Prostaglandin E1)
- Pentoxyfilline and lisofylline (phosphodiesterase inhibitors)
- Antibodies against particular pro-inflammatory mediators
- Antioxidants (vitamin E, vitamin C, glutathione)
- Aerosolized surfactant
- Organic Perfluorocarbon Liquid ventilation
- β-adrenergic agonists
- Nitric oxide

(AP Wheeler, GR Bernard. Lancet 2007;369:1553-1564)

Triage following (acute) inhalational exposure

Type II Prevent ventilator-induced lung damage

- "Protective" ventilation (tidal volume 6 ml versus 12 ml/kg)
- Prone positioning
- High versus low PEEP
- Recruitment manoeuvres

Fan et al. AJRCCM 2008;178:1156-1163

Triage following (acute) inhalational exposure

Type II Prevent ventilator-induced lung damage ECMO

If every else fails…?

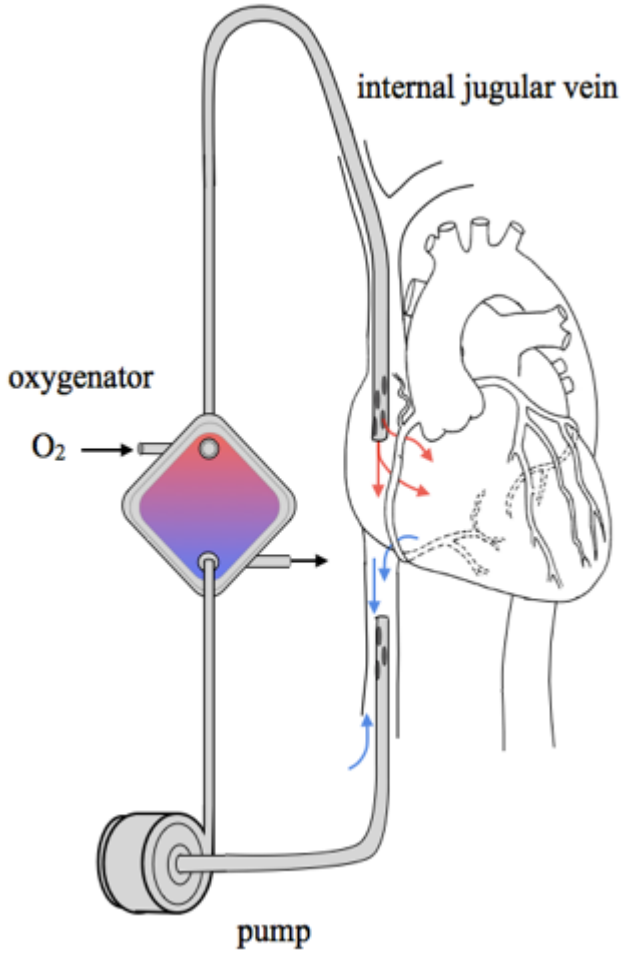
extracorporeal membrane oxygenation

Lange DW de, Sikma MA, Meulenbelt J. Extracorporeal membrane oxygenation in the treatment of poisoned patients. Clinical Toxicology 2013; 51: 385-393

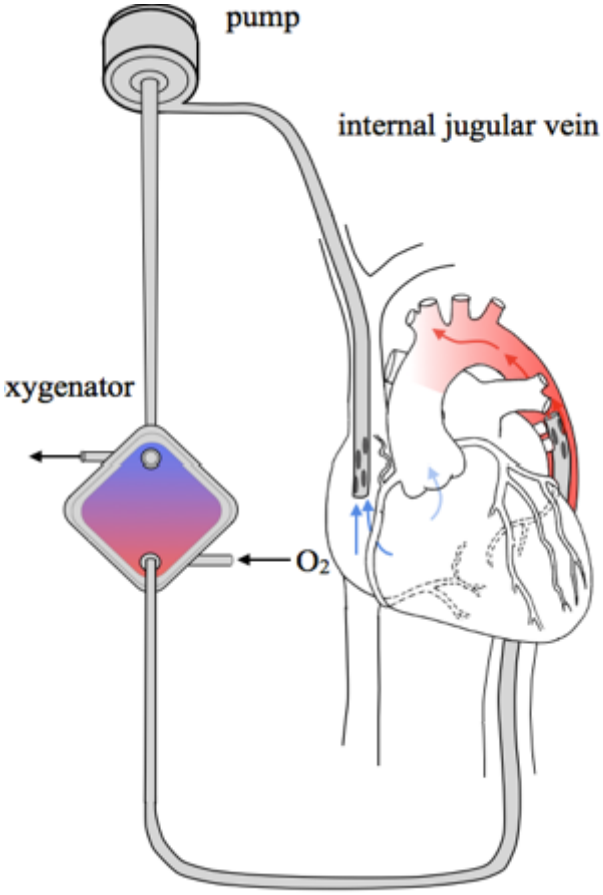
Triage following (acute) inhalational exposure

Type II Prevent ventilator-induced lung damage ECMO

VV-ECMO



VA-ECMO

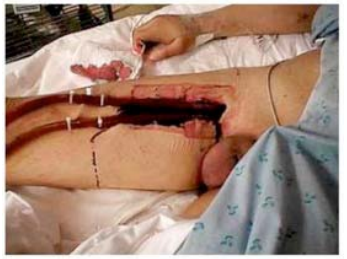


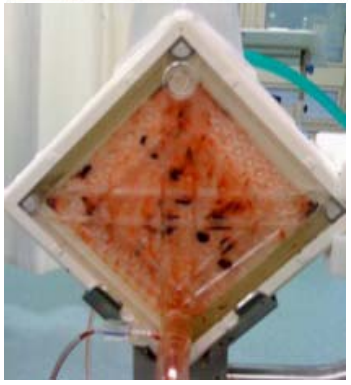
Lange DW de, Sikma MA, Meulenbelt J. Extracorporeal membrane oxygenation in the treatment of poisoned patients. Clinical Toxicology 2013; 51: 385-393

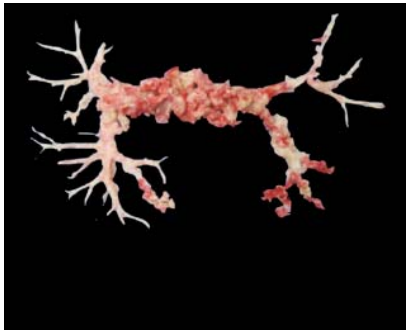
Triage following (acute) inhalational exposure

Type II Prevent ventilator-induced lung damage-ECMO complications

- bleeding (10-36%)
- thrombus (12-22%)
- thrombus/embolism (8%)
- thrombocytopenia (51%), cannula related
- infection (10-21%)
- limb ischemia (19-21%) etc.







Brodie et al. NEJM 2011;365:1905-1914

Triage following (acute) inhalational exposure

Type II Prevent ventilator-induced lung damage-ECMO complications

- Sometimes conventional therapy fails (severe ARDS or refractory shock)
- ECMO can prevent (further) organ damage
- ECMO is not "destination therapy", so it must result in:
  - *Reco*very
  - transplantation
  - other destination therapy (e.g. assist device)
- Many complications and cautions:
  - experienced centres
  - be quick and refer timely to an ECMO centre

Lange DW de, Sikma MA, Meulenbelt J. Extracorporeal membrane oxygenation in the treatment of poisoned patients. Clinical Toxicology 2013; 51: 385-393

Triage following (acute) inhalational exposure

Summary and consequences for triage

Agent determines the kind of lung injury

- type I — compounds dissolving easily in water cause primarily effects in the upper part of the airways. Effects are immediately present

- type II — compounds dissolving hardly in water cause primarily effects deep in the lung in the alveolar region. Effect manifest later

Triage following (acute) inhalational exposure

Summary and consequences for triage

When evaluating the patient think also about:

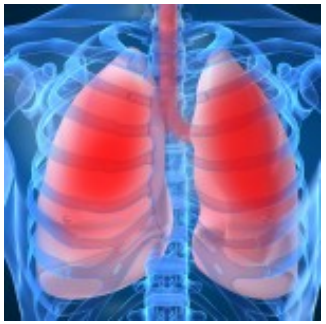
- Individual susceptibility:
  - for agent involved
  - pre-existent illness

Triage following (acute) inhalational exposure

Summary and consequences for triage

Special attention is needed for patients with pre-existent illnesses:

- chronic obstructive long disease such as
  - chronic bronchitis
  - emphysema
- asthma



- ischemic heart disease
- ischemic vascular disease

Triage following (acute) inhalational exposure

Summary and consequences for triage

- Treatment of lung injury following type I and type II compounds is primarily supportive
- Corticosteroids are not useful for improving survival
- Prophylactic antibiotics disputable

- Mechanical ventilation
  - has big consequences for triage
  - lung protective mechanical ventilation has considerably been improved in the last 15 years, which improved outcome

- ECMO (Extracorporeal Membrane Oxygenation)

Jean Geoffroy 1903 "Bon secours".
A l'Hôpital de Notre Dame du Perpétuel)

Thank you for your attention

Questions?