Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis & Regeneration

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Acute Lung Injury

Stefanie Nickl

Lab Meeting 14/11/2011

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Definition of ALI/ARDS

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Reference	Year	Definition or Criteria	Advantages	Disadvantages
Petty and Ashbaugh[3]	1971	Severe dyspnea, tachypnea Cyanosis refractory to oxygen therapy Decreased pulmonary compliance Diffuse alveolar infiltrates on chest radiography Atelectasis, vascular congestion, hemorrhage, pulmonary edema, and hyaline membranes at autopsy	First description Summarizes clinical features well	Lacks specific criteria to identify patients systematically
Murray et al.[4]	1988	Preexisting direct or indirect lung injury Mild-to-moderate or severe lung injury Nonpulmonary organ dysfunction	Includes 4-point lung-injury scoring system Specifies clinical cause of lung injury Includes consideration of the presence or absence of systemic disease	Lung-injury score not predictive of outcome Lacks specific criteria to exclude a diagnosis of cardiogenic pulmonary edema
Bernard et al.[5]	1994	Acute onset Bilateral infiltrates on chest radiography Pulmonary-artery wedge pressure ≤18 mm Hg or the absence of clinical evidence of left atrial hypertension Acute lung injury considered to be present if PaO_2:FiO_2 is ≤300 Acute respiratory distress syndrome considered to be present if PaO_2:FiO_2 is ≤200	Simple, easy to use, especially in clinical trials Recognizes the spectrum of the clinical disorder	Does not specify cause Does not consider the presence or absence of multiorgan dysfunction Radiographic findings not specific

*PaO_2 denotes partial pressure of arterial oxygen, and FiO_2 fraction of inspired oxygen.

N Engl J Med. 2000 May 4;342(18):1334-49.
Crit Care Med. 2000 Jan;28(1):232-5.

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Definition of ALI/ARDS

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Condition	Timing	Oxygenation	Chest Radiograph	Pulmonary Artery Occlusion Pressure
ALI	Acute onset	$Pao_2/Fio_2 \leq 300$ torr	Bilateral infiltrates on frontal chest radiograph	≤18 mm Hg when measured or no clinical evidence of left atrial hypertension
ARDS	Acute onset	$Pao_2/Fio_2 \leq 200$ torr	Bilateral infiltrates on frontal chest radiograph	≤18 mm Hg when measured or no clinical evidence of left atrial hypertension

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Some Facts…

…Risk Factors

Direct Lung Injury

Common causes

Pneumonia
Aspiration of gastric contents

Less common causes

Pulmonary contusion
Fat emboli
Near-drowning
Inhalational injury
Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy

Indirect Lung Injury

Common causes

Sepsis
Severe trauma with shock and multiple transfusions

Less common causes

Cardiopulmonary bypass
Drug overdose
Acute pancreatitis
Transfusions of blood products

…Epidemiology

- 190,000 cases / year in the US
  → 74,500 deaths
- In-hospital mortality
  → ALI 38.5%
  → ARDS 41.1%

…Outcome (survivors)

- restriction/obstruction
- gas-exchange abnormalities
- reduced health-related QOL
- fibrosis

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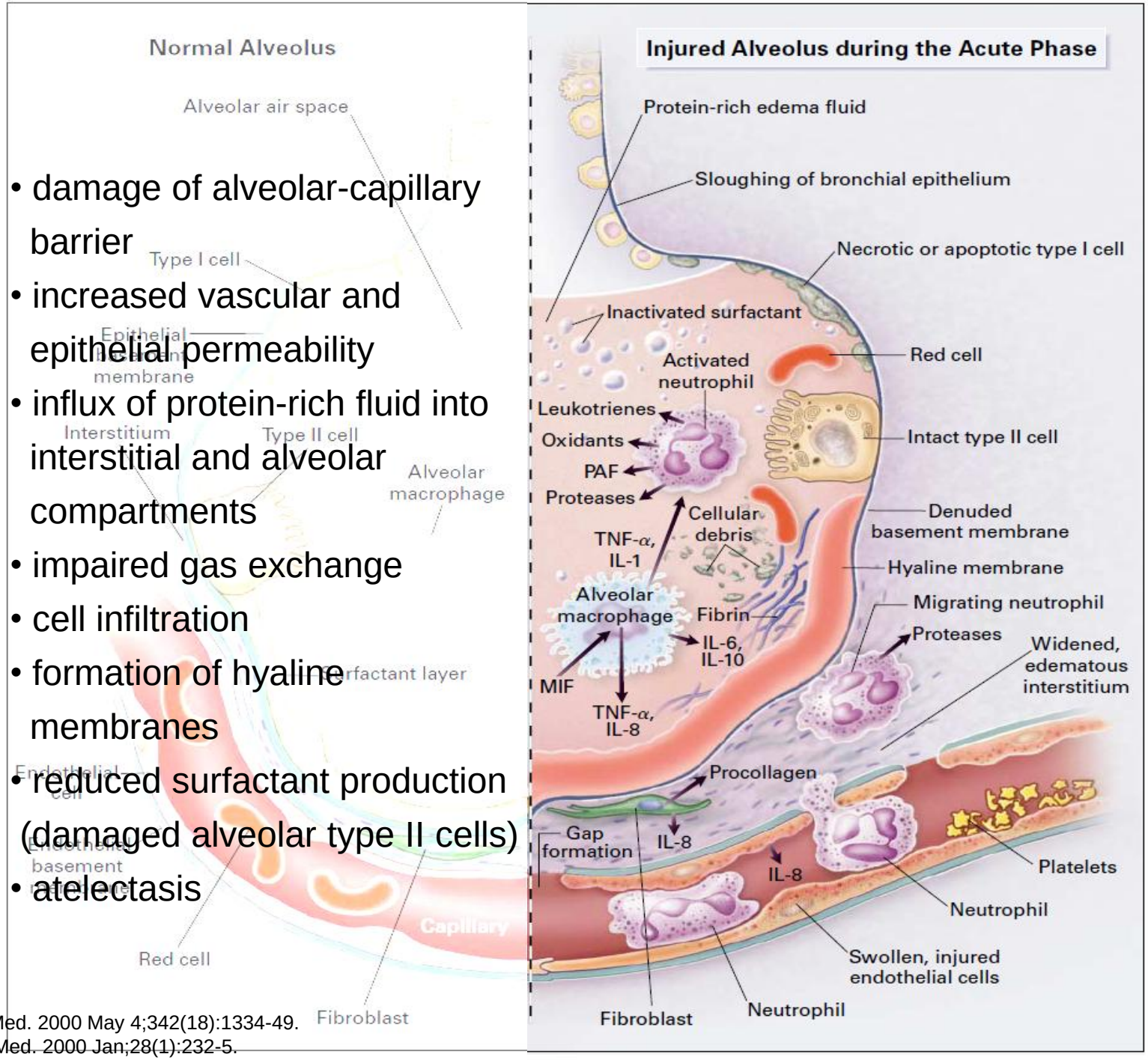
Inter Med 2009;48:621-30.

J Aerosol Med Pulm Drug Deliv. 2010 Aug;23(4):243-52.



- damage of alveolar-capillary barrier
- increased vascular and epithelial permeability
- influx of protein-rich fluid into interstitial and alveolar compartments
- impaired gas exchange
- cell infiltration
- formation of hyaline membranes
- reduced surfactant production (damaged alveolar type II cells)
- atelectasis

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Pathophysiology II
Proteins / Cytokines

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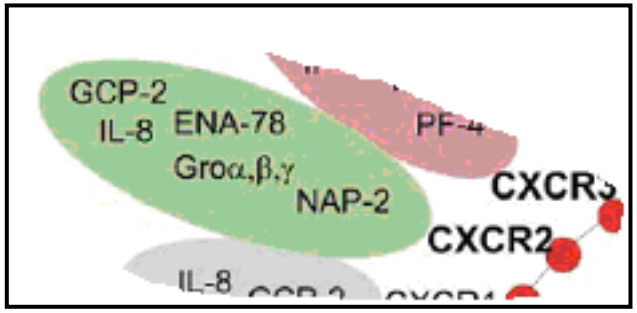
Pathobiology	*Biomarker*	*Abnormality in ALI/ARDS*	*Organ failure-free days*	*Ventilator-free days*	*Mortality*
Endothelium	VWF	Increased	Reduced[31,32]	Reduced[31–33]	Predictive[31–
Endothelium and epithelium	ICAM-1	Increased	Reduced[36]	Reduced[34,36]	Predictive[34–
	SP-D	Increased	Reduced[51]	Reduced[51]	Predictive[51]
	RAGE	Increased	Reduced[a(53)]	Reduced[a(53)]	Predictive[a(53
Inflammation	IL-6	Increased	Reduced[25]	Reduced[25]	Predictive[24,:
	IL-8	Increased	Reduced[25]	Reduced[25]	Predictive[24,:
Coagulation	Protein C	Decreased	Reduced[29]	Reduced[29]	Predictive[29]
	PAI-1	Increased	Reduced[29]	Reduced[29]	Predictive[29]

→ ALI induces production and release of cytokines and pro-inflammatory mediators

→ Amplification of inflammatory response in ALI

→ CXCR2 critically involved



N Engl J Med. 2000 May 4;342(18):1334-49.
APMIS. 2004 Jul-Aug;112(7-8):481-95.
Front Biosci. 2009 Jan 1;14:150-8.

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Animal Models for ALI

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Number of papers indexed in PubMed using animal models of acute lung injury in the English literature from 2003-2007

	n	%
Mechanical ventilation	436	30%
LPS	279	19%
Live bacteria	224	16%
Hyperoxia	175	12%
Bleomycin	149	10%
Oleic acid	79	5%
Cecal ligation and puncture	61	4%
Acid aspiration	38	3%
Total	1,441	100%

Am J Physiol Lung Cell Mol Physiol. 2008 Sep;295(3):L379-99.

Animal Models for ALI

Species differences in…

… Toll-like receptors

… the mononuclear phagocyte system

… nitric oxide

… chemokines and chemokine receptors

Animal	% Identity with Human TLR4 HVR	Pulmonary Intravascular Macrophages	LPS Sensitivity	Nitric Oxide Production
Human	100%	No	Intermediate	+
NHP	95%	No	Intermediate	+
Pig	ND	Yes	High	++
Dog	ND	No	Low	++
Sheep	ND	Yes	High	++
Rabbit	57%	No	Intermediate	++
Rat	48%	No	Low	+++
Mouse	48%	No	Low	+++

HVR, hypervariable region of TLR4; NH, nonhuman primate; ND, not determined.

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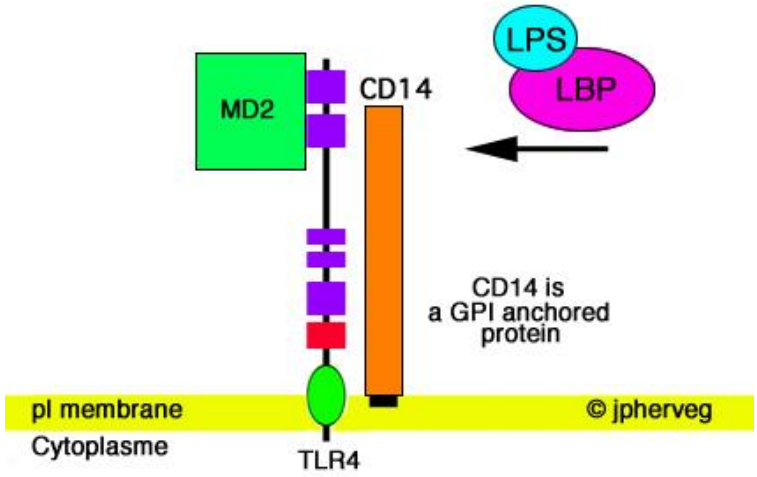
Animal Models for ALI
LPS



Initial mechanisms

- LPS i.v. → apoptosis of (capillary) endothelial cells
- initial phase of leukopenia
- ↓ cardiac output and ↓ arterial pressure
- ↑ pulmonary arterial pressure due to ↑ resistance of postcapillary veins

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http://genemol.org/genemol/pictures/TRL-04.html

Animal Models for ALI
LPS

…after the initial phase

- 4 – 6 hours → slow improvement in leucocyte counts and hemodynamic profile
- 2 – 4 hours → changes in the lung
  - hypoxemia
  - ↑ alveolar-arterial oxygen difference
  - changes in PMN deformability and entrapment of PMN in pulmonary capillaries

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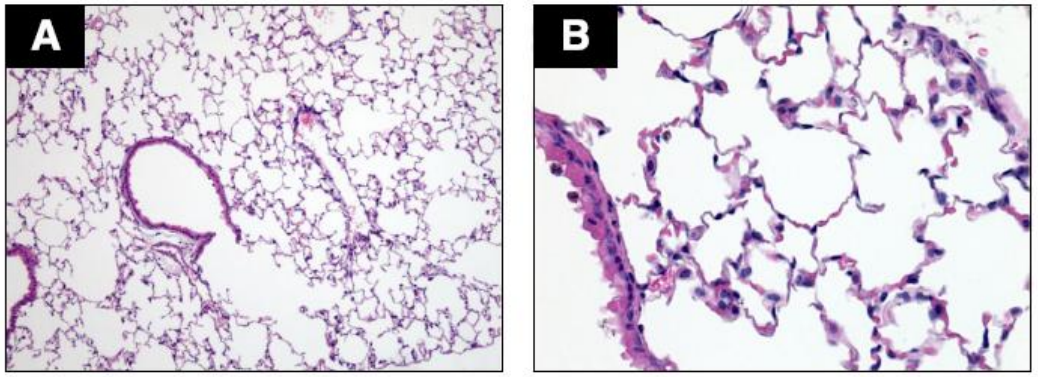
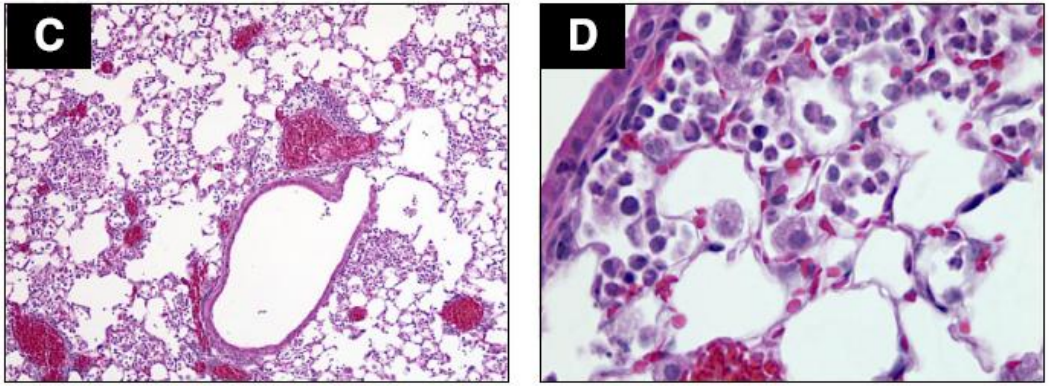


A, B: normal mouse lungs; thin alveolar walls, majority of alveoli contain no cells



C, D: 18h after intratracheal instillation of 5ng/g LPS; patchy nature of the injury, presence of inflammatory infiltrates and vascular congestion

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Animal Models for ALI
LPS

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Pros	Cons
Easy administration (intraperitoneal, intratracheal, i.v.)	Variable species responses to LPS
Potent activator of the innate immune responses via TLR4 and little direct toxicity to cells in vitro	Differences in LPS responses between different strains of same species (e.g. BALB/c vs. C57BL/6)
Reproducible results	LPS-preparations may contain contaminants

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Animal Models for ALI
Cecal Ligation and Puncture (CLP)

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Technique

- cecum ligation
- 3 – 5 x punction with a needle
  - severity of injury depends on no. of holes and size of the needle

Mechanisms

- effects develop over days
- less abrupt onset
  - 24 – 30 h: leukpenia, pulmonary hypertension
  - 18 – 72 h: lung injury

    (hypoxemia, neutrophilic inflammation, interstitial and alveolar edema)

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Animal Models for ALI
Cecal Ligation and Puncture (CLP)

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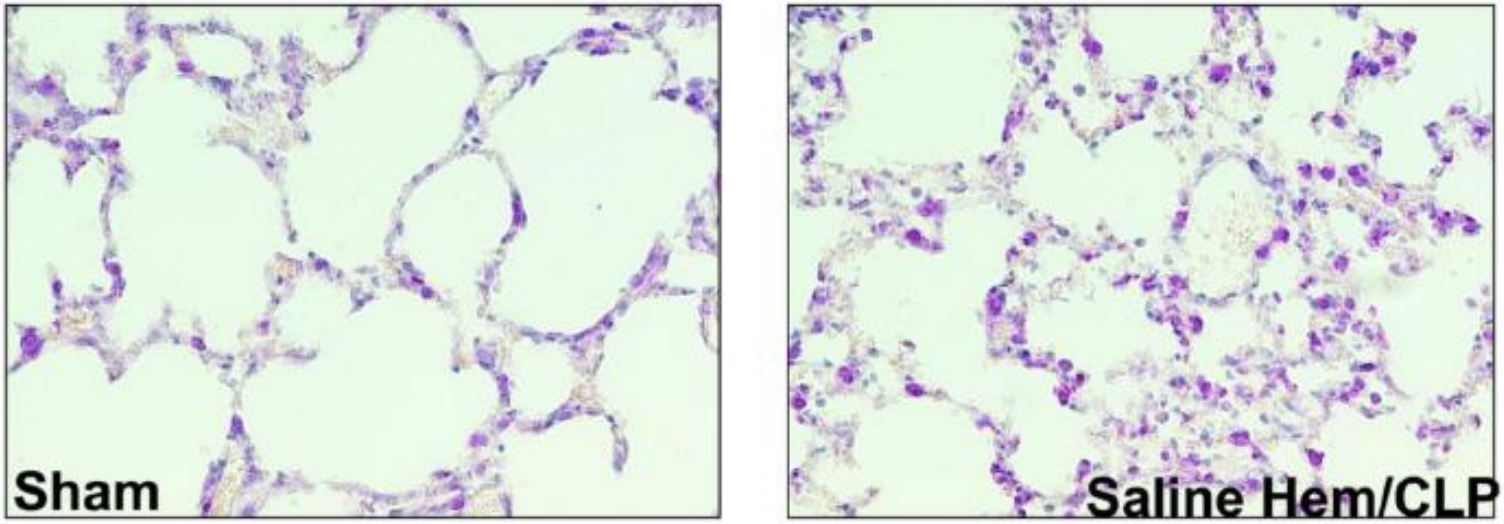

Fig. 5. Cecal ligation and puncture (CLP). Lungs from mice following sham surgery (*left*) or from mice subjected to 90 min of hemorrhagic shock (MAP = 30 mmHg) followed 24 h later by CLP (*right*). The lungs were stained for neutrophil-specific esterase (red). [From Lomas-Neira et al. (128).]

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Animal Models for ALI
Cecal Ligation and Puncture (CLP)

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Pros	Cons
Single best animal model of sepsis and organ injury	Major surgery required
Lung injury very similar to ALI/ARDS	High mortality
	Evtl. differences in colonic flora among animals

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http://science.kukuchew.com/tag/lab-rat/