Острый респираторный дистресс-синдром (ОРДС): определения и механизмы

К.М. Лебединский

История и терминология

Ashbaugh D.G., Bigelow D.B., Petty T.L. et al.

Acute respiratory distress in adults. *Lancet* 1967; 2: 319-23

- Респираторный дистресс-синдром взрослых
- Некардиогенный отек легких
- Легкое Дананга
- Посттрансфузионное, постперфузионное легкое
- Шоковое легкое
- Травматическое легкое
- Влажное легкое
- ~~Острое повреждение легких~~/острый респираторный дистресс

Что такое ОПЛ/ОРДС?

Международная согласительная конференция, 1994)

- Начало
- Рентгенография

Острое
Двухсторонняя инфильтрация

- Оксигенация (PaO_2/F_IO_2)
- Критерии исключения

- ОПЛ: ≤300 *мм Hg*
- ОРДС: ≤200 *мм Hg*
- ДЗЛА ≤18 *мм Hg*
- Нет признаков повышения ДЛП

Bernard GR et al. *Am J Resp Crit Care Med* 1994;149:818-824

Что такое ОРДС?

(Berlin ARDS definition –
V. Marco Ranieri, Gordon Rubenfeld, Arthur Slutsky et al., 2012)

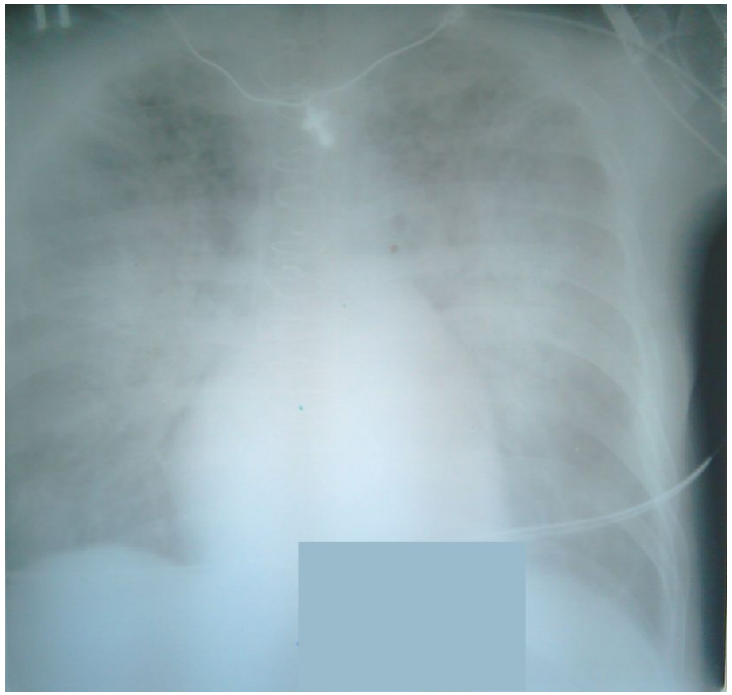
- Начало
- Рентгенография *или КТ*
- Оксигенация (PaO_2/F_IO_2 при PEEP 5 и выше)
- Критерии исключения

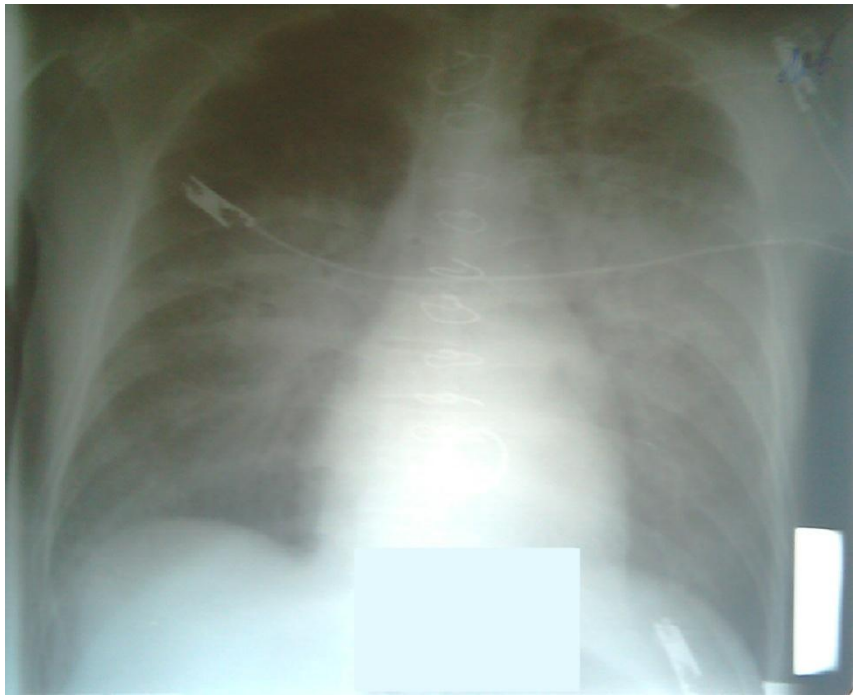
Острое (до 7 суток)
Двухсторонняя инфильтрация

- Легкий: 200…300 *мм Hg*
- Умеренный: 200…100
- Тяжелый: <100
- НЕТ (но можно сделать ЭхоКГ…)

The ARDS Definition Task Force // *JAMA.* 2012; 307(23): 2526-33.

Кардиогенный или некардиогенный?





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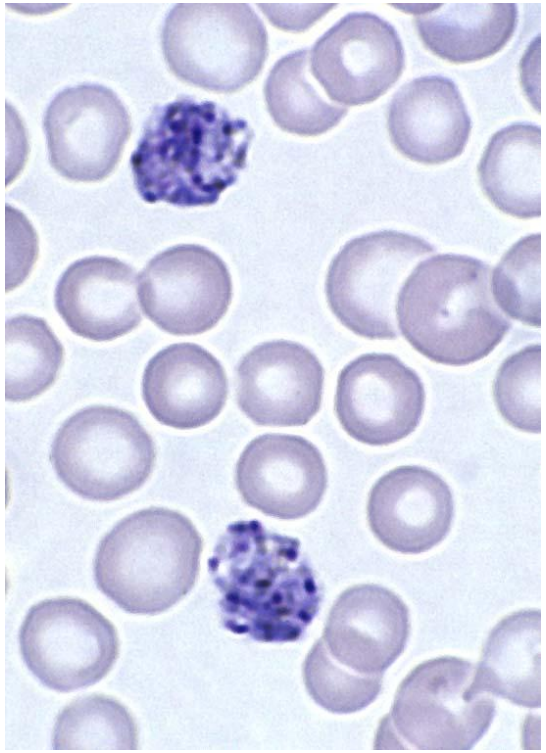
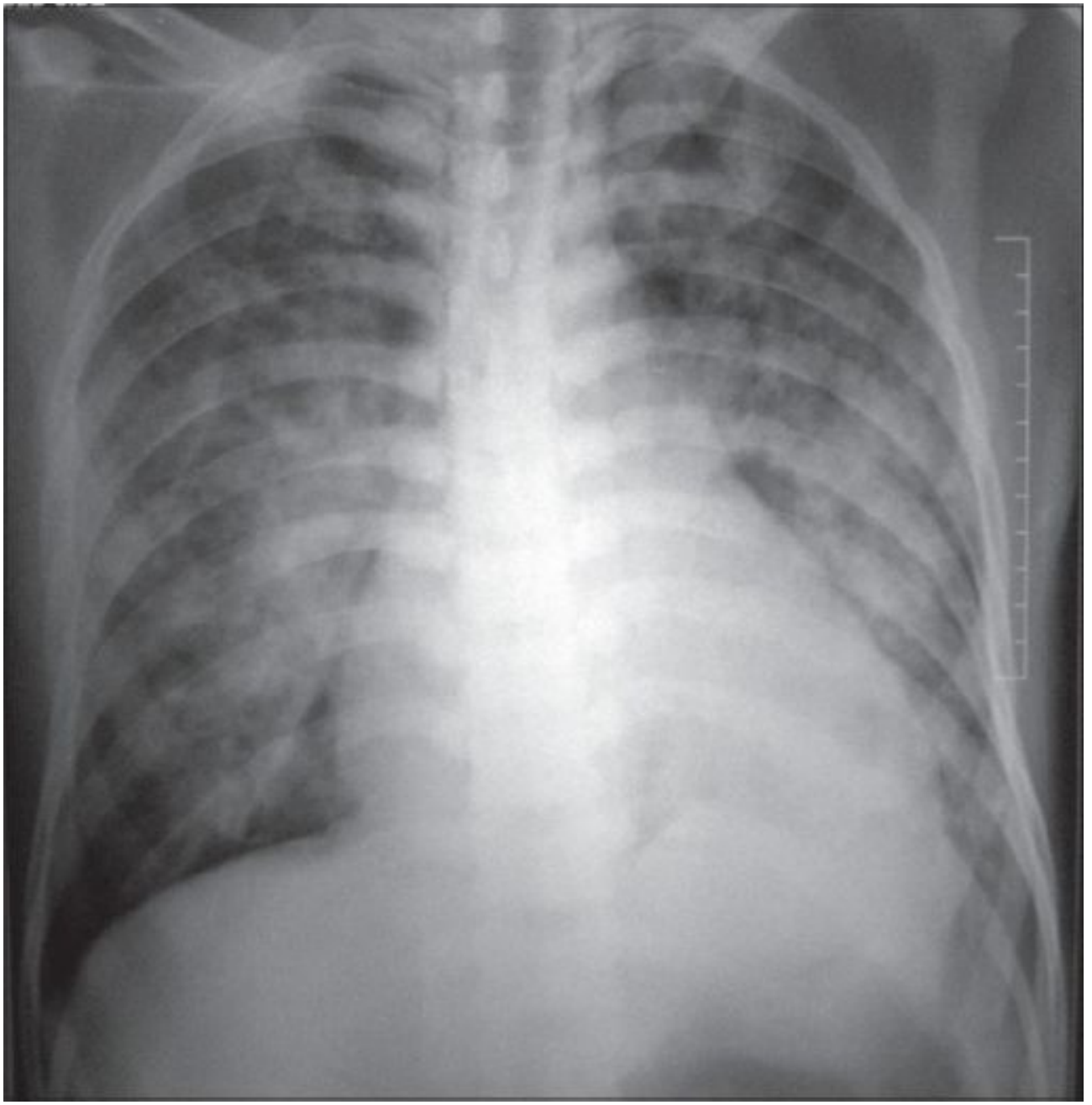


Pl. vivax



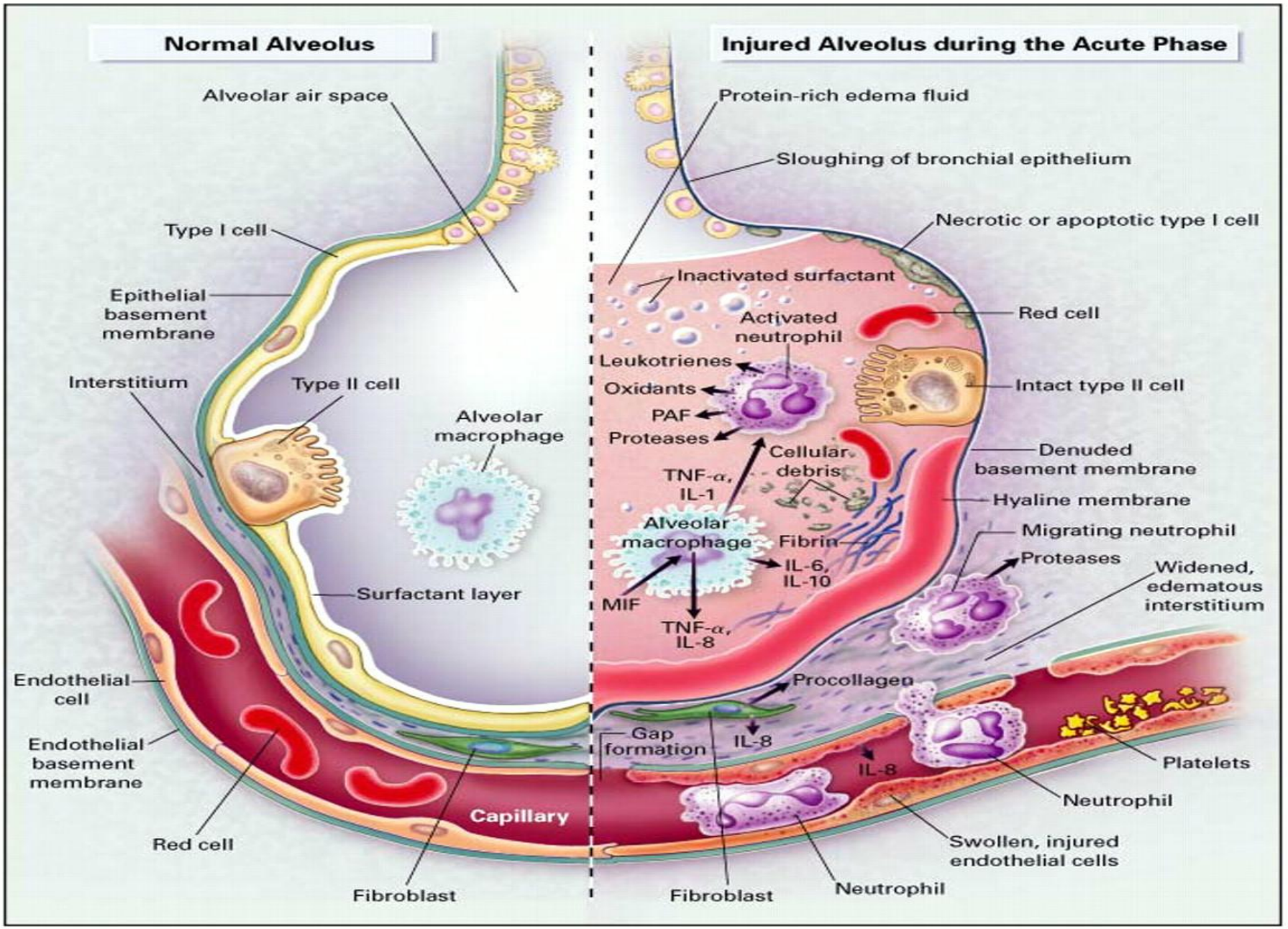
http://www.vivaxmalaria.com/images/vivax_in_smears_files/FIGvivax15.jpg
http://openi.nlm.nih.gov/imgs/rescaled512/2772242_IJCCM-13-103-g001.png

Причины ОРДС: внелегочные и легочные

- Шок
- Инфекция
- Травма
- Отравление
- Коагулопатия
- Разное…

- Аспирация
- Ингаляция
- Инфекция
- Радиация
- ТЭЛА
- Re-expansion
- Контузия

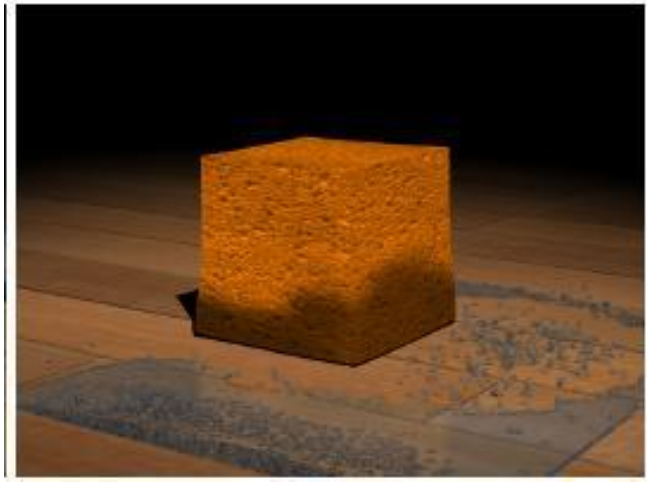
Красноярск, 2005



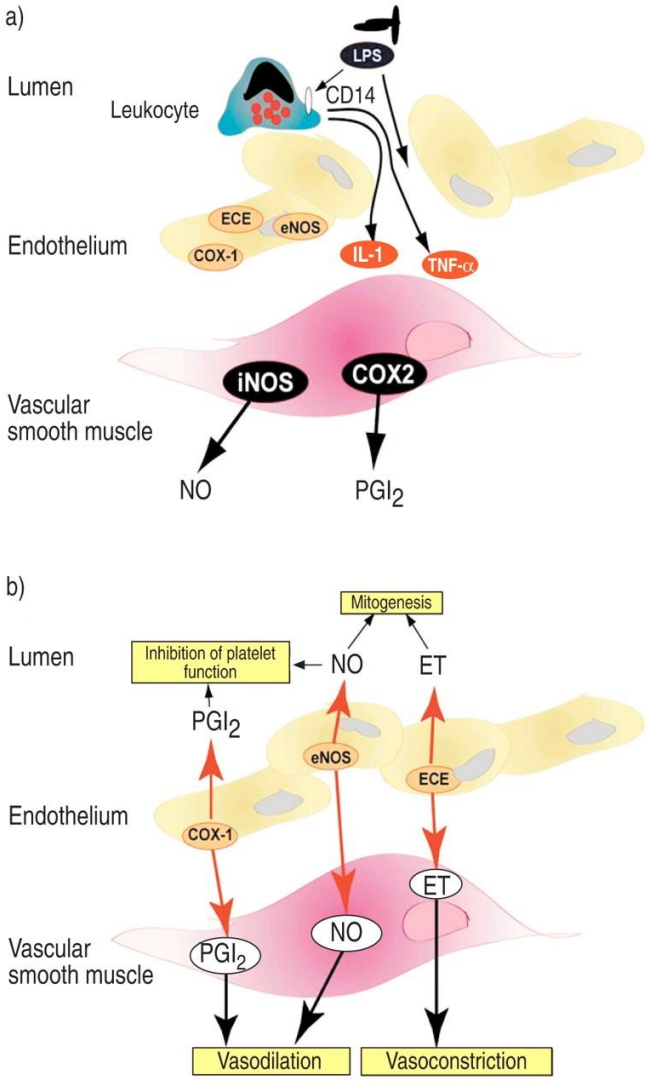
Ware and Matthay, NEJM, 2000

Лёгкое при ОРДС…

- Отечное
- Жесткое
- Неоднородное
- Маленькое (baby lung)
- Модель «мокрой губки»



http://www.stanford.edu/~patkar/lenaerts.JPG



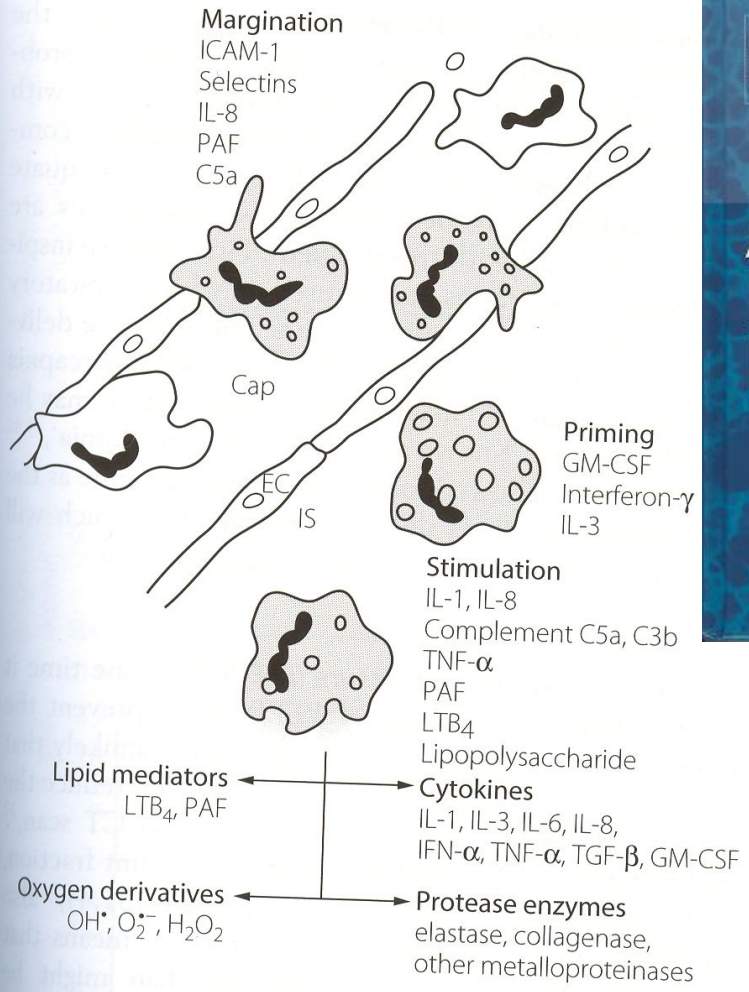
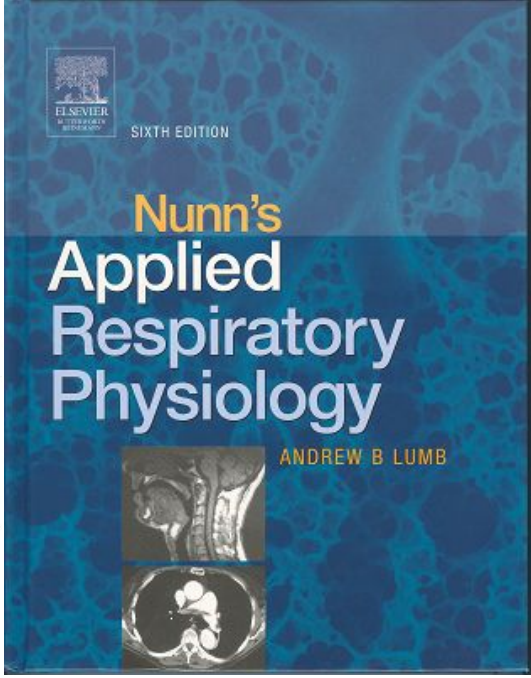


Figure 31.3 Neutrophil activation and the main cytokines and mediators involved. This takes place in three stages. *Margination*, when neutrophils adhere to the capillary (Cap) wall and migrate between endothelial cells (EC) into the interstitial space (IS); *priming*, when the cells generate preformed mediators and lysozomal contents; and *stimulation*, when neutrophils release the various mediators shown. The scheme shown is based on studies of both systemic and pulmonary inflammation. Neutrophil margination may occur by different mechanisms in pulmonary capillaries (see page 403). For explanation of abbreviations, see text.



http://www.erj.ersjournals.com/content/vol21/issue4/images/large/erj210720-1.jpeg

ПАТОФИЗИОЛОГИЯ ОПЛ/ОРДС:

почему мы так много знаем

и так мало можем?...

К.М. Лебединский

Так это всегда бывает...

Beetens JR, Loots W, Somers Y, Coene MC, biosynthesis of leukotrienes in vitro and in vivo. *I*

Slotman GJ, Burchard KW, D'Arezzo A, Gann D failure in critically ill surgical patients. *J Trauma*

Yu M, Tomasa G. A double-blind, prospecti thromboxane synthetase inhibitor, in the prop syndrome. *Crit Care Med* 1993; 21: 1635–1642.

Sinuff T, Cook DJ, Peterson JC, Fuller HD. Devel a ketoconazole practice guideline for ARDS propl

Ketoconazole for early treatment of acute lu syndrome: a randomized controlled trial. The ARI

CARING FOR THE CRITICALLY ILL PATIENT

Ketoconazole for Early Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

The ARDS Network Authors for the ARDS Network

THE ACUTE RESPIRATORY DISTRESS syndrome (ARDS) has been recognized for more than 30 years as a severe form of acute respiratory failure. Patients with this disorder are critically ill, require mechanical ventilation in an intensive care unit (ICU), and have a high mortality, ranging from 35% to 50% in recent reports.[1,2] Sepsis, severe trauma, aspiration of gastric contents, and massive blood transfusion are the most common clinical events that place patients at risk for the development of ARDS.[3] Recently, the concept of ARDS has been expanded to include milder forms of the same pathophysiologic process. The entire pathophysiologic spectrum is now called acute lung injury (ALI), whereas ARDS refers to the more severe end of that spectrum.[4] The degree of impairment of oxygenation of arterial blood is used to distinguish patients with ARDS from those with ALI. Despite this distinction, available data suggest the outcomes for patients with ALI are similar to outcomes of the subset of patients with ARDS.[5] Supportive care is the current state-of-the-art therapy for ALI and ARDS; no specific pharmacologic therapies have yet proved efficacious.[1]

ALI, including ARDS, is generally considered to be a consequence of an overaggressive inflammatory response that includes inflammatory cell migration into interstitial and alveolar

Context Three clinical studies have suggested that ketoconazole, a synthetic imidazole with anti-inflammatory activity, may prevent the development of acute respiratory distress syndrome (ARDS) in critically ill patients. However, the use of ketoconazole as treatment for acute lung injury (ALI) and ARDS has not been previously studied.

Objective To test the efficacy of ketoconazole in reducing mortality and morbidity in patients with ALI or ARDS.

Design Randomized, double-blind, placebo-controlled trial conducted from March 1996 to January 1997.

Setting Twenty-four hospitals associated with 10 network centers in the United States, constituting the ARDS Network.

Patients A total of 234 patients with ALI or ARDS.

Intervention Patients were randomly assigned to receive ketoconazole, 400 mg/d (n=117), or placebo (n=117), initiated within 36 hours of fulfilling study entry criteria and given enterally for up to 21 days.

Main Outcome Measures Primary outcome measures were the proportion of patients alive with unassisted breathing at hospital discharge and the number of days of unassisted breathing (ventilator-free days) during 28 days of follow-up. Secondary outcome measures included the proportion of patients achieving unassisted breathing for 48 hours or more, the number of organ failure–free days, and changes in plasma interleukin 6 (IL-6) and urinary thromboxane A_2 metabolites (thromboxane B_2 [TXB_2] and 11-dehydro-TXB_2).

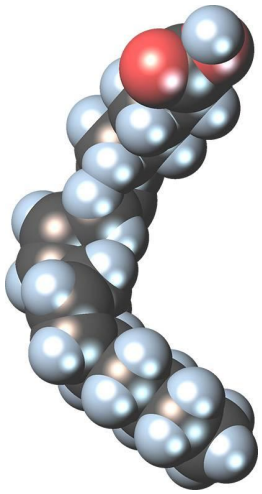
Results In-hospital mortality (SE) was 34.1% (4.3%) for the placebo group and 35.2% (4.3%) for the ketoconazole group ($P=.85$). The median number of ventilator-free days within 28 days of randomization was 9 in the placebo group and 10 in the ketoconazole group ($P=.89$). There were no statistically significant differences in the number of organ failure–free days, pulmonary physiology, or adverse events between treatment groups. The median serum ketoconazole level was 1.25 µg/mL and serum levels greater than 0.5 µg/mL were detected in 96% of patients assayed. Plasma IL-6, urinary TXB_2, and 11-dehydro-TXB_2 levels were unaffected by ketoconazole.

Conclusions In these patients with ALI or ARDS, ketoconazole was safe and bioavailable but did not reduce mortality or duration of mechanical ventilation or improve lung function. These data do not support the use of ketoconazole for the early treatment of ALI or ARDS.

JAMA. 2000;283:1995-2002 www.jama.com

Members of The ARDS Network are listed at the end of this article. A dagger identifies members who accept and fulfill authorship criteria.
Corresponding Author and Reprints: B. Taylor Thompson, MD, Pulmonary and Critical Care Unit, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (e-mail: ttthompson1@partners.org).
Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, *JAMA*.
Advisory Board: David Bihari, MD; Christian Brun-Buisson, MD; Timothy Evans, MD; John Heffner, MD; Norman Paradis, MD.

Figure 6. Metabolism of Dietary PUFAs (n-6 and n-3)



N-6

Polyunsaturated Fatty Acid Linoleic (18:2 n-6)

Δ-6 desaturase (decreased in trauma, sepsis)

N-3

Polyunsaturated Fatty Acid α-Linolenic (18:3 n-3)

γ-Linolenic (GLA) (18:3 n-6)

Δ-5 desaturase (decreased in trauma, sepsis)

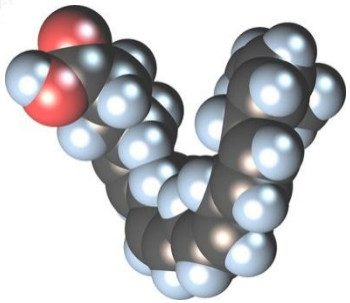
Stearidonic acid (18:4 n-3)

Dihomo-γ-linolenic (DGLA) (20:3 n-6)

Arachidonic (20:4 n-6)

20:4 n-3

Eicosapentaenoic (EPA) (20:5 n-3)



Cyclooxygenase 5-Lipoxygenase

Less inflammatory eicosanoids PGE_1

Inflammatory eicosanoids TXA_2, PGE_2, LTB_4

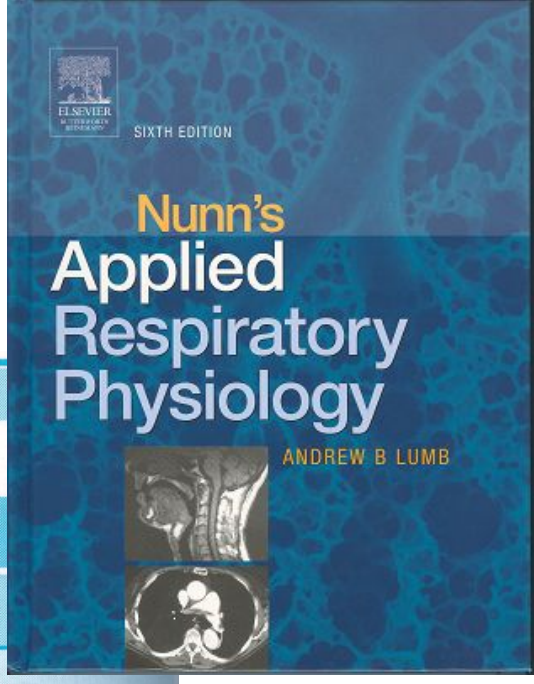
Less inflammatory eicosanoids TXA_3, PGI_3, LTB_5

TABLE 4. RESULTS OF CLINICAL TRIALS OF PHARMACOLOGIC TREATMENT FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME.

TREATMENT	YEAR	TYPE OF STUDY	NO. OF PATIENTS	FINDINGS	STUDY
Glucocorticoids (during the acute phase)	1987	Phase 3	87	No benefit	Bernard et al.[126]
Glucocorticoids (during the acute phase)	1988	Phase 3	59	No benefit	Luce et al.[127]
Alprostadil					
Intravenous	1989	Phase 3	100	No benefit	Bone et al.[124]
Liposomal	1999	Phase 3	350	Stopped for lack of efficacy	Abraham et al.[123]
Surfactant	1996	Phase 3	725	No benefit; new preparations and methods of delivery now being studied	Anzueto et al.[116]
Glucocorticoids during the fibrosing-alveolitis phase	1998	Phase 3	24	Decreased mortality, but study was small	Meduri et al.[131]
Inhaled nitric oxide	1998	Phase 2	177	No benefit	Dellinger et al.[119]
Inhaled nitric oxide	1999	Phase 3	203	No benefit	Payen et al.[120]
Ketoconazole	2000	Phase 2	234	No benefit	NIH Acute Respiratory Distress Syndrome Network[132]*
Procysteine	1998	Phase 3	214	Stopped for lack of efficacy	Bernard G: unpublished data
Lisofylline	1999	Phase 2–3	235	Stopped for lack of efficacy	Unpublished data

*NIH denotes National Institutes of Health.

И тем не менее…



2005

Acute lung injury

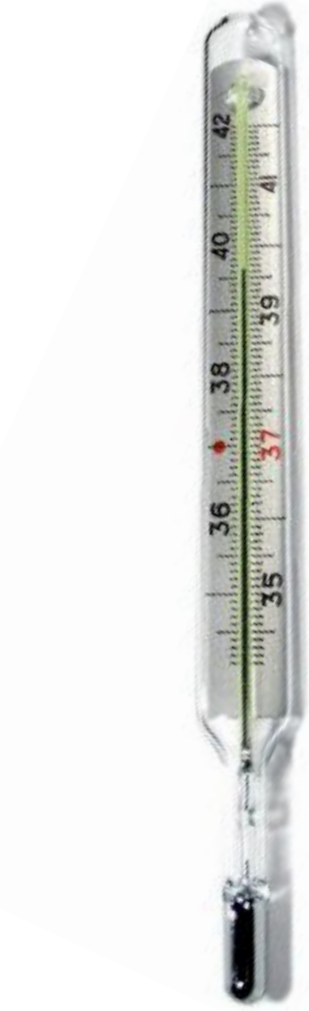
Table 31.3 Summary of pharmacological interventions suggested for the treatment of ALI or ARDS

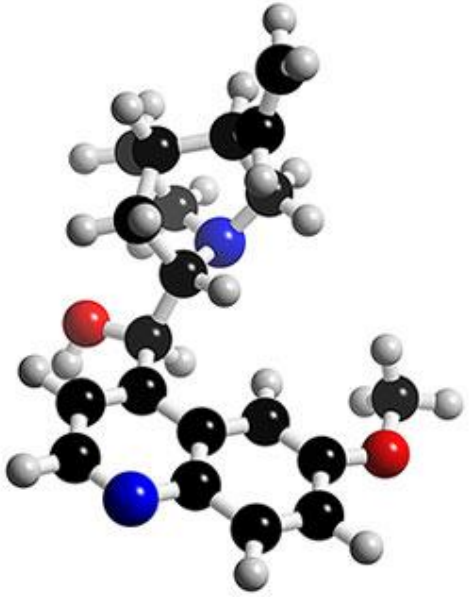
Therapy	Examples	Proposed mechanism
Pulmonary vasodilators	Prostacyclin	Non-specific pulmonary vasodilator
	Nitric oxide	Regional pulmonary vasodilator (see text)
	Almitrine	Enhancement of hypoxic pulmonary vasoconstriction
Surfactant	Artificial surfactants	Replace depleted alveolar surfactant, may also have antiinflammatory properties
Antiinflammatory	Steroids	General antiinflammatory
	Ketoconazole	Inhibits thromboxane synthesis
	Ibuprofen/Indomethacin	Inhibits prostaglandin production
	Prostaglandin E_1	Inhibits platelet aggregation, vasodilator
	Pentoxifylline	Reduces neutrophil chemotaxis and activation
	Endotoxin/TNF/IL-1 antagonists	Inhibition of specific aspects of inflammatory response
Antioxidants	*N*-acetylcysteine	Increased glutathione activity (page 356)
	Recombinant human manganese SOD	Replaces epithelial extracellular SOD (page 355)
Anticoagulants	Heparin	Reduces fibrin deposition in alveoli

NB All the therapies listed have been shown to have beneficial effects in *in vitro* or animal studies of ALI. There is insufficient evidence of improved outcome for any of the therapies listed to be recommended for routine use in human ALI. For further details see references 1, 36, 51, 52.
SOD, superoxide dismutase (page 355); TNF, tumour necrosis factor; IL-1, interleukin 1.

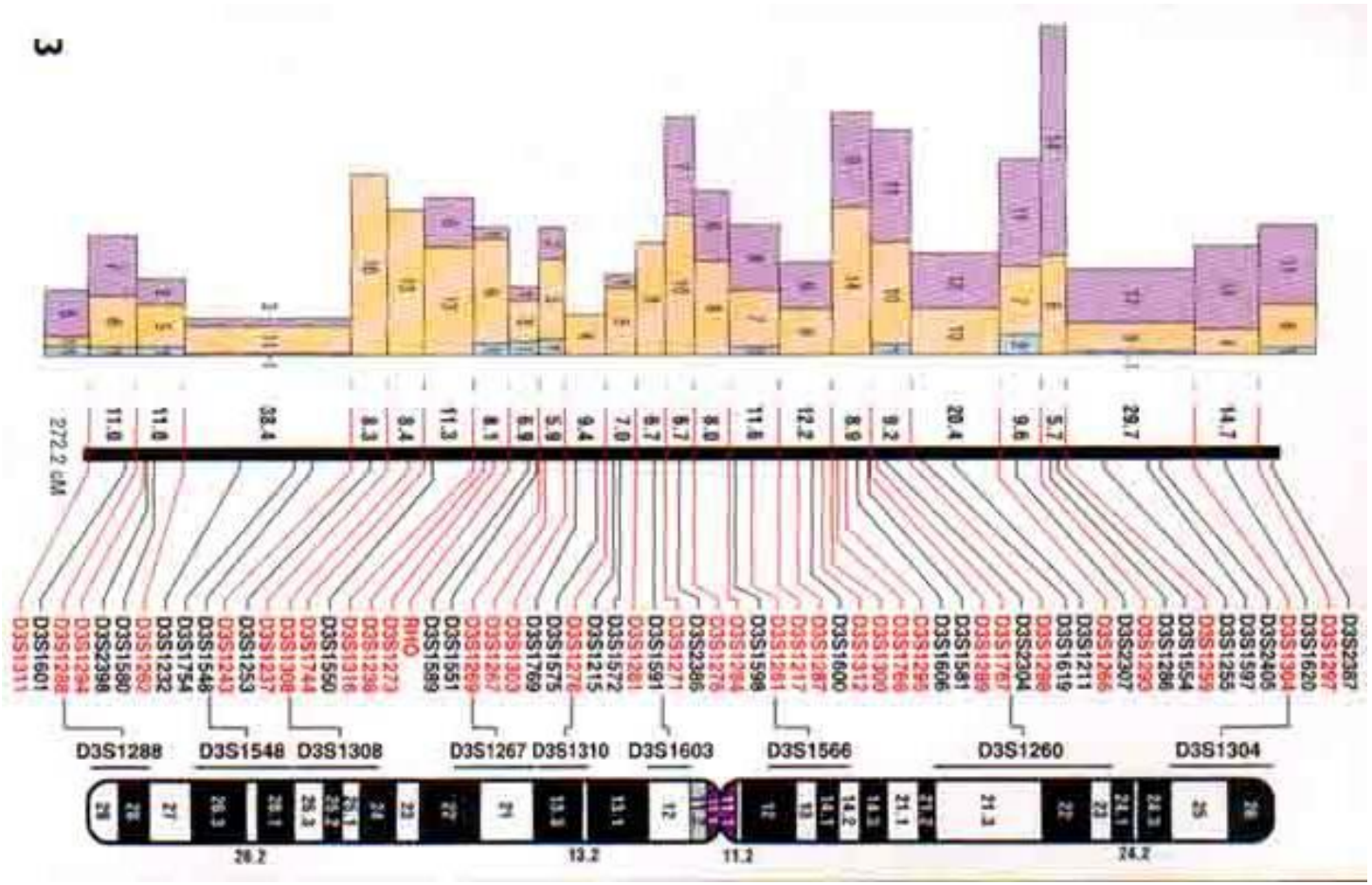
Почему неадекватны наши модели?

А не предпринять ли РКИ?...





Что может делать наши группы неоднородными?...



http://www.life.illinois.edu/ib/494/images/genome.jpg

«На любой предмет можно посмотреть с трех точек зрения: с точки зрения науки, с точки зрения права и с точки зрения здравого смысла...»

Людвиг Фейербах, 1804-1872

Вопросы?...