Raspunsul inflamator in ARDS

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- Acute respiratory distress syndrome (ARDS) este o reactie a parenchimului pulmonar la o gama larga de afectiuni directe sau indirecte.

Etiologia

- Afectiuni pulmonare
- pneumonia
- contuziile pulmonare
- inspirarea unei concentratii mari de O2
- inhalarea de vapori toxici
- Inecul
- Afectiuni la distanta
- socul
- transfuzia masiva
- pancreatita acuta severa
- hipertensiunea intracraniana
- arsurile extinse
- embolia cu lichid amniotic
- eclampsia
- politraumatismele, etc.

Definitie

- Definitia "clasica"

- Conform American -European Consensus (1994), ARDS se defineste prin

- debut rapid
- imagine radiologica sugestiva, caracterizata prin infiltrate bilateral si asa-zisul aspect de "furtuna de zapada"
- raport PaO2/FiO2< 200 mmHg
- absenta semnelor clinice de hipertensiune atriala stanga sau PAOP <18 mmHg masurata in aceleasi conditii

Bernard GR, Artigas A, Brigham KL, et al. The American-European consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149: 818-824.
Bernard GR, Artigas A, Brigham KL,et al. of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med. 1994; 20(3):225-32.

Limitari ale definitiei ‘’clasice’’

- Numeroase inadvertente si dificultati de definire clinica a ARDS:
- Ce inseamna ‘’acut’’ in definitie?
- legate de nivelul PEEP in influentarea raportului PaO2/FiO2 la pacientii ventilati mecanic
- variatiile si specificitatea uneori redusa a imaginii radiologice, etc
- Dificultatile de identifcare a edemului hidrostatic (posibilitatea de coexistenta a ARDS si a edemului hidrostatic)
- Nu includea factorii de risc, cel putin pentru edemul hidrostatic

- au dus la constituirea unui Task Force care a elaborat o noua definitie a ARDS in asa-zisa definitie Berlin

Ranieri MV, Rubenfeld GD, Taylor Thompson B, et al. ARDS Task Force. Acute Respiratory Distress Syndrome. : The Berlin Definition. JAMA 2012; 307 (23): 2526-2533. doi:10.1001/jama.2012.5669

Definitie

- Definitia Berlin.
- debut recent, adica in decurs de 1 saptamana de la o leziune potential generatoare sau prin simptome respiratorii noi sau in agravare,
- imagine radiologica/tomografica sugestiva cu opacitati bilaterale, care nu este argumentata de colectii, colaps sau noduli pulmonari
- raport PaO2/FiO2< 300 mmHg, defalcat pe cele 3 forme de gravitate a ARDS
- intre 200-300 mmHg pentru forma usoara,
- intre 100-200 mmHg pt forma medie si
- < 100 mmHg pentru forma severa
- Este inclus si nivelul de CPAP/PEEP la care se evalueaza raportul, adica CPAP/PEEP ≥ 5 mmHg pentru forma usoara si nivel PEEP ≥ 5 mmHg pentru formele medie/severa .
- Criteriu separat este constituit de originea edemului pulmonar care nu este explicat de insuficienta cardiaca sau incarcarea lichidiana .

Ranieri MV, Rubenfeld GD, Taylor Thompson B, et al. ARDS Task Force. Acute Respiratory Distress Syndrome. : The Berlin Definition. JAMA 2012; 307 (23): 2526-2533. doi:10.1001/jama.2012.5669

Acute Respiratory Distress Syndrome
The Berlin Definition

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

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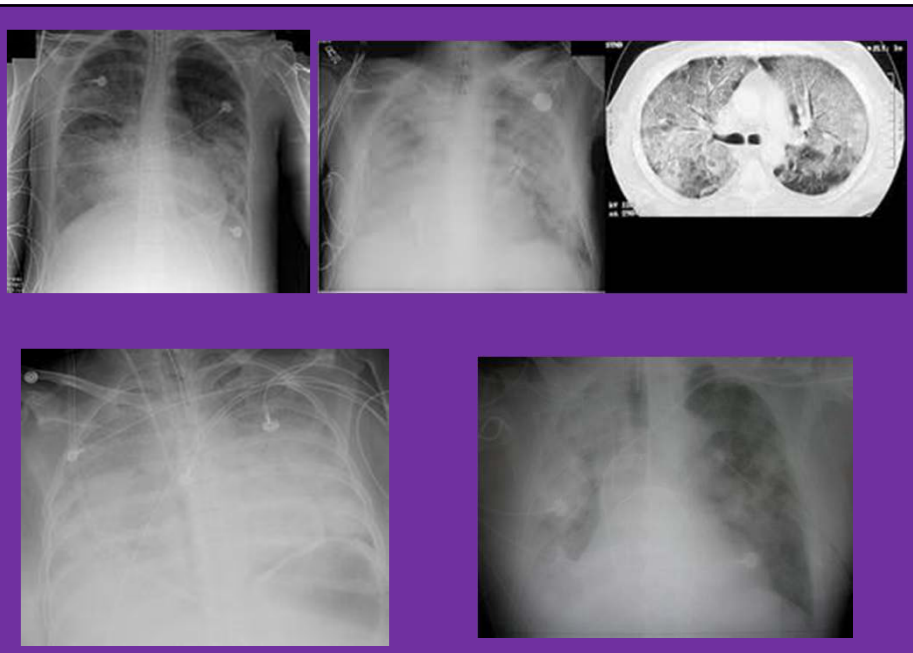
Table 4. Predictive Validity of ARDS Definitions in the Clinical Database

	Modified AECC Definition[a]		Berlin Definition ARDS[a]		
	ALI Non-ARDS	ARDS	Mild	Moderate	Severe
No. (%) [95% CI] of patients	1001 (24) [23-25]	3187 (76) [75-77]	819 (22) [21-24]	1820 (50) [48-51]	1031 (28) [27-30]
Progression in 7 d from mild, No. (%) [95% CI]		336 (34) [31-37]		234 (29) [26-32]	33 (4) [3-6]
Progression in 7 d from moderate, No. (%) [95% CI]					230 (13) [11-14]
Mortality, No. (%) [95% CI][b]	263 (26) [23-29]	1173 (37) [35-38]	220 (27) [24-30]	575 (32) [29-34]	461 (45) [42-48]
Ventilator-free days, median (IQR)[b]	20 (2-25)	12 (0-22)	20 (1-25)	16 (0-23)	1 (0-20)
Duration of mechanical ventilation in survivors, median (IQR), d[b]	5 (2-10)	7 (4-14)	5 (2-11)	7 (4-14)	9 (5-17)

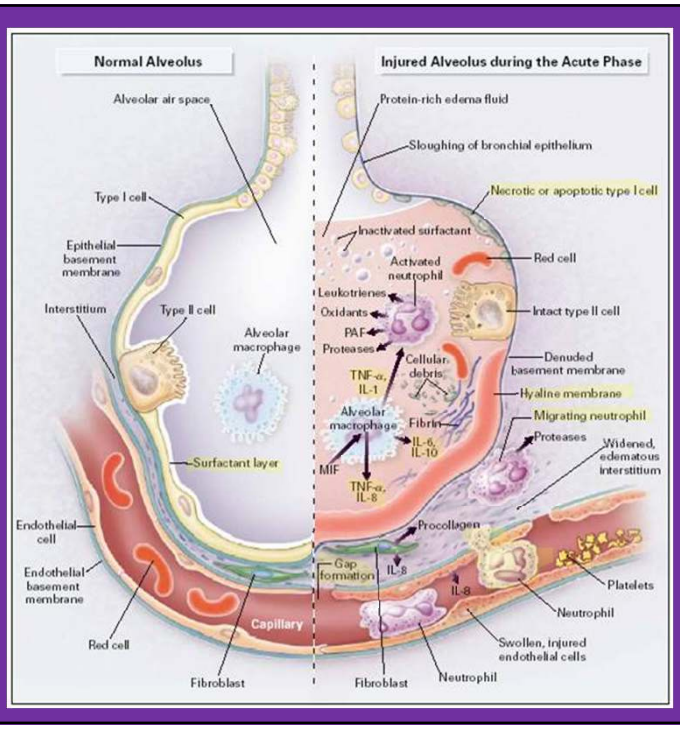
Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; Fio_2, fraction of inspired oxygen; IQR, interquartile range; Pao_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure.
[a] The definitions are the following for ALI non-ARDS (200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg, regardless of PEEP), ARDS (Pao_2/Fio_2 ≤ 200 mm Hg, regardless of PEEP), mild Berlin Definition (200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP ≥5 cm H_2O), moderate Berlin Definition (100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O), and severe Berlin Definition (Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O).
[b] Comparisons of mortality, ventilator-free days, and duration of mechanical ventilation in survivors across categories of modified AECC (ALI non-ARDS and ARDS) and across categories of Berlin Definition (mild, moderate, and severe) are all statistically significant ($P < .001$).



http://www.trauma.org/archive/thoracic/CHESTcontusion.html http://robochest.com/WebHelp/Edema_Stage_II.html
http://www.meddean.luc.edu/lumen/MedEd/medicine/pulmonar/diseases/pdis3.htm
http://www.trauma.org/archive/thoracic/CHESTcontusion.html

Mecanismele fiziopatologice

- inflamatia parenchimului pulmonar ca reactie la un numar de cause favorizante → alterarea schimburilor gazoase si hipoxemie consecutiva ce necesita in cele mai multe cazuri ventilatie mecanica pentru corectie
- aceasta inflamatie este cauzata de eliberarea locala sau sistemica de mediatori ai inflamatiei: cytokine, chemokine si alti mediatori ai inflamatiei, proteina C-reactiva, fibrinogen, inhibitorul-1 al activatorului de plasminogen
- se adauga extravazarea locala a leucocitelor (neutrofilelor) si eliberarea produsilor de degranulare leucocitara



pharmacology.wiki.usfca.edu

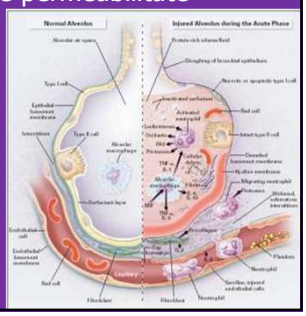
Evolutia raspunsului inflamator in ARDS

- Faza exudativa → faza proliferativa →

faza de fibroza → faza de rezolutie

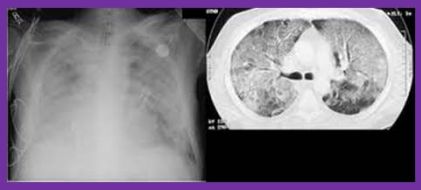
Evolutia raspunsului inflamator in ARDS

- eliberarea locala/sistemica (cu efect ulterior local la nivel pumonar) de mediatori ai inflamatiei →modifica permeabilitatea capilara si activeaza leucocitele care vor extravaza si la nivel pulmonar
- Faza exudativa.
- Inlocuirea spatiilor aerice ale plamanului (alveolele pulmonare) cu un exudat inflamator format, in principal, din neutrofile si macrophage
- la nivel vascular se produc pe langa modificarile de permeabilitate vasculara, procese de agregare leucocitara
  si trombocitara
  care pot obstrua lumenul microcirculatiei



Meduri GU, Annane D, Chrousos GP, Marik PE, Sinclair SE. Activation and regulation of systemic inflammation in ARDS. Rationale for prolonged glucocorticoid therapy. Chest 2009; 136 (6):1631–1643

- Faza exudativa (primele 7 zile)
- Depunere de mebrane hialine, eozinofilice, care contin Ig,C, fibrina
- distributie asimetrica, primele fiind interesate
  regiunile pulm post declive → infiltrate, consolidate sau inflamate,
  fapt vizibil si la examenul tomografic.



Evolutia raspunsului inflamator in ARDS

- Faza proliferativa in care are loc proliferarea pneumocitelor de tip II, transformarea in cel de tip I (necroza, apoptoza), apar fibrele de colagen→ fibroza
- Faza de fibroza in care are loc migrarea fibroblastilor si mioblastilor la nivelul spatiilor aerice , cont de colagen, fibroza
- Dupa unii procesul e fibroza poate incepe precoce, odata cu faza exudativa

Meduri GU, Annane D, Chrousos GP, Marik PE, Sinclair SE. Activation and regulation of systemic inflammation in ARDS. Rationale for prolonged glucocorticoid therapy. Chest 2009; 136 (6):1631–1643. Meduri GU, Muthiah MP, Carratu P, et al. Nuclear factor-kB- and glucocorticoid receptor α-mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome: evidence for inflammation-induced target tissue resistance to glucocorticoids. Neuroimmunomodulation 2005;12:321–338.
Meduri GU, Tolley EA, Chrousos GP, et al. Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome: evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. Am J Respir Crit Care Med 2002;165:983–991.

- La nivel leucocitar se produce activarea NF-kB si a receptorilor α pentru glucocorticoizi (GC- α).
- In functie de activarea uneia sau a alteia dintre linii, evolutia va fi spre
  - ameliorare, in cazul activarii predominante a receptorilor GC- α
  - agravare in cazul activarii predominante a NF-kB, care la randul sau, determina transcrierea in exces a mediatorilor inflamatiei

Rolul leucocitelor in patogeneza ARDS

- In ARDS, are loc activarea si migrarea leucocitelor la nivelul circulatiei pulmonare unde sunt sechestrate unele datorita CAMs produse in exces (in vasele de calibru mare), iar altele datorita marimii celulei (la nivelul microcirculatiei pumonare)
- O parte vor elibera local in circulatie mediatori ai inflamatiei, altele vor extravaza in spatiile aerice → participa la dezv fazei exudative a procesului inflamator prin producerea de mediatori ai inflamatiei,radicali liberi de O2 si proteaza si ocuparea sp aerice
- Degranularea si apoptoza leucocitara sunt alte posibilitati de evolutie a leucocitelor la nivel pulmonar care agraveaza tabloul inflamator si influenteaza evolutia pacientilor

Müller AM, Cronen C, Müller KM, Kirkpatrick CJ. Heterogeneous expression of cell adhesion molecules by endothelial cells in ARDS. *J Pathol* 2002; 198: 270–275.
Matute-Bello G, Liles WC, Radella F 2nd, Steinberg KP, Ruzinski JT, Hudson LD, Martin TR. Modulation of neutrophil apoptosis by granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor during the course of acute respiratory distress syndrome. Crit Care Med 2000;28(1):1-7.
26. Matute-Bello G, Liles WC, Radella F 2nd,et al. Neutrophil apoptosis in the acute respiratory distress syndrome. Am J Respir Crit Care Med 1997;156(6):1969-77.

Rolul citokinelor in producerea si evolutia ARDS

- principalele interleukine pro-inflamatorii eliberate in ARDS sunt TNF- α, IL-1β, IL-2, IL-6 si IL-8
- Se pot monitoriza atat nivelurile serice cat si cele pulmonare (BAL)
- Niveluri ridicate persistente ale TNF- α si IL-1β eliberate de sursele de infectie extrapulmonare (sepsis) sau pulmonare, contribuie la inducerea febrei si cresterea permeabilitaii capilare pulmonare care ambele contribuie la patogeneza ARDS.
- IL contribuie la dezvoltarea r. inflamatorii la nivel pulmonar si extrapulm
- IL proinflamatorii favorizeaza cresterea bacteriana la nivel pulmonar
- Evolutia ARDS depinde, de echilibrul interleukinelor pro- si anti-inflamatorii (Il-4, IL-10)
- Nivelurile serice si BAL ale IL servesc atat la diagnostic, cat si la monitorizarea evolutiei, evaluarea gravitatii si a prognosticului ARDS

Bauer TT, Montón C, Torres A, et al. Comparison of systemic cytokine levels in patients with acute respiratory distress syndrome, severe pneumonia, and controls. Thorax 2000;55:46–52.
Meduri GU, Headley S, Kohler G, Stentz F, Tolley E, Umberger R, Leeper K. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. Chest 1995;107(4):1062-73.
9. Roumen RM, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen GA, Sauerwein RW, van der Meer JW, Goris RJ. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg 1993 ;218(6):769-76.

In summary, we have found that at the onset of ARDS, high concentrations of antiinflammatory cytokines produce markedly lower molar ratios of proinflammatory to antiinflammatory mediators in the lungs. This provides a mechanism for dampening the otherwise intense inflammatory response in the airspaces. These results highlight the complexity of the inflammatory response in the lungs of patients with ARDS and show that individual cytokine measurements cannot be considered in isolation but must be understood in the context of the balance between agonistic and antagonistic responses in the lungs.

Am J Respir Crit Care Med Vol 164. pp 1896–1903, 2001

Cytokine Balance in the Lungs of Patients with Acute Respiratory Distress Syndrome

WILLIAM Y. PARK, RICHARD B. GOODMAN, KENNETH P. STEINBERG, JOHN T. RUZINSKI, FRANK RADELLA II, DAVID R. PARK, JEROME PUGIN, SHAWN J. SKERRETT, LEONARD D. HUDSON, and THOMAS R. MARTIN

tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6. We found that all three bacterial species showed concentration-dependent growth enhancement when incubated with one or more tested cytokines and that blockade by specific neutralizing cytokine MoAb significantly inhibited cytokine-induced growth. When compared with control, the 6-h growth response (cfu/ml) was maximal with IL-1β at 1,000 pg for *Staphylococcus aureus* (36 ± 16 versus 377 ± 16; p = 0.0001) and *Acinetobacter* spp. (317 ± 1,147 versus 1,124 ± 147; p = 0.002) and with IL-6 at 1,000 pg for *Pseudomonas aeruginosa* (99 ± 50 versus 509 ± 50; p = 0.009). The effects of cytokines were seen only with fresh isolates and were lost with passage *in vitro* on bacteriologic medium without added cytokines. In this study we provide additional evidence for a newly described pathogenetic mechanism for bacterial proliferation in the presence of exaggerated and protracted inflammation. **Meduri GU, Kanangat S, Stefan J, Tolley E, Schaberg D. Cytokines IL-1β, IL-6, and TNF-α enhance *in vitro* growth of bacteria.**

AM J RESPIR CRIT CARE MED 1999;160:961–967.

Cytokines IL-1β, IL-6, and TNF-α Enhance *In Vitro* Growth of Bacteria

G. UMBERTO MEDURI, SIVA KANANGAT, JENNIFER STEFAN, ELIZABETH TOLLEY and DENNIS SCHABERG

Rolul moleculelor de adeziune celulara in patogeneza ARDS

- Moleculele de adeziune celulara (CAMs) sunt proteine localizate pe suprafata celulara, implicate in procesul de adeziune celulara, ce implica atat adeziunea intercelulara, cat si adeziunea de matricea extracelulara
- CAMs apartin superfamiliei imunoglobulinelor, dar si integrinelor, caderinelor si selectinelor
- sunt secretate si exprimate la nivelul memebranei celulelor endoteliale la nivel pulmonar (in ARDS) fie sub influenta directa a TNF, IL-1 si a IL-6, fie prin alte mecanisme
- In ARDS, CAMs sunt implicate in adeziunea intercelulara a celulelor inflamatorii, in principal a leucocitelor, dar si de adeziunea acestora de endoteliile vasculare si transvazarea acestora in alveole si interstitii unde se constituie procesul inflamator

Brackenbury R, Rutishauser U, Edelman GM . Distinct calcium-independent and calcium-dependent adhesion systems of chicken embryo cells. Proc Natl Acad Sci U.S.A. 1981;78 (1): 387–91. DOI:10.1073/pnas.78.1.387.
Müller AM, Cronen C, Müller KM, Kirkpatrick CJ.Heterogeneous expression of cell adhesion molecules by endothelial cells in ARDS. *J Pathol* 2002; 198: 270–275

Rolul moleculelor de adeziune celulara in patogeneza ARDS

- s-a demonstrat ca expresia PECAM este puternica in vasele pulmonare atat ale pacientilor cu ARDS cat si in parenchimul pulmonar normal, indiferent de calibrul vascular, in timp ce ICAM-1,CD14 si TNFR2 sunt intens exprimate doar la pacientii cu ARDS
- E-selectina si VCAM sunt de asemenea intens exprimate doar la pacientii cu ARDS si doar la nivelul vaselor cu calibru mare (nu si in vasele mici)
- Mecanismul datorita caruia comportamentul vascular in producerea moleculelor de adeziune celulara este diferit in functie de calibrul vascular incomplet cunoscut.

- Obs! Nu este cert daca exista diferente intre capacitatea/incapacitatea celulelor endoteliale de a secreta molecule de adeziune celulara sau daca exista in conditiile ARDS un comportament diferit al vaselor sanguine pulmonare in functie de calibrul acestora

Lucas R, Lou J, Morel DR, Ricou B, Suter PM, Grau GE.TNF receptors in the microvascular pathology of acute respiratory distress syndrome and cerebral malaria. J Leukoc Biol 1997; 61 (5):551-8.

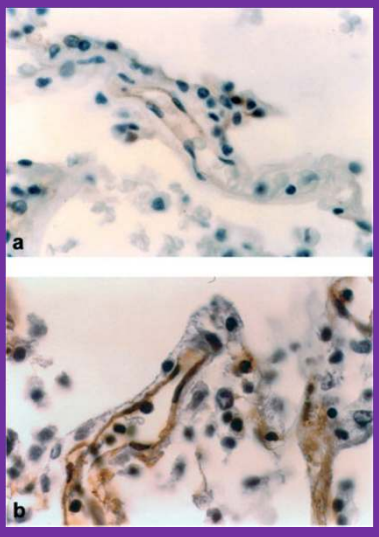
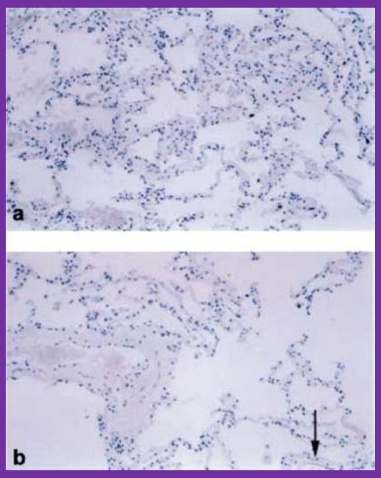


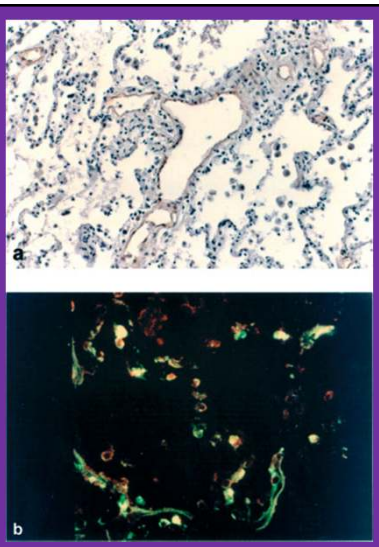
Fig 1. Evidentierea ICAM-1 prin reactii de culoare (anticorpi anti ICAM-1 la nivelul cel endoteliale in tes pulm normal unde reactia este slaba (a) si tes pulm septic unde reactia este f puternica la nivelul tuturor vaselor (b).

Müller AM, Cronen C, Müller KM, Kirkpatrick CJ.Heterogeneous expression of cell adhesion molecules by endothelial cells in ARDS. J Pathol 2002;198:270–275



Tes pulmonar normal in coloratie cu anticorpi anti selectina E, (a) si VCAM (b). Nu exista coloratie pt selectina - E (a), in timp ce pt VCAM exista coloratie slaba la nivelul catorva celule endoteliale venoase (→) (b)

Müller AM, Cronen C, Müller KM, Kirkpatrick CJ.Heterogeneous expression of cell adhesion molecules by endothelial cells in ARDS. J Pathol 2002;198:270–275



(a) Tes pulm de la un pacient cu ARDS cu coloratie puternic pozitiva pentru E-selectina a cel endoteliale din vasele pre- and post-capillare. Se observa absenta coloratiei cel endoteliale ale capilarelor intra-alveolare.
(b) Co-exprimarea vWf (rosu) si E-selectin (verde) in plamanul septic sub forma de mozaic de culoare galbena (combinatie de rosu si verde in immunfluorescenta). Unele cel endoteliale sunt colorate cu rosu, iar altele in verde (pt vWf) (rosu pt E-selectin), demonstrand expresia inomogena a acestor molecule

Müller AM, Cronen C, Müller KM, Kirkpatrick CJ.Heterogeneous expression of cell adhesion molecules by endothelial cells in ARDS. J Pathol 2002;198:270–275

Concluzii

- Evolutia ARDS este dominant conditionata de evolutia procesului inflamator
- Procesul inflamator se poate stinge de la sine, sau se poate autointretine in pofida tratamentului agravand evolutia
- Mentinerea echibrului intre latura pro- si cea antiinflamatorie a raspunsului imun conditioneaza, ca si in alte stari caracterizate de raspuns inflamator accentuat, evolutia ARDS.
- Intelegerea acestor mecanisme si a implicarii mediatorilor inflamatori in patogeneza ARDS este extrem de importanta in identificarea viitoarelor abordari in managementul ARDS, chiar daca incercarile intreprinse pana in acest moment
- In baza mec de act al rasp inflamator s-au incercat terapii cu antiinflamatoare, NO, surfactant, antioxidante, anti IL-8, 6, 1, anti TNF care, pana in prezent, nu au dat rezultatele scontate sau nu s-au validat inca pe grupuri mari populationale.