ADJUNCTS IN TREATMENT OF ARDS

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ABJUNCTS IN TREATMENT OF ARDS

1. Ventilatory Strategies other than Lung Protective Strategy.
   - Prone Ventilation
   - Liquid Ventilation
   - High Frequency Ventilation
   - Tracheal Gas Insufflation
   - Extracorporeal Gas Exchange
2. Hemodynamic Management – Fluids, Vasopressors.
3. Selective Pulmonary vasodilators.
4. Surfactant replacement therapy.
5. Anti-inflammatory Strategies.
   a) Corticosteroids.
   b) Cycloxygenase & lipoxygenase inhibitors.
   c) Lisofylline and pentoxifylline.
6. Antioxidants – NAC : Procysteine
7. Anticoagulants.

PRONE VENTILATION

Effect on gas exchange

Improves oxygenation – allows decrease Fio_2; PEEP

- Variable
- not predictable

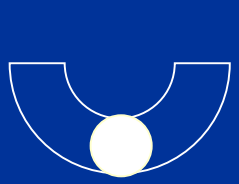
response rate – 50-70%

Proposed mechanism – how it improves oxygenation

1) Increase in FRC
2) Improved ventilation of previously dependent regions.

(a) Difference in diaphragmatic movement

- supine : dorsal and ventral portion move symmetrically
- prone : dorsal > ventral



Supine +2.8

prone +1.0

P_{PL} at dorsal	Higher	Less
TP pressure	Lower	More
Result	Atelactasis	opening

c) Decrease chest wall compliance in p.p
Redistribution of tidal volume to atelactatic dorsal region.

d) Weight of heart may affect ventilation.

3. Improvement in Cardiac output
4. Better clearance of secretions
5. Improved lymphatic damage

CONTRAINDICATION

- Unresponsive cerebral hypertension
- Unstable bone fractures
- Left heart failure
- Hemodynamic instability
- Active intra abdominal pathology

TIMING ARDS > 24 hrs./ 2nd day

FREQUENCY Usually one time per day

DURATION 2 to 20 hrs/day.

OUTCOME

Improvement in oxygenation

No improvement in survival

POSITIONING ACHIEVED BY

Circ Olectric, bed (Late 1970s).

Manual 2 step

Light weight portable support frame (Vollman prone positioner)

NO. OF PERSONS 3-5

POSITION OF ABDOMEN

allowed to protude ; partial/complete restriction

POSITION OF HEAD

Head down/ Head up position.

ADEQUATE SEDATION +/- NMBA

COMPLICATIONS

- pressure sore
- Accident removal of ET; Catheters
- Arrhythmia
- Reversible dependent odema (Face, anterior chest wall)

Gattinoni et al, in a MRCT evaluated the effect of 7 hr / day prone positioning x 10 day

improvement in oxygenation, no survival benefit

NEJM 2001, Vol 345 No 8 568-573

PARTIAL LIQUID VENTILATION

In ARDs there is increased surface tension which can be eliminated by filling the lungs with liquid (PFC).

Perflurocarbon:

Colourless, clear, odourless, inert, high vapour pressure

Insoluble in water or lipids

MC used – perflubron (Perfluoro octy bromide) (Liquivent)

Bromide → radiopaque

ANIMAL EXPERIENCE

- Improved
  - Compliance
  - Gas exchange (dose dependent)
  - lung function
  - Survival
- Anti-inflam. properties
- Decrease risk of nosocomial pneumonia.
- Reduces pulm. vascular resistance.
- Little effect on central hemodynamics.

Mechanism of action

i) Reduces surface tension

ii) Alveolar recruitment – liquid PEEP. Selective distribution to dependent regions.

iii) Increases surfactant phospholipid synthesis and secretion.

iv) Anti Inflam. Properties

A. Indirect

Mitigation of VILI

B. Direct

a) decrease endotoxin stimulated release of TNF; IL-1; IL-8.

b) decrease production of reactive oxygen species.

c) Inhibit neutrophil activation and chemostaxis.

d) Lavage of cellular debris.

Technique of PFC Ventilation :

1. Total liquid ventilation
2. Partial liquid ventilation

	TLV	PLV
1. Ventilator	Liquid	Conventional
2. Tidal volume delivered of	Oxygenated PFC	Gas
3. Lungs are filled	Completely by PFC	Filled till FRC by PFC
4. Feasibility	Expt.	Yes
5. Disadvantage		Loss of gas by evap., cost.

Recommended dose of PFC

-20 ml/kg

Beyond this dose – decrease co.

More clinical trials are req. to demonst. efficacy.

Additive effect of PLV has been shown in combination with:

- NO
- HFOV
- Surfactant
- prone ventilation

2 published adult trials of PLV in ARDS have confirmed its safety but not efficacy.

Hirschl et al JAMA 1996, 275; 383-389

Gauger et al, CCM 1996, 24; 16-24

TRACHEAL GAS INSUFFLATION (TGI)

In ARDS/ALI

1. Increase physiological dead space
2. OLS / permissive hypercapnia

DURING CONVENTIONAL VENTILATION :

Bronchi and trachea are filled with alveolar gas at end exhalation which is forced back into the alveoli during next inspiration.

IN TGI

Stream of fresh air (4 to 8 L/min) insufflated thr. – small cath. or through small channel in wall of ET into lower trachea flushing Co_2 laden gas.

COMPLIC.

1) Dissecation of secretions
2) Airway mucosal injury
3) Nidus for accumulation of secretions
4) Auto – PEEP

HIGH FREQUENCY VENTILATION

Utilizes small volume (<V_D) and high RR (100 b/min)

- Avoids over distention (Vili).
- Alveolar recruitment.
- Enhances gas mixing, improves V/Q.

APPLIC.

1. Neonatal RDS.
2. ARDS.
3. BPF.

COMPLIC.

1. Necrotizing trachebronchitis.
2. Shear at interface of lung.
3. Air trapping.

Two controlled studies (113 and 309) no benefit.

Carlon et al, 1983, Chest 84; 551-559

Hurst et al, 1990, Ann Surg 211; 486-91

Comparison of HFV Vs Conv. Ventil.

	JET	Oscillator	Conventional
Freq avail	upto 600 b/min	300-3000 b/min	2-60 b/min
Tidal volume delivered	<or> V_D	< V_D	>> V_D
Expiration	Passive	Active	Passive
Potentiation of intrinsic PEEP	3+	2+	1+
VT x f product for effective V_A	>> Conv	>> Conv	
P_{PK}	< Conv	< Conv	
P mean	<or> conv	<or> conv	

EXTRACORPOREAL MEMBRANE OXYGENATION

Adaptation of conventional cardiopulmonary bypass technique.

Oxygenate blood and remove CO_2 extracorporally.

TYPES

1. High-flow venoarterial bypass system.
2. Low-flow venovenous bypass system.

Criteria for treatment with extracorporeal gas exchange

Fast entry criteria

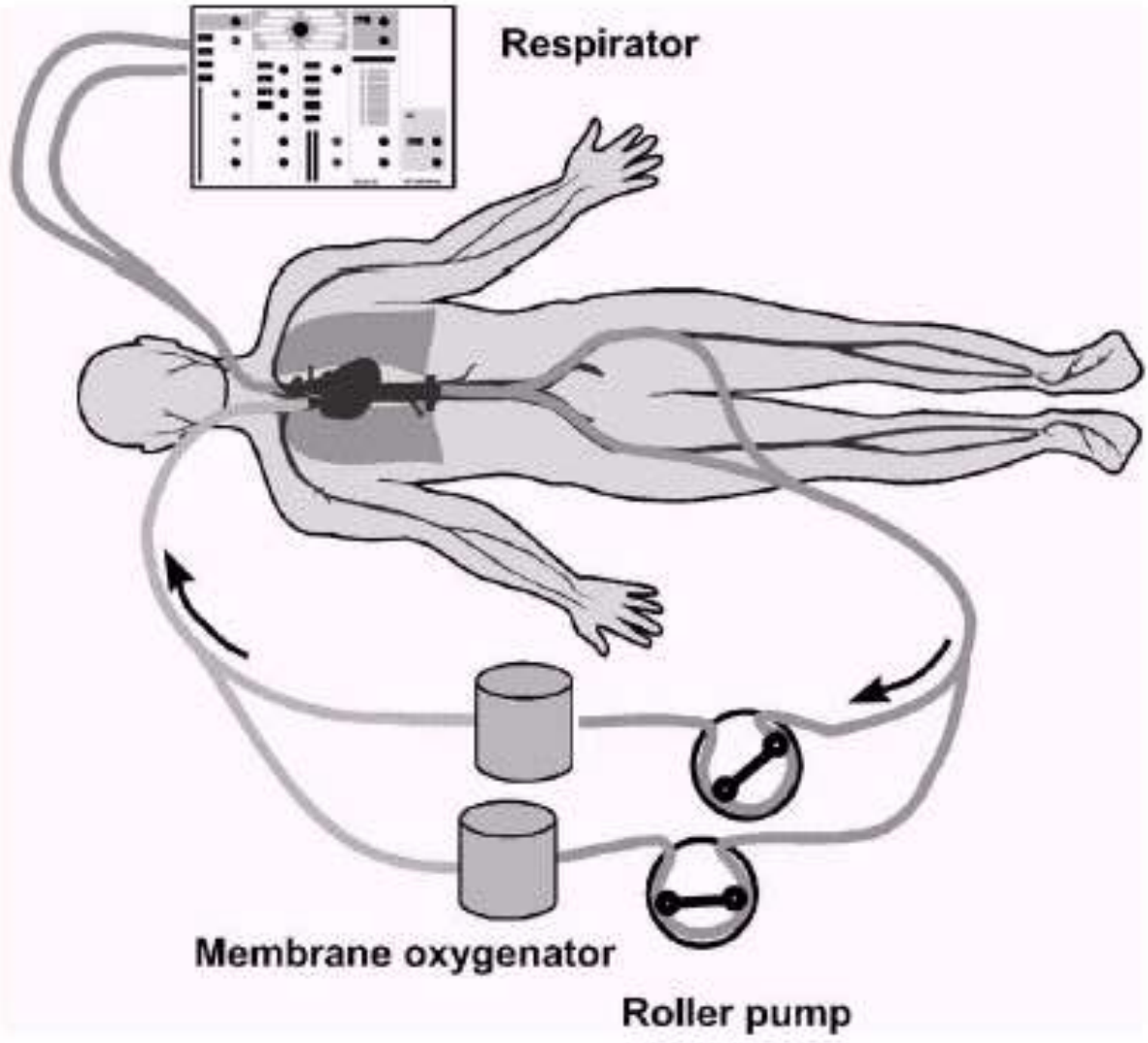
PaO_2 <50 mmHg for >2 h at FiO_2 1.0; PEEP $\geq$ 5 cmH_2O

Slow entry criteria

PaO_2 <50 mmHg for >12 h at FiO_2 0.6; PEEP $\geq$ 5 cmH_2O

maximal medical therapy >48 h

Q_s/Q_t > 30%; CTstat <30 ml/cmH_2O



Schematic drawing of a low-flow venovenous ECMO circuit.

Complication

Mechanical	**Patient related Problem**
1. Oxygenator failure	Bleeding
2. Circuit disruption	Neurological complications
3. Pump or heat exchanger mal functioning.	Additional organ failure
4. Cannula placement/removal	Barotrauma, infection, metabolic

Year	**Survival**
1966 – 1975	10-15%
1980 onward	40-50%

Critical care 2000, 4; 156-168

HEMODYNAMIC MANAGEMENT

Controversial

Restriction of Fluid

Benefit

Obs. Studies Show

↓pulm. edema formation

↑ compliance, lungs fn.

Improved survival

Negative fluid balance is associated with improved survival

Humphrey et al., 1990 Chest 97 ; 1176-80.

Net positive balance <1 lt. in first 36 hrs. a/w improved survival decrease length of ventilation, ICU stay and hospitalization.

Shorter duration of mech. venti., stay in ICU in pat. managed by fluid restriction directed by EVLV c/w PAOP. No mortality benefit.

Mitchell JP, Am Rev. Respr. Dis. 1992; 145; 990-998.

Detrimental

Ineffective Circulatory Volume (Sepsis). Reduced co & ts perfusion.

Goal

- Correct Volume deficit

  Guidelines for management of tissue hypoxia International consensus conference

  (AJRCCM- 1996)

1. **Promote oxygen delivery**

   Adequate volume CVP – 8-12 mmHg

   PAOP-14-16 mmHg (Optimal co; less risk of Edema)

- Crystalloids vs Colloids
- Transfuse < 10 gm/dl

2. **Reduce oxygen demand :**

   a) Sedation : Analgesia, NMBA

   b) Treat Hyperpyrexia

   c) Early institution of mech. vent. (shock).

No role of supraphysiol. oxygen delivery

Vasopressors

- Following fluid resuscitation
- Norepinephrine vs Dopamine
- GOAL to achieve MAP 55 to 65 mmHg

Inotropes

Co. is low

PULMONARY VASCULAR CHANGES IN ARDS/ALI

1. Reduced pulmonary vasoconstriction in hypoxic shunt areas, along with vasoconstriction in well ventilated areas.
2. PAH (Pulm. Vasoconst. ; Thromboembolism; Interstitial edema)
   - PAH aggravates edema by increasing inflow pressure.
   - So role of pulm. vasodilators

Selective Pulmonary Vasodilators :

1. Inhaled Nitric oxide (iNo)
2. iv almitrine with/without iNo.
3. Aerosolized prostacyclins.
4. Inhibition of cyclic nucleotide phosphodiesterase.
5. Inhalation of Endothelin receptor antagonists.

1. **Inhaled Nitric Oxide**

How it is beneficial in ARDs

1. Improves Oxygenation
   - Selective vasodilatation of vessel a/w better ventilation → (decrease shunt)
   - Improves v/q mismatch.
2. Reduction in pulmonary artery pressure
   - Improves oxygen
   - direct smooth muscle relaxation
   - improved RV Fn.
   - reduced capillary leak.
3. Inhibit platelet aggregation and neutrophil adhesion.

Selectivity of iNO

Rapid inactivation on contact with hemoglobin.

- 60 % of pat respond to iNo by increase in PO_2 >20%.

- **DOSAGE**

Effect	Dose
Increase PaO_2	1-2 ppm to <10 ppm
decrease PAP	10-40 ppm

Time of Response

- <10 min to several hours.
- Response to iNo is not static phenomenon.

Intra-individual variation in response :

- lung recruitment
- Coexistent pathology
- resolution of inflammation

Mortality Benefits – None

S/E

Minimal

1. Rebound pulm. hypertension & hypoxemia
2. Methemoglobinemia
3. Toxic NO_2 ; Nitrous & Nitric Acid

   Prevent by decrease – contact time & conc. of gas.

Table 1 Randomised controlled trials of inhaled nitric oxide (NO) in patients with ARDS

Author	No of patients	Diagnosis	Blinded	Inhaled NO dose (ppm)	Duration	Outcome
Lundin *et al* (1999)[20]	260	ALI (American-European Consensus Conference) and 18-96 hours ventilation with Pa_{O_2}/Fi_{O_2} <22 kPa, PEEP at least 5 cm H_2O, mean airway pressure >10 cm H_2O and I:E 1:2–2:1	No	2–40	30 days	180 randomised responded to NO. The frequency of reversal of ALI did not differ from controls. Development of severe respiratory failure less (2.2% *v* 10.3%) in NO treated group. Mortality not altered (44% *v* 40% control).
Dellinger *et al* (1998)[11]	177	ARDS (American-European Consensus Conference) within 72 hours of onset and PEEP at least 8 cm H_2O and Fi_{O_2} >0.5	Yes	1.25–80	28 days	Pa_{O_2} increased >20% in first 4 hours in 60% of patients treated with NO and 24% of controls. Fi_{O_2} and intensity of ventilation could be reduced in first 4 days. No difference in mortality (30% *v* 32–38% in NO treated groups).
Michael *et al* (1998)[13]	40	ARDS (American-European Consensus Conference) and Fi_{O_2} at least 0.8 for 12 hours or 0.65 for 24 hours	No	5–20	3 days	NO improved Pa_{O_2}/Fi_{O_2} by at least 20% and allowed a decrease in Fi_{O_2} of at least 0.15 only in the first 24 hours in more treated patients than controls.
Troncy (1998)[14]	30	Murray score at least 2.5	No	0.5–40	30 days	NO improved oxygenation only in the first 24 hours in more treated patients than controls. Mortality (60% *v* 67% in control) not altered.

Almitrine

- iv : low dose
- Potentates hypoxic vasoconstriction
- Decrease shunt, improved oxygenation

Has additive effect with

iNo

iNo + prone position

3. **Aerosolized Prostacyclin**

- iv prostacyclin decrease pulm. a. pressure (non selective vasodilatation) can increase shunt; worsen oxygenation.
- Inhaled prostacyclin selectively vasodilates the well perfused areas
- Selectivity in dose of 17-50 ng/kg/min.

PGI_2- Not metabolized in lung so selectively lost at higher doses.

PGE_1- 70-80% is metabolized in lung.

4. **Inhibition of cyclic nucleotide phosphodiesterases**

a) No $\rightarrow$ increase CGMP $\rightarrow$ Protein G-Kinase
Calcium gated potassium
Channels
$\downarrow$
Vasodilatation

PDE prevent degradation of CGMP (PDE-5)

PDE –5 Inhibitors

Dipyridamole ; Sildenafil

Ziegler et al. 1998	11 paed PAH	Augmentation of iNo-induced vasodilate by dipyridamol in 50% pt.

Sildenafil

- Oral or iv
- Animal Exp. – decrease P_{PA}

Inhaled $PGI_2 \rightarrow$ CAMP

PDE-2, PDE-3 : PDE-4 – Selectively degrade CAMP.

Inhalation of Endothelin receptor antagonist

In ARDS – increased Endothelin levels

ENDOTHELIN
- $ET_A \rightarrow$ Vasoconst.
- $ET_B \rightarrow$ release No; PGI_2

Non Selective ET antagonist Bosentan (oral)

Selective ETA_2 antagonist LU-B135252 (Neb)

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SURFACTANT REPLACEMENT THERAPY

In ARDs there is deficiency and fn abn. of surfactant

1. Decrease production (injury to type-2 pneumocytes)
2. Abn. composition (decrease phosphatidyl choline, phosphotidylglycerol, Sp.A & Sp. B)
3. Inhibitors of surfactant fn (TNF- α, reactive oxygen sp. Peroxynitrite, neutrophil elastases)
4. Conversion of large to small surfactant aggregates
5. Alteration/Destruction caused by substances in alveolar space (plasma, fibrinogen, fibrin, alb; Hb)

Impaired surfactant fn $\rightarrow$ 1) Atelactasis / collapse

2) Increase edema formation

In experimental ALI models surfactant replacement.

- Improved lungs fn., compliance, oxygenation.

Surfactant of possible therapeutic use :

	Class	Origin	Example
1.	Natural	Amniotic	Human amniotic fluid surfactant
2.	Modified Natural	- Bovine	Infasurf, alveofact
			BLESS, Survanta
		- Procine	Curosurf
3.	Synthetic		Exosurf, ALEC, KL_4 Surfactant, Venticute

DOSE

Sufficient dose should reach alveolar environment

TIMING

- As early as possible [<48 hr]
- Little benefit at 3 to 5 days [Fibrosis already set]

Surfactant Delivery Techniques

Instillation	Lavage	Aerosolization
• Rapid • Can deliver large volume • Homogenous distribution • Efficacious in clinical trials	• May remove toxic subst. • Can deliver large vol. • Homogenous distrib. • Lab studies suggest efficacy	Continuous smaller vol. Non uniform distribution. Lab. Studies show efficacy
• Techn. Not standardized • Short term impairment in ventilation	• Vol. recover can be poor • Short term impairment in ventil.	Slow, no optimal device, Filters may plug.

GLUCOCORTICOIDS IN ARDS

Two meta analysis of short course (≤ 48hr) of high dose methyl pred. (30mg/kg/d) in early sepsis and ARDS found no evidence of beneficial effects.

- LEFERING et al CCM 1995, CRONIN l et al., CCM 1995

In a Recent Randomized control trial prolonged administration of methyl pred. in patients with unresolving ARDS was a/w improved LIS, MODS, mortality

JAMA 1998 Vol. 280 ; 159 –165.

Randomized double blind, placebo controlled trial

24 pat. with severe ARDS who failed to improve LIS by 7th day of mech. ventil.

16 received methyl pred. while 8 rec. placebo 4 pat. whose LIS failed to improve by at least 1 point after 10 days of treatment were blindly crossed over to alternate treatment.

SIGNIFICANT IMPROVEMENT IN :

- LIS (1.7 v 3.0)
- Pao_2/Fio_2 (262 v 148)
- ↓ MODS score (.7 v 1.8)
- Successful Extubation (7 v 0)
- ↓ mortality (0 v 62 %)
- No signif. differences in nosocomial episode

PROTOCOL

Day	Dose (Methy. Pred.) (mg/kg/d)
1-14	2.0
15-21	1.0
22-28	0.5
29-30	0.25
31-32	0.125

HOW STEROIDS ARE BENEFICIAL :

i. Inhibit transcriptional activation of various cytokines.

ii. Inhibit synthesis of phospholipase A_2 : cycloxygenase.

iii. Reduced prod. of prostanoids, PAF, No.

iv. ↓ fibrinogenesis

LISOPHYLLINE AND PENTOXIFYLINE

PDE-I

Inhibit neutrophil chemostaxis and activation.

Lisophylline inhibit release of FF from cell memb. under oxidative stress

↓ TNF : IL-1 ; IL-6

NIH ARDS trial no benefit.

CYCLOOXYGENASE INHIBITORS

TxA_2 and Prostaglandin produced from AA by Cyclooxygenase pathway.

Cause

1) Neutrophil chemostaxis and adhesion
2) Broncho constriction
3) ↑ vascular permeability
4) platelet aggregation

Animal studies shown that C.I

- Attenuate lung injury
- Improve pulm. hypertension and hypoxia

Bernard et al. 1997 RDB PCT iv Ibuprofen	455 sepsis	No reduction in mort.,duration of shock; ARDS
Arons et al. 1999	Subgroup analysis of above study	In hypothermic pt Ibuprofen - trend towards ↑ in no. of days free of MODS. Sig. ↓ in mort.

KETOCONAZOLE

TxA_2

1) Pulmonary vasoconstriction
2) Platelet and neutrophil aggregation

Blockade of Tx synthesis or receptor antagonism ameliorates experimental lung injury

Ketoconazole

1) Specific inhibitor of thromboxane synthetase
2) Inhibits 5 – Lipoxygenase [LTB_4 & procoag activity]

Summary of trials of Ketoconazole in ALI/ARDS

Study, yr	No. of Pat.	Outcome
Slotmann, 1988	71 high risk surgical	• Reduced Incidence of ARDS, ICU stay, cost • No improve in mortality
Yu & Tomasa, 1993	54 sepsis	• Reduced incidence of ARDS • Significant lower mortality
NIH ARDS Network, 1997 Trial	234 ALI/ARDS	No – Mortality benefit No effect on lung function, duration of Ventilat.

ANTIOXIDANTS

Reactive oxygen metabolites derived from neutrophils, macrophages and endothelial cells

OXIDANTS INCLUDE

- Super oxide ion (0_2^-), hydrogen peroxide (H_2O_2)
- hypochlorous acid (Hocl), hydroxyl radical ($OH^{\cdot\cdot}$)

Interact with proteins, lipid and DNA

ENDOGENOUS ANTIOXIDANTS

- Superoxide dismutase, Glutathione, Catalase
- Vit E & Vit C
- Sulfhydryls

IN EXPERIMENT (ANIMALS)

A : ENZYMES

SOD – Variable response

CATALASE – some benefit

REPLENISH GLUTATHIONE

1) Glutathione itself
2) Glutathione ethyl esters
3) Cysteine derivatives
   a) NAC
   b) Procysteine

SUMMARY OF TRIALS OF NAC IN ALI/ARDS

Study, yr	No. of Patients	Therapy	Outcome
Jepsen, 1992	66	Placebo, NAC	No effect – Pao_2/Fio_2 time to improve LIS. Improve – compl.*NS. Mortality – No diff.
Suter 1994	61	Placebo, NAC	Improve – Pao_2/Fio_2; Lis; need for M.V. Mortality – No diff.
Bernard 1997	48	Placebo, NAC OTZ	Improve – ALI free days & cardiac index ↓ new organ failure. Mortality – No diff.
Domenighetti, 1997	42	Placebo, NAC	Improved – LIS No effect – Pao_2/Fio_2, mortality.

ANTICOAGULANT THERAPY IN ALI/ARDS

- In ARDS – Fibrin deposition intra-alveolar and interstitial.
- Local procoagulant activity and reduced fibrinolysis.

↑ <u>Procoagulant</u>

↑ TF (VII_a)

↓ <u>Fibrinolysis</u>

Fibrinolytic inhibitors

↑ PAI–1 ; PAI-2, $\alpha 2$ antiplasmin

↓ urokinase and tPA

↑ **Fibrin**

1) Inhibit surfactant → atelactasis
2) + Fibrinonectin → Matrix on which fibroblast aggregate
3) $+^N$ Fibroblast proliferation
4) Potent chemotactic (Neutrophil recruitment)
5) Lung vasculature → PAH

TF PATHWAY INHIBITORS AND FACTOR Vll ai

In Expt studies

- ↓ Cytokine [IL-6, IL-10, IL-13]
- ↓ Fibrin clot
- ↓ Sepsis related organ damage
- ↓ LIS
- Improved survival

20 % RR reduction in 28 days all cause mortality and improvement in organ dysfn. in patient with severe sepsis.

ABRAHAM E, ; CCM 2001 29 2081

HEPARIN

Effectiveness in blocking fibrin deposition debatable.

In Expt. animals large doses of UFH reduced fibrin deposition; prevent ↑ EVLV; improved Pao_2/Fio_2

Human data lacking.

ANTITHROMBIN

Broad spectrum serine protease Inhibitor.

Action of Antithrombin

1. Inhibits

   a) Thrombin

   b) Inactivates T_F – VIIa complex

(2) Stimulate prostacylin release

(- plat. aggreg. neut. activation, cytokine rel.)

In animal studies

↓vascular injury; leukocyte accumulation ; vascular permeability.

Kybersept trial, 2314 pat. with severe sepsis

No reduction in 28 days all cause mortality but excess rate of bleeding events in pat. receiving concomitant heparin prophylaxis.

Expl.

i) AT levels below expected levels.

ii) Heparin prophylaxis must have influenced efficacy.

Improvement in 90 days survival rate in pat. receiving

antithrombin without heparin.

Warren BL et al ; Jama 2001; 286; 1869-1878

PROTEIN- C

i) Inactivates Va & VIIa – limit thrombin generation.

ii) Inhibit PAI-1 activity - ↑ fibrinolysis.

iii) Anti-inflam. - ↓ cytokines, inhibit apoptosis.

In the PROWESS study APC administ. Improved survival.

28 days absolute risk reduction in mortality – 6.1%. 19.4% reduction in relative risk.

↑ Risk of bleeding (3.5% vs 2.0%)

Faster resolution of respiratory dysfun.

↑ ventilatory free days (14.3 vs 13.2 days)

Bernad GR ; NEJM 2001; 344; 699-709

ENHANCED RESOLUTION OF ALVEOLAR EDEMA

Alveolar clearance of edema depends on active sodium transport across the alveolar epithelium

β2 adrenergic stimulation :

1. Salmetrol
2. Dopamine
3. Dobutamine

ENHANCED REPAIR :

Mitogen for type-II pneumatocyte :

1. Hepatocyte growth factor
2. Keratinocyte growth factor.