Acute lung injury in sepsis: new trends in pathophysiology and therapy

Mikhail Kirov
Northern State Medical University, Arkhangelsk, Russia
Sepsis-induced ALI: epidemiology


ALIVE study: 78 ICUs of 10 European countries

- Sepsis is the most common cause of ALI, accounting for >50% of cases
- Pneumonia - 40% for ALI and 46% for ARDS
- Non-pulmonary sepsis (abdominal, urological, vascular, etc.) – 11% for ALI and 25% for ARDS
Incidence of ALI/ARDS in severe sepsis

Rubenfeld GD et al. NEJM 2005;353:1685-1693

- ALI develops in 62% of cases (1.6% of ICU admissions)
- ARDS develops in 25-55% of cases

![Bar chart showing the number of patients with organ dysfunction](chart.png)

n=62
Sepsis-induced ALI: hospital mortality


Sepsis-induced ALI results in a higher mortality rate (50% vs. 33% in non-sepsis ALI) due to increased severity of illness and organ dysfunction

- Pulmonary sepsis-induced ALI – 50.7%
- Non-pulmonary sepsis-induced ALI – 50%
- Pneumonia + septic shock – 72.2%
Pathophysiology of sepsis and ALI:
PIRO concept

**Predisposition:** genetic factors, immune dysbalance, concomitant diseases, age, gender, social factors

**Infection**

**Response of inflammation**

**Organ dysfunction**

Therapy
Sepsis-induced ALI: modulation of transcriptional mechanisms


- LBP
- MD2
- LPS
- Peptidoglycan
- Fungal constituents
- Lipopeptides
- Prokaryotic DNA
- Viral RNA
- Flagellin
- TLR 3
- TLR 5
- TLR 9
- TLR 4
- NFκB
- Gene transcription

Macrophage
Mechanisms of ALI and inflammation

- Modulation of transcriptional mechanisms: activation of NF-κB
- Release of inflammatory mediators (cytokines, NO, ROS, chemokines, arachidonic acid metabolites, proteases, endothelins, etc.)
- Neutrophil accumulation in the lungs

Martin GS et al. *Intensive Care Med* 2001;27:S63-S79
Lang JD et al. *Chest* 2002;122:S314-S320
Mechanisms of ALI and inflammation

Martin GS et al. *Intensive Care Med* 2001;27:S63-S79
Lang JD et al. *Chest* 2002;122:S314-S320

- Endothelial and epithelial injury
- Mild or moderate pulmonary hypertension
- Increased permeability: accumulation of extravascular lung water and exudation of plasma proteins into the alveolar space
- Surfactant inactivation and atelectases
Mechanisms of ALI and inflammation

Martin GS et al. *Intensive Care Med* 2001;27:S63-S79
Lang JD et al. *Chest* 2002;122:S314-S320

- Hypoxemia: V/Q abnormalities, intrapulmonary shunt, and blunted HPV
- Increased work of breathing: dead space ventilation, loss of compliance, and increased airflow resistance
- Impairment in lung mechanics: “baby” lung and “stiff” lung
Validation of extravascular lung water (EVLW) vs. gravimetry in ALI

Kirov MY et al. *Crit Care* 2004;8:R451-R458

After LPS in sheep

\[ \text{EVLW}_{\text{TDD}} \text{ (ml/kg)} \]

\[ y = 1.14x + 2.45 \]

\( n = 18 \)

\( r^2 = 0.80 \)

\[ \text{EVLW}_{\text{ST}} = 1.30 \times \text{EVLW}_{\text{G}} + 2.32 \]

\( n = 18, r = 0.85, p < 0.0001 \)
EVLWI, CVP, and lung injury score


EVLWI and LIS: $r^2=0.18$, EVLWI and radiograph score: $r^2=0.28$, $p<0.0001$
More than 50% of the patients with severe sepsis but without ARDS have increased EVLW, possibly representing sub-clinical lung injury.
EVLW and prognosis in sepsis and ALI

Sakka SG et al. *Chest* 2002;122:2080-2086
Kuzkov VV et al. *Crit Care Med* 2006;34:1647-1653

EVLW is increased in 95% patients with pulmonary sepsis-induced ALI and in 50% with non-pulmonary sepsis-induced ALI.
EVLW and predicted body weight


Predicted body weight improves the determination of pulmonary edema
Sepsis-induced ALI: inflammatory markers in serum and BAL


- Endotoxin
- Flagellin
- Gene expression
- NF-κB
- BAL proteins, neutrophiles, and macrophages, measures of cellular apoptosis
- Cytokines (TNF-α, IL-8)
- Selectins
- Surfactants
- Procollagen peptide
Sepsis-induced ALI: inflammatory markers in serum and BAL


- Procalcitonin
- Elastase and other proteases
- Oxidants/antioxidants - NO, nitrotyrosine, catalase, hypoxantine, lipid products, superoxide dismutase, ceruloplasmine, transferrin, glutathione, ascorbate, ubiquinol, α-tocopherol, β-carotene, selenium
- Protein kinase C
- von Willebrand factor antigen
- Protein C
- Endothelin-1
Sepsis-induced pulmonary edema and endothelin-1 (ET-1)

Kuzkov VV et al. *Crit Care Med* 2006;34:1647-1653
Ventilator-induced lung injury

Mechanical Ventilation

Biochemical Injury (Biotrauma)
- Epithelium/interstitium
  - cytokines, complement, PGs, LTs, ROS, proteases
  - bacteria
  - neutrophils
  - mφ

Biophysical Injury
- barotrauma - high pressure
- volutrauma - high volume
- atelectotrauma - low volume
- oxygen toxicity - high FiO₂

↑ alveolar-capillary permeability
↓ cardiac output
↓ organ perfusion

Distal Organ Dysfunction
Therapy of sepsis-induced ALI

Martin GS et al. Intensive Care Med 2001;27:S63-S79

- Treatment of sepsis: general approach
- Fluid and hemodynamic management
- Respiratory support
- Pharmacological agents
Immediate resuscitation

- Oxygen therapy/ventilatory support
- Hemodynamic support
- Identify/treat infection
- Metabolic control
- Supportive care

Take microbiology specimens

- Immediate broad-spectrum antibiotics
- Assess for surgery/drainage
- Identify pathogen
- Change treatment as necessary

- Prevention of pressure sores
- DVT prophylaxis
- Nutrition
- Stress ulcer prophylaxis
- Renal replacement therapy
- Good practice basics
Rationale for the hemodynamic monitoring in sepsis-induced ALI

Severe sepsis

Septic shock

ALI/ARDS

CVP
Pulmonary arterial catheter
Extravascular lung water

Monitoring
Fluids
Diuretics

Inotrope/vasopressor support
Renal replacement therapy
Mechanical ventilation
- Swan-Ganz catheter – no improvement in clinical outcome
- Necessity of goal-directed therapy
Sepsis-induced ALI: fluid and hemodynamic management

Rivers E et al. *NEJM* 2001;345:1368-1377

Goal-directed therapy in severe sepsis: reduction in mortality at Day 28 from 49.2% to 33.3%

- CVP=8-12 mm Hg, achieved by 500 mL bolus of cristalloids every 30 min
- MAP=65-90 mm Hg. If <65 mm Hg, give vasopressors; if >90 mm Hg, give vasodilators
- When ScvO₂<70%, transfuse RBC to reach Ht=30% or, if Ht>30%, administer dobutamine
**Sepsis-induced ALI: fluid and hemodynamics**

*Crit Care Med* 2008;36:296-327

- Fluid restrictive strategy in ARDS (zero or negative fluid balance): maintain preload at the lowest level that is consistent with adequate systemic perfusion

- Sepsis-induced ALI/shock – combination of adequate initial fluid resuscitation (first 6 hrs) followed by conservative late fluid balance (even-to-negative at least 2 days) reduces mortality
Sepsis-induced ALI: fluid and hemodynamic management


- Colloids/cristalloids (?) – Cristalloids result in more edema
- Hypo-oncotic patients (protein<50 g/L):
  - gelatins
  - hydroxyethylstarch
  - albumin
  - furosemide (?)
Hydroxyethylstarch 130 kDa in sepsis-induced ALI: improvement of hemodynamics and attenuation of pulmonary capillary leak

Tian J. Anesth Analg 2004

Pulmonary vascular permeability  Molecular adhesion CD11b
Sepsis-induced ALI: fluid and hemodynamic management

Vincent JL et al. Crit Care 2002;6:S1-S18

- Inotrope/vasopressor support if MAP<65 mm Hg
  - CVP<8 mm Hg: volume
  - CVP=8-12 mm Hg and CI>3.5 L/min/m²: dopamine 5-10 mcg/kg/min; noradrenaline 0.01-3 mcg/kg/min, if ineffective - adrenaline
  - CVP>8 mm Hg, CI<3.5 L/min/m², or SvO₂<70%: add dobutamine 2-20 mcg/kg/min
Clinical value of EVLW


Management based on a protocol using EVLW measurements may hasten the resolution of pulmonary edema and decrease mortality.
• Monitoring of oxygen transport: evaluation of the novel methods of therapy (optimal recruitment etc.)

• Maintenance of DO\textsubscript{2}I within 400-600 ml/min/m\textsuperscript{2} (?)
Sepsis-induced ALI: respiratory support

- Adequate oxygenation: maintain SaO$_2$ > 90% (PaO$_2$ > 60 mm Hg), FiO$_2$ < 0.6
- Mechanical ventilation when
  - PaO$_2$ < 60 mm Hg despite flow O$_2$
  - RR > 35 breaths/min
  - CNS depression
- Prevention of baro- and volutrauma: low tidal volumes (6-8 mL/kg of predicted body weight),
  $P_{plateau}$ < 30 cm H$_2$O, $P_{peak}$ < 35 cm H$_2$O, PEEP
Sepsis-induced ALI: respiratory support


- The study of low tidal volumes in 861 ARDS patients: reduction of mortality by 22%
- Permissive hypercapnia
Sepsis-induced ALI: respiratory support

Martin GS et al. *Intensive Care Med* 2001;27:S63-S79

- Semirecumbent position 30-45°
- Inversed I/E ratio ventilation (?): improves oxygenation but can decrease CO and produce intrinsic PEEP
- Pressure- or volume-controlled ventilation (?)
Sepsis-induced ALI: respiratory support

Hemmila MR et al. *Crit Care Med* 2006;34:S278-S290

- Biphasic Positive Pressure Ventilation (BiPAP), Airway Pressure Release Ventilation (APRV): preserving spontaneous ventilation, decrease in airway pressures, decrease of the duration of mechanical ventilation and sedation

BiPAP: I/E = 1/2
APRV: I/E > 1/2
Sepsis-induced ALI: respiratory support

Martin GS et al. Intensive Care Med 2001;27:S63-S79
Lachmann et al. Euroanesthesia 2003, Refresher Course Lectures
Marini JJ, Gattinoni L. Crit Care Med 2004;32:250-255

Concept of “open lungs“:

- Open the atelectatic areas (increase of Ppeak to 40-60 cm H₂O for 3-5 respiratory cycles, return to Ppeak providing tidal volume 6-8 ml/kg)
- Keep the lungs opened with PEEP level that provides optimal oxygenation and compliance (ALI 8-12, ARDS 12-18 cm H₂O)
After recruitment
MacIntyre N, 2006
PEEP – 2-3 cm above lower inflection point;
alternative – incremental or decremental PEEP
Effect of recruitment

5 cmH$_2$O
PaO$_2$: 34 mmHg
d. 70%

10 cmH$_2$O
PaO$_2$: 49 mmHg
d. 52%

15 cmH$_2$O
PaO$_2$: 121 mm Hg
d. 32%

L. Gatinonni, 2003
Sepsis-induced ALI: respiratory support

- Requirement for FiO$_2$ > 0.6:
  - prone positioning - 57-71% of responders (increase in PaO$_2$ > 10%)

Hemmila MR et al. *Crit Care Med* 2006;34:S278-S290
Prone position: redistribution of fluid

\[ \text{PaO}_2 \text{ 59 mmHg} \]
PEEP 10 SUPINE

\[ \text{PaO}_2 \text{ 93 mmHg} \]
PEEP 10 PRONE
Sepsis-induced ALI: respiratory support

**Requirement for FiO$_2$ > 0.6:**
- inhaled NO attenuates pulmonary hypertension and improves oxygenation; can be a rescue therapy in refractory hypoxemia
Sepsis-induced ALI: nitric oxide donors

Sepsis-induced ALI: respiratory support

Martin GS et al. *Intensive Care Med* 2001;27:S63-S79
Kopp R et al. *Intensive Care Med* 2002;28:244-255

- **High frequency oscillatory ventilation (HFOV):** very small $V_T$ and very high RR

![Diagram showing HFOV and conventional ventilation](image-url)
Sepsis-induced ALI: respiratory support


Recruitment
40x40 + HFOV
– TOOLS Trial:
↑oxygenation

Indications for HFOV in adults:
- FiO₂ > 0.6 and SatO₂ < 88%
  when PEEP > 15 cm H₂O
- Pplateau > 30 cm H₂O or
- Pmean > 24 cm H₂O
  or APRV(BIPAP) > 35 cm H₂O

p = 0.057
Sepsis-induced ALI: respiratory support

Martin GS et al. *Intensive Care Med* 2001;27:S63-S79
Kopp R et al. *Intensive Care Med* 2002;28:244-255
Blanch L, 2007

- Partial liquid ventilation (?): fluorocarbons
- Heliox (?)
- Tracheal gas insufflation (?)
- Independent lung ventilation in unilateral ARDS (?)
- ECMO when $\text{PaO}_2<50$ mm Hg with $\text{FiO}_2=1.0$ and PEEP $>10$ cm H$_2$O
Sepsis-induced ALI: weaning from respiratory support

Fredriksson K et al. Crit Care Med 2007;32[suppl]:S449-S453

- Polyneuromyopathy (desensitization of receptors, mitochondrial dysfunction)
- Early weaning from respirator, importance of spontaneous breathing
- Prediction of weaning success: weaning indexes
  
  \[
  \frac{f}{V_t} < 105 \quad (\text{AuROC} = 0.85)
  \]
  \[
  Cst.rs \times \text{SatO}_2 / \left( \frac{f}{V_t} \right) > 25 \, \text{ml/cm H}_2\text{O breath/min/L} \quad (\text{AuROC} = 0.96)
  \]
Sepsis-induced ALI: control of metabolism

- Normoglycemia
- Early enteral nutrition
- Immunonutrition: glutamin, vit. E,C, ω3 non-saturated fat acids, fibers
- Pulmodiets with lipid content up to 55% for the decrease of CO2 production
Sepsis-induced ALI: pharmacological agents

Meduri GU et al. *JAMA* 1998;280:159-165
Hemmila MR et al. *Crit Care Med* 2006;34:S278-S290

- **Heparins**
- **Corticosteroids**
  
  Methylprednisolone 0.5-2 mg/kg in patients with refractory ARDS and fibroproliferative stage (?)
  
  Hydrocortisone 200-300 mg/day in refractory septic shock

- **Surfactant (?)** - can improve gas exchange, can be used in very early ARDS

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Odds ratio</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1,000</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>1,500</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>2,000</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>2,500</td>
<td>10,000</td>
<td></td>
</tr>
<tr>
<td>3,000</td>
<td>100,000</td>
<td></td>
</tr>
</tbody>
</table>

- Anti-prostaglandin
- TNF-Mab
- Anti-IL-1ra
- PAFra
- Anti-bradykinin
- Anti-prostaglandin
- rhAPC
- TNF-Mab
- sTNFr
- Anti-bradykinin
- Anti-prostaglandin
- Steroid
- TNF-Mab
- sTNFr
- in severe sepsis, APC has been recommended in high risk of death (APACHE II > 25)
- promotes the resolution of respiratory and cardiovascular dysfunctions
- decreases mortality in adults
ALI in sepsis: summary

- In sepsis, ALI continues to be a complex problem with high mortality.
- Fluid and hemodynamic therapy should be titrated using appropriate monitoring and goal-directed approach.
- Lung-protective low-volume ventilation provides distinct survival benefit.
ALI in sepsis: summary

- New trials will provide more insight into the treatment of sepsis-induced ALI
- The success of therapy is the combination of evidence-based and physiological approaches