Prevention of the Acute Respiratory Distress Syndrome

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Anesthesia, Critical Care and Pain Medicine

HUMAN FIRST

Beth Israel Deaconess Medical Center
Acute Respiratory Distress Syndrome

Ware and Mathay, NEJM 2001

Beth Israel Deaconess Medical Center
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL
ARDS Research

• Despite improved understanding of ARDS, the clinical impact has been limited to improvements in supportive treatment
  – Mechanical ventilation, fluid management, sedation, rehabilitation
  – Mechanistic treatments uniformly negative
    • When applied late in the course of illness?

• Surprisingly little research has been done on the prevention of ARDS
Potentially Preventable Complications of Critical Illness

- Stress ulcer bleeding
- Pulmonary embolism
- Ventilator associated pneumonia
- Nosocomial infections

Why not ARDS?
ALI: “Multiple hit” Hypothesis

Risk modifiers that may \^ risk of ALI (2\textsuperscript{nd} hit):
- High tidal volume, transfusion, delayed resuscitation, inappropriate antibiotics, aspiration, high FiO2

Risk modifiers that may \_ risk of ALI:
- PEEP, modulators of oxidative stress, inflammation and coagulation
What can we do?

**Not Modifiable**
- Age
- Restrictive lung disease
- Pneumonia
- Trauma
- Sepsis
- Increasing ASA score
- Initial P/F ratio
- Acidemia

**Modifiable**
- Transfusion
- Positive net fluid balance
- Delayed resuscitation
- Aspiration
- Disynchrony
- Injurious ventilation
ARDS in Olmstead County

Li et al AJRCCM 2011
Beyond Mortality
Future Clinical Research in Acute Lung Injury

Roger G. Spragg¹, Gordon R. Bernard², William Checkley³, J. Randall Curtis⁴, Ognjen Gajic⁵, Gordon Guyatt⁶, Jesse Hall⁷, Elliott Israel⁸, Manu Jain⁹, Dale M. Needham³, Adrienne G. Randolph¹⁰, Gordon D. Rubenfeld¹¹, David Schoenfeld¹², B. Taylor Thompson¹³, Lorraine B. Ware², Duncan Young¹⁴, and Andrea L. Harabin¹⁵

Interventions appropriate for testing in prevention trials should be able to be rapidly administered, inexpensive, and safe. Such interventions may occasionally be identified in hospital quality assurance programs.

Other prevention trials to consider include those designed to decrease the incidence of specific adverse outcomes of ALI, including cognitive, psychological, and neuromuscular complications.
Barriers to Prevention of ARDS

• Need to identify those at high risk for ARDS early during their hospital presentation.

• Under-utilization and practice variation in clinical practices that may influence development and outcome of ARDS.

• Lack of safe and effective pharmacologic therapies to prevent ARDS.
The first USCIIT Group study in 22 hospitals who joined USCIITG-LIPS1.

Researchers in emergency medicine, trauma surgery, anesthesiology and pulmonary medicine.
A minority of Patients at Risk Develop ARDS

5992 Patients with at least one predisposing condition at the time of ED evaluation of hospital admission for elective surgery

5584 Patient enrolled

Excluded:
- 166 ALI on admission
- 124 Hospital transfer
- 44 Readmission
- 28 comfort care
- 46 other (died in the ED, no research authorization – prisoner, incomplete records)

377 ALI/ARDS
- 148 ALI
- 229 ARDS

5213 NO ALI/ARDS
Results

% ALI development according to predisposing conditions

- Smoke inhalation: 7/27
- Shock: 72/403
- Aspiration: 35/212
- Aortic surgery: 21/127
- Lung contusion: 27/190
- Cardiac surgery: 55/541
- Acute abdomen: 27/295
- Traumatic brain injury: 45/495
- Pneumonia: 102/1234
- Multiple fractures: 26/332
- Sepsis: 124/1815
- Thoracic surgery: 7/175
- Spine surgery: 16/486
- Pancreatitis: 9/325

LIPS Score

<table>
<thead>
<tr>
<th>Predisposing conditions</th>
<th>LIPS points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>2</td>
</tr>
<tr>
<td>Aspiration</td>
<td>2</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.5</td>
</tr>
<tr>
<td>High risk surgery*</td>
<td></td>
</tr>
<tr>
<td>Thoracic (noncardiac)</td>
<td>-</td>
</tr>
<tr>
<td>Orthopedic spine</td>
<td>1</td>
</tr>
<tr>
<td>Acute abdomen</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2.5</td>
</tr>
<tr>
<td>Aortic vascular</td>
<td>3.5</td>
</tr>
<tr>
<td>High risk trauma</td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>2</td>
</tr>
<tr>
<td>Smoke inhalation</td>
<td>2</td>
</tr>
<tr>
<td>Near drowning</td>
<td>2</td>
</tr>
<tr>
<td>Lung contusion</td>
<td>1.5</td>
</tr>
<tr>
<td>Multiple fractures</td>
<td>1.5</td>
</tr>
<tr>
<td>Risk modifiers</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>1</td>
</tr>
<tr>
<td>Obesity (BMI&gt;30)</td>
<td>1</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1</td>
</tr>
<tr>
<td>FiO₂ &gt;0.35 (&gt;4L/min)</td>
<td>2</td>
</tr>
<tr>
<td>Tachypnea (RR&gt;30)</td>
<td>1.5</td>
</tr>
<tr>
<td>SpO₂ &lt;95%</td>
<td>1</td>
</tr>
<tr>
<td>Acidosis (pH&lt;7.35)</td>
<td>1.5</td>
</tr>
<tr>
<td>Diabetes mellitus**</td>
<td>-1</td>
</tr>
</tbody>
</table>

AUC=0.80 (95% CI 0.79 to 0.80)
Can We Improve on the LIP Score?

**TABLE 2. THE ASSOCIATION BETWEEN ANGIPOIETOITIN-2 AND PREDICTION OF ACUTE LUNG INJURY IN MULTIVARIATE ANALYSES**

<table>
<thead>
<tr>
<th>Models</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ang-2</td>
<td>2.4</td>
<td>1.3–4.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ang-2 + sepsis Day 1</td>
<td>2.2</td>
<td>1.2–4.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ang-2 + severe sepsis Day 1</td>
<td>2.2</td>
<td>1.2–3.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Ang-2 + ED vasopressors</td>
<td>2.5</td>
<td>1.4–4.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ang-2 + APACHE II</td>
<td>1.9</td>
<td>1.0–3.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Ang-2 + infection-related ALI risk</td>
<td>2.1</td>
<td>1.1–4.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Ang-2 + APACHE II + severe sepsis Day 1</td>
<td>1.8</td>
<td>1.0–3.4</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Can We Improve on the LIP Score?
Barriers to prevention of ARDS

• Need to identify those at high risk for ARDS early during their hospital presentation.
  • → LIPS: Lung Injury Prediction Score
• Under-utilization and practice variation in clinical practices that may influence development and outcome of ARDS.
• Lack of safe and effective pharmacologic therapies to prevent ARDS.
## Checklist for Lung Injury Prevention: CLIP

<table>
<thead>
<tr>
<th>CLIP Element</th>
<th>Clinically Supported Practices</th>
<th>AHA grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate empiric antimicrobial treatment and source control</td>
<td>According to suspected site of infection, health care exposure, and immune suppression</td>
<td>Class I</td>
</tr>
<tr>
<td>Lung protective mechanical ventilation</td>
<td>Tidal volume &lt;6-8 mL/kg predicted body weight and plateau pressure &lt;25 cm H2O; PEEP≥5 cm H2O, minimize FIO2 (target O2sat 88-92%)</td>
<td>Class Iia-Ilb</td>
</tr>
<tr>
<td>Aspiration precautions</td>
<td>Rapid sequence intubation supervised by experienced providers, elevated head of the bed, oral care with chlorhexidine, gastric acid neutralization</td>
<td>Class IIA-Ilb</td>
</tr>
<tr>
<td>Early reassessment of noninvasive ventilation (to prevent delayed intubation)</td>
<td>Early reassessment of the work of breathing 30 minutes into the onset of noninvasive ventilation</td>
<td>Class Ilb</td>
</tr>
<tr>
<td>Fluid management:</td>
<td>- Resuscitation according to institutional protocol and IHI sepsis bundle</td>
<td>Class Ila</td>
</tr>
<tr>
<td>- Early fluid administration in septic shock</td>
<td>- Modified ARDSnet FACCT protocol after early shock (first 12 hours)</td>
<td>Class Ila</td>
</tr>
<tr>
<td>- Limiting fluid overload after resuscitation</td>
<td></td>
<td>Class Ila</td>
</tr>
<tr>
<td>Restrictive transfusion</td>
<td>Hemoglobin target &gt;7 g/dL in the absence of acute bleeding and/or ischemia</td>
<td>Class Ila</td>
</tr>
<tr>
<td>Appropriate handoff of patients at risk</td>
<td>Structured handoff such as SBAR</td>
<td>Class Ila</td>
</tr>
</tbody>
</table>
### Questions to be answered by clinician

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the patient have a suspected infection? *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- If YES, is there a potentially removable or drainable source? (Such as abscess, line, hardware/implant, renal or gallstones, empyema, perforated viscus, acute abdomen, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Is the patient CURRENTLY in shock? *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- If NO, was patient in shock at any time in the last 12 hours?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Does the patient CURRENTLY have acute bleeding? *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Does the patient CURRENTLY have acute ischemia? (acute coronary syndrome, acute stroke, acute bowel ischemia) *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. CURRENT respiratory status *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Is admission/transfer to intensive care unit likely in the next 24 hours? *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Will patient possibly need surgery in the next 24 - 48 hours? *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* indicates a required field
CLIP Study

Tidal volume by Vent Day after Intubation

% Patients on Acid Blocker

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL
Barriers to Prevention of ARDS

• Need to identify those at high risk for ARDS early during their hospital presentation.
  • → LIPS: Lung Injury Prediction Score

• Under-utilization and practice variation in clinical practices that may influence development of ARDS or outcomes of patients at risk for ARDS.
  • → CLIP: Checklist for Lung Injury Prevention

• Lack of safe and effective pharmacologic therapies to prevent ARDS.
Pathophysiology of ARDS

- **Chemical**
  - Acid aspiration
  - Indirect: SIRS, reperfusion, IL2, TRALI

- **Biological**
  - Direct: SARS, Influenza, RSV, PCP
  - Indirect: SIRS, reperfusion, IL2, TRALI

- **Mechanical**
  - Capillary stress failure

- **Inflammatory**
  - Coagulation
  - Oxidative stress

- **Consequences**
  - Permeability pulmonary edema and its consequences

- **QALY**
Platelets and Platelet-Neutrophil Interactions in ARDS

Katz et al. Chest 2011;139:658-668
Platelet Depletion Reduces ARDS

Figure 9
Platelet depletion protects mice from 2-hit THAI. (A) Peripheral blood platelet counts in HALH/wc WT mice at baseline and after receiving either control or antiplatelet (α-PI) serum. **P < 0.05 vs. baseline. (B) Extravascular lung water and EVPEs in mice challenged with i.t. LPS (0.1 mg/kg) and MHC I mAb (4.5 mg/kg) and pretreated with either control or antiplatelet serum. **P < 0.05 vs. control. (C) Extravascular lung water and EVPEs in mice challenged with i.p. LPS (0.1 mg/kg) and MHC I mAb (1.0 mg/kg) and pretreated with either control or antiplatelet serum. **P < 0.05 vs. control. (D) Survival curves from mice in C. **P < 0.05 vs. antiplatelet serum.
Protective Effects of Anti-Platelet Agents in Patients at Risk for ALI

- ARDS in anti-platelet group: 12.7% vs. 28.1%
- Unadjusted OR: 0.37 (0.16 to 0.84; p = 0.02)

Table 3. Cox-proportional hazard analysis for event-free survival through 28 days from hospital admission.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-platelet therapy</td>
<td>0.34</td>
<td>0.13 – 0.88</td>
<td>0.03</td>
</tr>
<tr>
<td>Propensity for anti-platelet therapy*</td>
<td>1.08</td>
<td>0.93 – 1.26</td>
<td>0.32</td>
</tr>
<tr>
<td>APACHE III at ICU hour 1</td>
<td>1.02</td>
<td>1.00 – 1.04</td>
<td>0.08</td>
</tr>
<tr>
<td>Lung Injury Prediction Score</td>
<td>1.67</td>
<td>1.33 – 2.12</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Erlich et al. Chest 2010
Lung Injury Prevention with Aspirin (LIPS-A): a protocol for a multicentre randomised clinical trial in medical patients at high risk of acute lung injury

Daryl Jon Kor,\textsuperscript{1} Daniel S Talmor,\textsuperscript{2} Valerie M Banner-Goodspeed,\textsuperscript{3} Rickey E Carter,\textsuperscript{4} Richard Hinds,\textsuperscript{5} Pauline K Park,\textsuperscript{6} Ognjen Gajic,\textsuperscript{7} Michelle N Gong,\textsuperscript{8} On behalf of the US Critical Illness and Injury Trials Group: Lung Injury Prevention with Aspirin Study Group (USCIITG: LIPS-A)
Emergency Room Visit
Planned Hospital Admission
LIPS score ≥ 4
< 12 hours

Aspirin 325 mg and then 81 mg PO/NG once daily vs. Placebo

Randomization
Baseline Plasma
7 days
Day 3 Plasma

Plasma Evaluation
- Thromboxane B$_2$
- 15-epi lipoxins
- IL-6, PAI-1, RAGE

Assessment for adverse events
- Bleeding risk
- Renal dysfunction
- Allergic reaction

Outcome Assessment
- ∆ PaO2/FiO2
- ∆ SaO2/FiO2
- ∆ LIS

Clinical Outcomes
- ALI/ARDS
- ∆ Mortality
- Length of Stay
- Duration of ventilation

Inclusion Criteria
- Emergency Room Visit
- Planned Hospital Admission
- LIPS score ≥ 4
- < 12 hours

Exclusion Criteria
- Age < 18 years
- Current anti-platelets
- Bleeding Diathesis
- Planned surgery
- Allergy to aspirin
- No consent

Baseline Plasma
Day 3 Plasma

Physiologic Outcomes
Screening Burden

Percentage of screened patients who were enrolled

- Site 14: 14.0%
- Site 07: 12.0%
- Site 02: 10.0%
- Site 16: 9.0%
- Site 13: 8.0%
- Site 08: 8.0%
- Site 15: 6.0%
- Site 12: 6.0%
- Site 01: 4.0%
- Site 04: 4.0%
- Site 10: 4.0%
- Site 06: 2.0%
- Site 05: 2.0%
- Site 11: 2.0%
- Site 09: 2.0%
Main Exclusions:
All Screened Pt with LIPS >=4
Characteristics of Screened v. Enrolled: Predisposing Conditions

- Non-cardio shock
- Aspiration
- Sepsis
- PNA
- TBI
- Lung contusions
- Mult fx
- Smoke inh
- Near-drowning

Enrolled: [Bar Chart]
Not enrolled: [Bar Chart]
Barriers to prevention of ARDS

• Need to identify those at high risk for ARDS early during their hospital presentation.
  • → LIPS: Lung Injury Prediction Score

• Under-utilization and practice variation in clinical practices that may influence development of ARDS or outcomes of patients at risk for ARDS.
  • → CLIP: Checklist for Lung Injury Prevention

• Lack of safe and effective pharmacologic therapies to prevent ARDS.
  • → LIPS-A: Lung Injury Prevention Study - Aspirin
Is Preventing ARDS Important?

- ARDS is a difficult outcome to adjudicate.
- ARDS is not a patient centered outcome.
- ARDS *per se* may not be associated with increased mortality.

What is the appropriate outcome?

Rubenfeld. AJRCCM
PETAL Network

• Goals
  – Conduct 3-5 Phase III clinical treatment trials which PREVENT or provide EARLY treatment for patients at risk for, or with, ARDS.
  – Establish and utilize a central IRB.
  – Collect and bank high quality biospecimens for molecular definitions of illness, recovery, susceptibility.

• Mechanism
  – 12 Clinical Sites – each with at least one satellite.
    • Two PIs – one ED, one Critical Care
  – 1 Clinical Coordinating Center – MGH
  – SC Chair – Roy Brower, JHU
Differences Between PETAL and ARDSNet

- Prevention and Early Treatment
- Acute Care/EM/Trauma + Critical Care
- Dialog, Collaboration, Exchange
  - International Partnership Committee
  - Canadian Critical Care Trials Group Representative
  - International Scientific Advisory Committee with members from CCTG, UK-CRN, ANZIC, etc.
  - Website portal for feedback and suggestions
    http://petalnet.org
• Objective: To assess the efficacy and safety of early NMB in reducing mortality and morbidity in patients with moderate-severe ARDS in comparison to a control group with no routine early NMB.

• Hypothesis: Early NMB will improve mortality prior to discharge home before day 90, in patients with moderate-severe ARDS.
VIOLET: Vitamin D to Improve Outcomes by Leveraging Early Treatment

Rationale for Vitamin D-ARDS Prevention:

(1) Vitamin D deficiency common in critical illness;

(2) Strong preclinical data, plausible mechanisms;

(3) Observational data → key ARDS risk factor;

(4) Phase II data → vitamin D repletion cheap, simple/rapid, safe, and improves outcomes in infection and non-infection ARDS prevention
LOTUS: **Low Tidal volume Universal ventilator Support**

- **Objective**: A pragmatic trial of lung protective ventilation in patients with acute respiratory failure to improve *patient-centered outcome(s)*
- **Hypothesis**: Patients with acute respiratory failure who received low tidal volume ventilation (≤ 6 cc/kg PBW) will have improved *patient-centered outcome(s)* than patients receiving tidal volumes as set by usual care.
Conclusions

• ARDS is a potentially preventable complication.
• Early identification of patients at risk:
  – Avoid “second hit” exposures
  – Facilitate mechanistic studies and prevention trials
  – Mechanistic treatments may have a better chance to work early in the course of illness
• Appropriate therapies need to be identified.
• When such therapies are identified they should be tested in rapid cycle phase 2 trials.
• Appropriate endpoints need to be worked out.
Prevention of the Acute Respiratory Distress Syndrome

Daniel Talmor M.D., M.P.H.
Anesthesia, Critical Care and Pain Medicine

HUMAN FIRST
Beth Israel Deaconess Medical Center
ABCs of ARDS prevention

- LIPS-A Aspirin
- LIPS-B Inhaled steroids (nebulized budesonide)
- LIPS-C Curcumin
- LIPS-D Vit D
- LIPS-H Inhaled heparin
- LIPS-Z…..