Diagnosis and Management of Respiratory Failure in the Pediatric Oncology Patient

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Diagnosis and Management of Respiratory Failure in the Pediatric Oncology Patient

- Ventilator Induced Lung Injury
- What the most recent pediatric studies reveal
- Strategies for mechanical ventilation for the pediatric oncology patient
- The ‘bundle’ of evidence-based interventions: it is more than just the ventilator

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Diagnosis and Management of Respiratory Failure in the Pediatric Oncology Patient

• **Ventilator Induced Lung Injury**
• What the most recent pediatric studies reveal
• Strategies for mechanical ventilation for the pediatric oncology patient
• The ‘bundle’ of evidence-based interventions: it is more than just the ventilator
Ventilator Associated Lung Injury (VILI)

Mechanical Ventilation supports life but injures the lung in three ways

- **Volutrauma** – overdistension of normal alveoli
- **Atelectrauma** – repetitive opening and closing of alveoli
- **Biotrauma** – release of inflammatory cytokines in response to above

JAMA (2005) 294:2889

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Avoid de-recruitment and over distention

“Lung Protective” Ventilation

Add PEEP

Limit Distending Pressure

Volume

Pressure
Summary: prevention of VILI

- Maximize lung recruitment
- Prevent end expiratory collapse
- Minimize cyclic stretch
- Avoid end inspiratory overdistension
Diagnosis and Management of Respiratory Failure in the Pediatric Oncology Patient

- Ventilator Induced Lung Injury
- *What the most recent pediatric studies reveal*
- Strategies for mechanical ventilation for the pediatric oncology patient
- The ‘bundle’ of evidence-based interventions: it is more than just the ventilator

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Inclusion criteria: endotracheal intubation and mechanical ventilation after bone marrow transplantation; patients with perioperative ventilation were excluded.

Overall survival rate to PICU discharge was 44% (17 of 39 patients). Six months after PICU discharge, 14 of these children were still alive, for a medium-term survival rate of 36%.

Preexisting conditions (primary disease, bone marrow engraftment, or graft-vs.-host disease) had no significant effect on survival. Multiple organ failure, especially pulmonary failure and neurologic deterioration, were significant determinants of patient survival.

Were these findings due to less severity of illness?

• Admission pediatric risk of mortality score of 11.8, the definition of respiratory failure used by these authors was PaO2/FIO2 ratio < 300 torr;

• Half of the patients in this study had maximum positive end-expiratory pressure < 10 cm H2 O, suggesting that many did not have catastrophic pulmonary illness, in contrast to the patients reported in other studies.
Pediatric Acute Lung Injury
Prospective Evaluation of Risk Factors Associated with Mortality

Heidi R. Flori, David V. Glidden, George W. Rutherford, and Michael A. Matthay

Department of Critical Care, Children’s Hospital and Research Center at Oakland, Oakland; Department of Epidemiology and Biostatistics, University of California, San Francisco; Department of Pediatrics, and Departments of Medicine and Anesthesia and the Cardiovascular Research Institute, University of California, San Francisco Medical Center, San Francisco, California
(1) Pediatric ALI has a high mortality (22%) compared with the overall mortality of pediatric intensive care unit patients.

(2) Several clinical risk factors contribute independently to an increased risk of death and prolonged mechanical ventilation, including the initial oxygenation defect, as measured by the PaO2/FiO2 ratio, the presence of nonpulmonary, non-CNS organ system dysfunction (hepatic, renal, hematologic, or gastrointestinal dysfunction), and the presence of CNS dysfunction, all of which are identifiable and interpretable in the clinical and research settings.

(3) Three independent predictors of death were identified. Two of the three represent clinical factors (presence of renal, hepatic, hematologic, or gastrointestinal dysfunction, and presence of CNS dysfunction) and the third is an objective physiologic measure of lung dysfunction (decreasing PaO2/FiO2).
• The top three diagnoses associated with ALI or ARDS are similar in both children and adults (pneumonia, aspiration, and sepsis).

• The presence of nonpulmonary organ system dysfunction shares a markedly increased risk of death in both children and adults.

• As in adult studies, (26, 36) presence of airleak at the onset of ALI does not seem to have independent predictive value for mortality. The overall mortality of pediatric patients with ALI or ARDS was significantly lower than that reported in adults (22% versus 35–45%)
TABLE 3. MULTIVARIATE ANALYSES: CLINICAL VARIABLES AT ONSET OF PEDIATRIC ACUTE LUNG INJURY ASSOCIATED WITH MORTALITY AND CATEGORIZED VENTILATOR FREE DAYS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Mortality</th>
<th>Ventilator-free Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>$P_{\text{a}}O_2/F_{\text{i}}O_2$ (per 20 point decrease)</td>
<td>1.14</td>
<td>1.04, 1.25</td>
</tr>
<tr>
<td>Other nonpulmonary, non-CNS* organ system dysfunction</td>
<td>2.16</td>
<td>1.67, 2.78</td>
</tr>
<tr>
<td>CNS* dysfunction</td>
<td>7.35</td>
<td>3.69, 14.63</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: CNS = central nervous system.*
Oxygenation Index Predicts Outcome in Children with Acute Hypoxemic Respiratory Failure

Daniel Trachsel, Brian W. McCrindle, Satoshi Nakagawa, and Desmond Bohn

Departments of Critical Care Medicine and Pediatrics, Divisions of Cardiology and Respiratory Medicine, and Department of Anesthesia, The Hospital for Sick Children, University of Toronto, Toronto, Canada
Study focused on the impact of the severity of oxygenation failure on outcome:

A higher peak Oxygenation Index (OI), younger age, and need for renal replacement therapy were found to be independently associated with longer duration of mechanical ventilation.

For all patients still intubated at any point in time, death was a fairly constant risk throughout the entire period of mechanical ventilation. In this cohort, the risk of dying within the next time interval exceeded the chances of successful extubation after approximately 4 weeks.
Relationship of probability of dying and OI stratified by the time

PRISM score within the first 12 hours of mechanical ventilation and peak OI at any point in time of AHRF were identified as independent predictors of outcome.

OI was found to be less predictable within the first 24 hours after intubation but remained consistent throughout the observational period thereafter.

- “11 patients were included in this study, with a mortality of 64%...but lower than reported fatality rates of 89 to 95% in BMT patients with AHRF (11, 12, 28).

- Thus, mortality observed in AHRF cohorts is dependent on the variety and distribution of underlying conditions.”
# Mechanisms of disease

<table>
<thead>
<tr>
<th>Direct lung injury</th>
<th>Indirect lung injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Shock</td>
</tr>
<tr>
<td>Submersion injury</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>Inhalational injury</td>
<td>Transfusion related lung injury</td>
</tr>
</tbody>
</table>

*Ware L and Matthay M. N Engl J Med 2000;342:1334-1349*
Effect of Prone Positioning on Clinical Outcomes in Children With Acute Lung Injury
A Randomized Controlled Trial

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Patricia L. Hibberd, MD, PhD
Lori D. Fineman, RN, MS
David Wypij, PhD
Mei-Chiung Shih, PhD
John E. Thompson, RRT
Mary Jo C. Grant, RN, PhD
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Michael A. Mathay, MD
John H. Arnold, MD

Context In uncontrolled clinical studies, prone positioning appeared to be safe and to improve oxygenation in pediatric patients with acute lung injury. However, the effect of prone positioning on clinical outcomes in children is not known.

Objective To test the hypothesis that at the end of 28 days infants and children with acute lung injury treated with prone positioning would have more ventilator-free days than those treated with supine positioning.

Design, Setting, and Patients Multicenter, randomized, controlled clinical trial conducted from August 28, 2001, to April 23, 2004, of 102 pediatric patients from 7 US pediatric intensive care units aged 2 weeks to 18 years who were treated with supine vs prone positioning. Randomization was concealed and group assignment was not blinded.

Intervention Patients were randomized to either supine or prone positioning within 48 hours of meeting acute lung injury criteria, with those patients in the prone group being positioned within 4 hours of randomization and remaining prone for 20 hours each day during the acute phase of their illness for a maximum of 7 days, after which they were positioned supine. Both groups were treated using lung protective ventilation and sedation protocols, extubation readiness testing, and hemodynamic, nutrition, and skin care guidelines.

Main Outcome Measure Ventilator-free days to day 28.

Results The trial was stopped at the planned interim analysis on the basis of the prespecified futility stopping rule. There were no differences in the number of ventilator-free days between the 2 groups (mean [SD], 15.8 [8.6] supine vs 15.6 [8.6] prone; mean difference, −0.2 days; 95% CI, −3.6 to 3.2; P=.91). After controlling for age, Pediatric Risk of Mortality III score, direct vs indirect acute lung injury, and mode of mechanical ventilation at enrollment, the adjusted difference in ventilator-free days was 0.3 days (95% CI, −3.0 to 3.5; P=.87). There were no differences in the secondary end points, including proportion alive and ventilator-free on day 28 (P=.45), mortality from all causes (P>.59), the time to recovery of lung injury (P=.78), organ failure-free days (P=.88), and cognitive impairment (P=.16) or overall functional health (P=.12) at hospital discharge or on day 28.

Conclusion Prone positioning does not significantly reduce ventilator-free days or improve other clinical outcomes in pediatric patients with acute lung injury.

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For editorial comment see p 248.

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Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, JAMA.
Nitric Oxide

- Selective pulmonary vasodilator
- Increases systemic oxygenation in newborns with PPHN
- Improves the pulmonary outcome for premature infants at risk for BPD

*Ballard et al, NEJM 2006;353*

- No effect on mortality, ventilator free days in adults with ARDS in 2 RCT’s

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Figure 1. Patient Flow Through Clinical Trial

8017 Patients Screened

7915 Excluded
- 7833 Did Not Meet Study Criteria
- 51 Parent Refusal
- 15 Missed Enrollment Window
- 10 Parent or Guardian Unavailable
- 3 Language Barrier
- 3 Physician Refusal

102 Randomized

51 Assigned to Receive Supine Positioning
- 50 Received Supine Positioning as Assigned
- 1 Parental Consent Withdrawn (Day 1)
- 0 Lost to Follow-up
- 50 Included in Analysis

51 Assigned to Receive Prone Positioning
- 47 Received Full Course of Prone Positioning as Assigned
- 4 Withdrawn
  - 1 Unstable After Consent (Day 1)
  - 1 Extracorporeal Membrane Oxygenation (Day 2)
  - 1 Required Supine Assessments (Day 2)*
  - 1 Persistent Hypercarbia in Prone Position (Day 3)
- 0 Lost to Follow-up
- 51 Included in Analysis

*Prone positioning alone was stopped on day 2 in a patient with sickle cell disease because of splenic sequestration.
• **CONCLUSION:** Prone positioning does not significantly reduce ventilator-free days or improve other clinical outcomes in pediatric patients with acute lung injury.
Effect of Exogenous Surfactant (Calfactant) in Pediatric Acute Lung Injury
A Randomized Controlled Trial

Douglas F. Willson, MD
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Barry P. Markovitz, MD, MPH
Loren A. Bauman, MD
Joseph V. DiCarlo, MD
Steven Pon, MD
Brian R. Jacobs, MD
Larry S. Jefferson, MD
Mark R. Conaway, MD
Edward A. Egan, MD
for the Pediatric Acute Lung Injury and Sepsis Investigators

Context Despite evidence that patients with acute lung injury (ALI) have pulmonary surfactant dysfunction, trials of several surfactant preparations to treat adults with ALI have not been successful. Preliminary studies in children with ALI have shown that instillation of a natural lung surfactant (calfactant) containing high levels of surfactant-specific protein B may be beneficial.

Objective To determine if endotracheal instillation of calfactant in infants, children, and adolescents with ALI would shorten the course of respiratory failure.

Design, Setting, and Patients A multicenter, randomized, blinded trial of calfactant compared with placebo in 153 infants, children, and adolescents with respiratory failure from ALI conducted from July 2000 to July 2003. Twenty-one tertiary care pediatric intensive care units participated. Entry criteria included age 1 week to 21 years, enrollment within 48 hours of endotracheal intubation, radiological evidence of bilateral lung disease, and an oxygenation index higher than 7. Premature infants and children with preexisting lung, cardiac, or central nervous system disease were excluded.

Intervention Treatment with intratracheal instillation of 2 doses of 80 mL/m² calfactant or an equal volume of air placebo administered 12 hours apart.

Main Outcome Measures Ventilator-free days and mortality; secondary outcome measures were hospital course, adverse events, and failure of conventional mechanical ventilation.

Results The calfactant group experienced an acute mean (SD) decrease in oxygenation index from 20 (12.9) to 15.9 (9.6) after 12 hours compared with the placebo group’s decrease from 20.5 (14.7) to 15.1 (9.0) (P=.01). Mortality was significantly greater in the placebo group compared with the calfactant group (27/75 vs 15/77; odds ratio, 2.32; 95% confidence interval, 1.15-4.85), although ventilator-free days were not different. More patients in the placebo group did not respond to conventional mechanical ventilation. There were no differences in long-term complications.

Conclusions Calfactant acutely improved oxygenation and significantly decreased mortality in infants, children, and adolescents with ALI although no significant decrease in the course of respiratory failure measured by duration of ventilator therapy, intensive care unit, or hospital stay was observed.

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www.jama.com

Author Affiliations and Participating Hospitals and Collaborating Investigators are listed at the end of this article.

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Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, JAMA.
Surfactant in Pediatric ARDS

Eligibility

(a) age 1 wk to 21 yrs;
(b) respiratory failure due to bilateral parenchymal lung disease
(c) enrollment within 24 hrs of initiation of mechanical ventilation (extended to 48 hours after the initial 50 patients)
(d) Oxygenation Index (OI) > 7

Willson et al., JAMA 293:470-476, 2005

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Outcome Measures

- Primary Outcome: Ventilator-free days
- Secondary Outcomes:
  - Mortality
  - PICU and hospital LOS
  - Hospital charges
  - Duration of supplemental O₂
  - Failure of conventional ventilation

*Willson et al., JAMA 293:470-476, 2005*
<table>
<thead>
<tr>
<th>Table 2. Clinical Outcomes*</th>
<th>Calfactant (n = 77)</th>
<th>Placebo (n = 75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In hospital</td>
<td>15 (19)</td>
<td>27 (36)</td>
<td>.03</td>
</tr>
<tr>
<td>Without extubation</td>
<td>12 (16)</td>
<td>24 (32)</td>
<td>.02</td>
</tr>
<tr>
<td>Immunocompromised, No./total (%)</td>
<td>11/22 (50)</td>
<td>18/30 (60)</td>
<td>.58</td>
</tr>
<tr>
<td>Immune-competent, No./total (%)</td>
<td>4/55 (7)</td>
<td>9/45 (20)</td>
<td>.08</td>
</tr>
<tr>
<td>Conventional mechanical ventilation failure†</td>
<td>13 (21)</td>
<td>26 (42)</td>
<td>.02</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>3 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Use of nitric oxide</td>
<td>9 (12)</td>
<td>10 (13)</td>
<td>.80</td>
</tr>
<tr>
<td>High-frequency oscillatory ventilation after entry</td>
<td>7 (9)</td>
<td>15 (20)</td>
<td>.07</td>
</tr>
<tr>
<td>Secondary outcomes, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric intensive care unit</td>
<td>15.2 (13.3)</td>
<td>13.4 (11.6)</td>
<td>.71</td>
</tr>
<tr>
<td>Hospital</td>
<td>25.0 (22.5)</td>
<td>24.8 (32.3)</td>
<td>.78</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>17.3 (16)</td>
<td>18.3 (31)</td>
<td>.97</td>
</tr>
<tr>
<td>Hospital charges, $‡</td>
<td>205 (220)</td>
<td>299 (640)</td>
<td>.68</td>
</tr>
</tbody>
</table>

*Values are number (percentage) unless otherwise indicated.
†Some patients had more than 1 alternative treatment.
‡In thousands.
Surfactant in Pediatric ARDS

- Primary outcome (VFD’s): not statistically different (13.2 vs. 11.5, p = 0.21)

*Willson et al.*, *JAMA* 293:470-476, 2005
Proportion of Calfactant Compared With Placebo Patients Successfully Extubated in the 28 Days After Study Entry

![Graph showing the proportion of patients successfully extubated over 28 days for Calfactant and Placebo groups. The Log-Rank P-value is 0.13.](image)

## Surfactant in Pediatric ARDS

<table>
<thead>
<tr>
<th></th>
<th>Surfactant (n = 77)</th>
<th>Control (n = 75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (in hospital)</td>
<td>19%</td>
<td>36%</td>
<td>.03</td>
</tr>
<tr>
<td>Died on vent.</td>
<td>16%</td>
<td>32%</td>
<td>.02</td>
</tr>
<tr>
<td>Failed CMV (HFO, NO, ECMO)</td>
<td>21%</td>
<td>42%</td>
<td>.02</td>
</tr>
</tbody>
</table>
Results

• Co-morbidity immuncompromized children calfactant (13%) vs. placebo (20%)

No significant effect on mortality after adjustment via logistic regression
“Direct” versus “Indirect” Acute Lung Injury

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Calfactant</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Direct”</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>48</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>(OI ↓ 25% +)</td>
<td>31%</td>
<td>66%</td>
<td>0.0006</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>17±10</td>
<td>13±9</td>
<td>0.05</td>
</tr>
<tr>
<td>Died</td>
<td>37%</td>
<td>8%</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>“Indirect”</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>27</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>(OI ↓ 25% +)</td>
<td>41%</td>
<td>37%</td>
<td>0.79</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>17±10</td>
<td>18±10</td>
<td>0.75</td>
</tr>
<tr>
<td>Died</td>
<td>33%</td>
<td>41%</td>
<td>0.65</td>
</tr>
</tbody>
</table>

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Conclusions surfactant

- Multivariate analysis altered the primary analysis
- Further clinical trial data are needed
- Inclusion of immunocompromised patients is problematic
- ALI due to direct lung injury may provide a less heterogeneous study sample

Willson et al., JAMA 293:470-476, 2005
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- *Strategies for mechanical ventilation for the pediatric oncology patient*
- The ‘bundle’ of evidence-based interventions: it is more than just the ventilator
What to do: Managing Oxygenation

- General goal is to optimize lung volume (FRC)
- Maintain SpO2 in range of 88 – 90%, and optimize Hct /Hgb
- Target FiO2: 0.40 - 0.50
- Optimize PEEP
  - If FiO2 > 0.50, increase PEEP in increments of 2- 4 cmH2O
    - Perform a recruitment maneuver prior to increasing PEEP, if indicated (see below)
    - Monitor for adverse reactions
      - Hemodynamic compromise (Decrease in BP > 10%)
      - Decreased lung compliance (Decrease in tidal volume > 20% after 10 minutes)
      - Decreased CO2 elimination after 10 minutes
    - With adverse reactions
      - Return PEEP to previous level
      - Consider need for intravascular volume
- If FiO2 < 0.40, decrease PEEP by 2 cmH2O
What to do: Managing Ventilation

- General goal is to avoid over-distension during inspiratory phase
  - Maintain appropriate tidal volume / maximum ventilating pressure
  - Maintain Vt: 5 – 7 mL/kg IBW
  - Insure Pplat $\leq$ 30 cmH20 (In PC, Pplat $\approx$ PIP if Inspiratory flow reaches 0)
  - If Pplat $>30$ cmH20 to achieve Vt 5 mL/kg, decrease Vt target to 4 mL/kg
What to do: Managing Ventilation

Maintain pH $\geq 7.25$

a. If pH < target
   i. Increase set rate until pH within range or there is evidence of gas trapping despite optimizing I:E, and
   ii. If PaCO2 < 55 mmHg, give NaHCO3 or THAM (if renal function acceptable)

b. If pH still < target
   i. Accept lower pH ($\geq 7.20$) or
   ii. Increase target Vt to 8 mL/kg if VD/Vt > 0.70

c. If pH > target (Assumes Vt 5 – 7 mL/kg)
   i. Decrease set rate incrementally
   ii. If patient breathing spontaneously

   • Maintain acceptable total RR for patient age
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Defining optimal care for the patient with or at risk for Acute Lung Injury

  – Tidal volumes of 6cc/kg are protective against a hyperinflammatory response leading to multiple organ failure and death.

  – Elevate the head of the bed by 30 degrees to prevent aspiration and subsequent ventilator associated pneumonia

  – Administer antibiotics immediately when ventilator-associated pneumonia is identified.
Defining optimal care for the patient with or at risk for Acute Lung Injury

  – Daily extubation readiness trials in adults reduce time on the ventilator and therefore morbidity and cost.

  – Daily “wake-up” trials in adults reduce time on the ventilator and therefore morbidity and cost.

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# The Daily Rounds “Simple” checklist

**S**

- **Sedation and Analgesia**
  - Short Term Pathway
  - Long Term Pathway: Phase (acute, titration, extubation, post-extubation)
  - SBS goal (-2 to 0)
  - Daily Arousal Assessment (DAA)
  - Paralytic Holiday
  - Signs of withdrawal/WAT-1 score
  - Weaning plan for sedatives and analgesics

**I**

- **Invasive Lines/Invasive Tubes**
  - CVL day #, remove?
  - CVL in ___ days
  - Arterial line day #, remove?
  - Arterial line in ___ days
  - Foley catheter day #, remove?
  - Foley in ___ days

**M**

- **Medications/Measurements**
  - Discontinue or change to enteral
  - Therapeutic drug levels
  - Adjustment for organ system dysfunction
  - Ideal body weight for calculations?

**P**

- **Prophylaxis**
  - GI prophylaxis
  - DVT prophylaxis
  - PT consult
  - POOP protocol

**L**

- **Labs**
  - Lab schedule
  - Parameters for labs

**E**

- **Evaluation Readiness/External robbed**
  - Initiate or advance feeds?
  - ERT result: Pass/Fail/Ineligible
  - P / F / N/A
  - Leak assessed?
  - Hold feeds for extubation?
  - Comments

---

DO NOT place in the medical record - for Quality Improvement Purposes Only
Conclusions

• ALI and ARDS have multiple causes
• The host inflammatory response is a key feature in the pathogenesis
• Low tidal volumes is the one component associated with a mortality benefit
• Surfactant, HFOV, iNO will not benefit all children when applied indiscriminately
No conflicts or financial disclosures to convey