Critical Review Form
Therapy

Mechanical ventilation and acute lung injury in emergency department patients with severe sepsis and septic shock: an observational study. Acad Emerg Med. 2013 Jul;20(7):659-69.

Objectives: **"We hypothesized that lung-protective ventilation would be uncommon in the ED and would not differ based on ALI status; we also hypothesized that ALI in the ED and progression to ALI after ED admission would be common and that factors present during the ED stay would influence this outcome." (p. 660)**

Methods: **This retrospective, observational study used data collected at a large tertiary care hospital associated with an emergency medicine residency. Patients enrolled in a severe sepsis registry (suspected infection and either a lactate ≥ 4 mmol/L or systolic blood pressure (SBP) ≤ 90 mmHg after IV hydration) from June 2005 to May 2010 were eligible for enrollment. Ventilator parameters were abstracted from the record by trained data collectors using a standardized format. Two separate data abstractors verified all records for accuracy and cross-checked data with the electronic medical record. Lung-protective ventilation was defined as use of a tidal volume (V_T) of < 8 mL/kg of ideal body weight.**

Acute lung injury (ALI) was defined by the presence of all of the following:

1. **Bilateral alveolar infiltrates on chest x-ray (CXR)**
2. **Hypoxemia defined by a PaO_2:FiO_2 ratio ≤ 200**
3. **No evidence of left atrial hypertension (defined by a history of congestive heart failure or end-stage renal disease requiring dialysis, depressed left ventricular function on echocardiography within 24 hours of development of CXR findings, or a widened vascular pedicle on CXR).**

The primary outcome was the incidence of progression to ALI within 5 days after ICU admission and risk factors in the ED associated with this outcome. Secondary outcomes included change in Sequential Organ Failure Assessment (SOFA) score, dialysis-dependent acute kidney injury, duration of mechanical ventilation, duration of vasopressor use, hospital length of stay (LOS), and in-hospital mortality in patients who developed ALI compared to those who did not develop ALI. The incidence of ALI in the ED was also assessed.

There were 251 patients included in the study, with a median V_T of 8.8 mL/kg (IQR 7.8-10.0, range 5.2-14.6). The mean age was 62.9 and 51.4% were male. Lung-protective ventilation was employed in 68 (27.1%) patients. There were 69 patients (27.5%) who progressed to ALI, with a mean onset of 2.1 days. After excluding patients with ALI on presentation to the ED, those with a history of CHF or dialysis, and those who died within 24 hours of admission, there were 135 patients assessed for

risk factors for ALI progression. Twenty-two patients (8.8%) had ALI at the time of ED presentation.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	No. This was a retrospective, observational trial.
2.	Was randomization concealed (blinded)?	N/A
3.	Were patients analyzed in the groups to which they were randomized?	Patients were analyzed primarily by whether or not they developed acute lung injury, rather that by treatment group.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Uncertain. For the clinical question at hand, the treatment group would be those who received low tidal volume ventilation (< 8 mL/kg of ideal body weight), and the control group would be those with more traditional tidal volumes. We are not given information specific to these groups of patients.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	There was no blinding. However, all patients were intubated during the treatment period and were likely unaware of group allocation. Performance bias would be unlikely to affect the outcomes.
2.	Were clinicians aware of group allocation?	Yes. This was a retrospective observational study, and hence clinicians were aware of all treatment modalities administered, including tidal volume.
3.	Were outcome assessors aware of group allocation?	Yes. There was no specific intervention being assessed to which assessors could be blinded. There is therefore, a risk of **observer bias**, though this seems unlikely, as there was no specific hypothesis regarding treatment effect being studied.
4.	Was follow-up complete?	Yes. Outcomes were measured during inpatient stay, therefore no follow-up was conducted beyond chart review. Outcome data was recovered on all patients.
II.	**What are the results (answer the questions**	

<table>
<tr><td></td><td>posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>Median tidal volume was 9.0 mL/kg IBW (IQR = 8.0 to 10.1) in ALI patients, compared to 8.7 mL/kg IBW (IQR = 7.8 to 9.9) in patients without ALI (p = 0.40).

To assess the ability of low V_T to protect against acute lung injury, we exclude those with ALI on ED arrival and those with CHF or dialysis, and draw the following 2X2 table for exposure and outcome (Table 1):

Table 1. V_T and progression to ALI
<table><tr><td></td><td>Low V_T</td><td>Traditional V_T</td></tr><tr><td>Progression to ALI</td><td>18</td><td>43</td></tr><tr><td>No progression to ALI</td><td>24</td><td>50</td></tr></table>
We can therefore calculate an unadjusted RR of 0.93 (95% CI 0.61-1.4) for developing ALI with low V_T, compared to traditional V_T.

In univariate analysis, the only factors found to be significantly associated with progression to ALI were weight, BMI, APACHE II score, SOFA score, and vasopressor use (Table 2).

Table 2. Factors associated with progression to ALI in univariable analysis
<table><tr><td>Factor</td><td>Progression to ALI (n=61)</td><td>No progression to ALI (n=74)</td><td>p-value</td></tr><tr><td>Weight (kg)</td><td>80.6 (60.0-93.2)</td><td>69.7 (57.2-81.8)</td><td>0.02</td></tr><tr><td>BMI</td><td>27.5 (22.7-32.3)</td><td>23.9 (20.4-28.7)</td><td>0.006</td></tr><tr><td>APACHE II</td><td>24.0 (±5.9)</td><td>21.8 (±5.9)</td><td>0.03</td></tr><tr><td>SOFA</td><td>9.0 (±3.3)</td><td>7.3 (±3.8)</td><td>0.01</td></tr><tr><td>Vasopressor use, n (%)</td><td>50 (82.0)</td><td>46 (62.2)</td><td>0.01</td></tr></table>
In multivariate analysis, the only factors found to be significantly associated with the development of ALI were BMI, SOFA score, and vasopressor use (Table 3).</td></tr>
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<tr><td></td><td></td><td>Table 3. Factors associated with progression to ALI in multivariate analysis<table><tr><td>Variable</td><td>aOR</td><td>95% CI</td><td>p-value</td></tr><tr><td>BMI</td><td>1.09</td><td>1.03-1.14</td><td><0.001</td></tr><tr><td>SOFA</td><td>1.13</td><td>1.03-1.25</td><td>0.03</td></tr><tr><td>Vasopressor use</td><td>2.80</td><td>1.16-7.20</td><td>0.02</td></tr></table></td></tr>
<tr><td>2.</td><td>How precise was the estimate of the treatment effect?</td><td>See above.</td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were the study patients similar to my patient?</td><td>Yes. These were Emergency Department patients with sepsis who were intubated. These were actually patients from our own institution. One could argue that septic patients in a community or rural ED may be somewhat different (e.g. lower rates of transplant, chemotherapy. It is unclear how this would affect the development of ALI and its risk factors.</td></tr>
<tr><td>2.</td><td>Were all clinically important outcomes considered?</td><td>No. This was a retrospective study designed to look at the development of ALI. The study did not specifically address other relevant outcomes, such as mortality, healthcare costs, or quality of life. The increased mortality associated with the development of ALI and ARDS has been well-documented.</td></tr>
<tr><td>3.</td><td>Are the likely treatment benefits worth the potential harm and costs?</td><td>Uncertain. This study was designed primarily to assess the epidemiology of ALI in septic patients intubated in the ED. In this study, V_T was NOT associated with an increased risk of developing ALI. However, this was a retrospective study and the reasoning behind V_T selection for each patient cannot be deduced. In addition, there were very few patients with low V_T settings, and thus the study was likely underpowered to demonstrate an association between V_T and ALI development. Further prospective studies will need to assess this further, to determine whether such strategies, when instituted in the ED, reduce the risk of developing ALI.</td></tr>
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Limitations:

1. **The retrospective design of the study allows for a demonstration of association between certain factors and the development of ALI, but could not demonstrate a causal relationship.**

2. **Patient with a history of congestive heart failure or dialysis were presumed not to have ALI, despite abnormal chest x-ray findings. While may of these patients likely had hydrostatic pulmonary edema, it is likely that some of them had ALI.**

3. **ALI was diagnosed based on CXR reads, however there was no blinded interpretation of CXRs.**

4. **The small number of patients receiving low V_T ventilation (n = 68) likely precludes the ability to detect a protective benefit, if one indeed exists.**

5. **This was a single-center study performed at a large, academic teaching hospital. The external validity of the findings to community and/or rural hospitals remains uncertain.**

6. **This study included only patients with sepsis, a high-risk group for the development of ALI. The findings may not be relevant in intubated patients at lower risk of ALI.**

Bottom Line:

This retrospective study of intubated, septic ED patients demonstrated an association between BMI, SOFA score, and vasopressor use and the development of ALI on multivariate regression analysis. While no association between low V_T ventilation and ALI risk reduction was observed, this was a small study with significant practice variation, and does not rule-out the possibility of a protective effect. Further prospective studies will need to be performed to establish whether prophylactic use of lower tidal volumes in the ED protects against ALI development.