

# Investigating the Literature: The Good, The Bad, The Ugly

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# Objectives

- 1. Discuss how to locate literature.
- 2. Discuss how to look at literature and determine if it is statistically significant and/or clinically relevant.
- 3. Discuss and assess literature and analyze the outcomes.
- 4. Identify future areas of research in Respiratory Therapy.

I have no disclosures or conflicts of interest to report

# Experience vs. Evidence

## Experience

- Expert
- Deduction from Experience
- Induction from Basic Science
- Creates variation in clinical approach based on “Who” is the Expert

## Evidence

- Evidence from clinical trials
- Attempt to Standardize Clinical Practice
- “Cookbook” approach may limit creative decision making

Thanks to Dr. Joe Coyle for this slide



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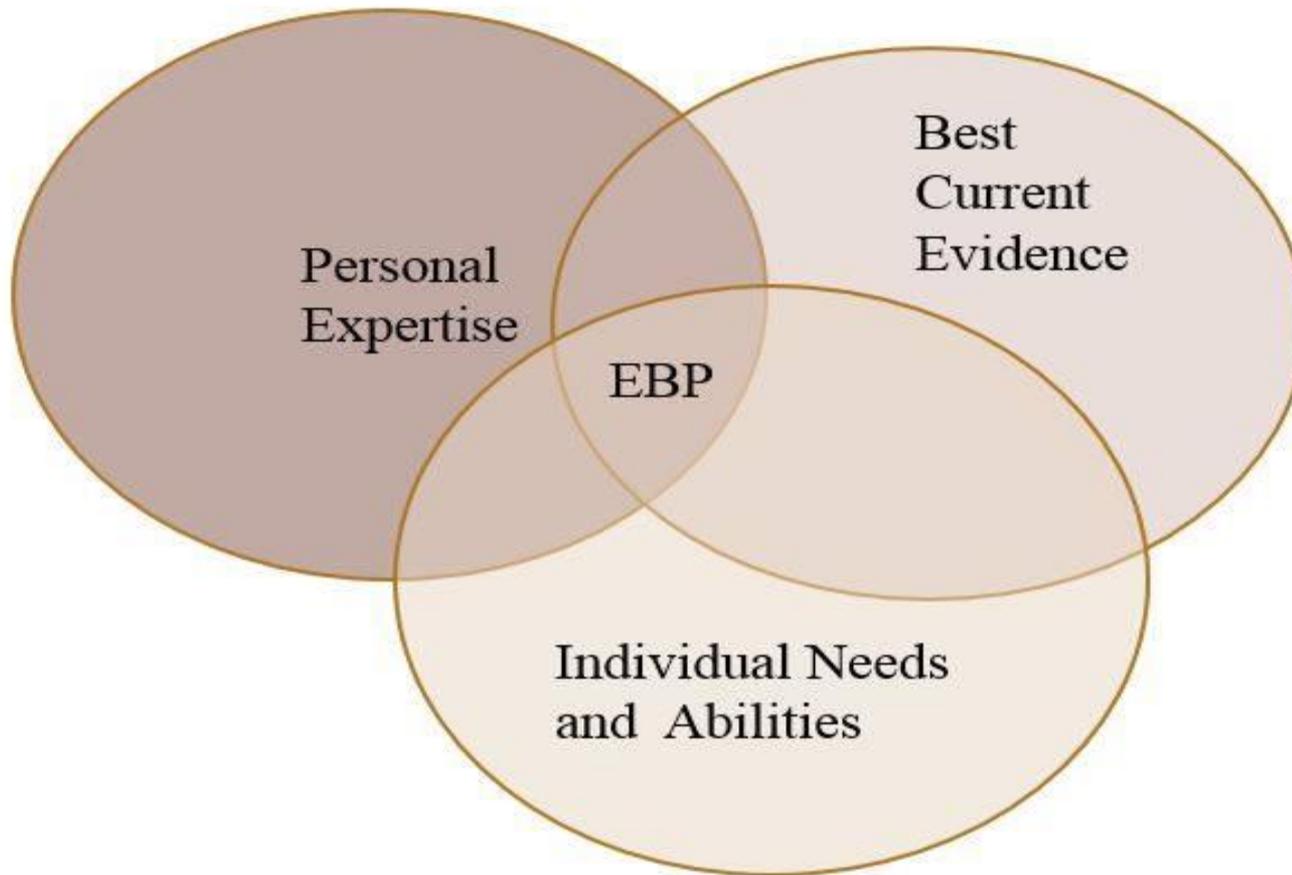


Image courtesy of Google



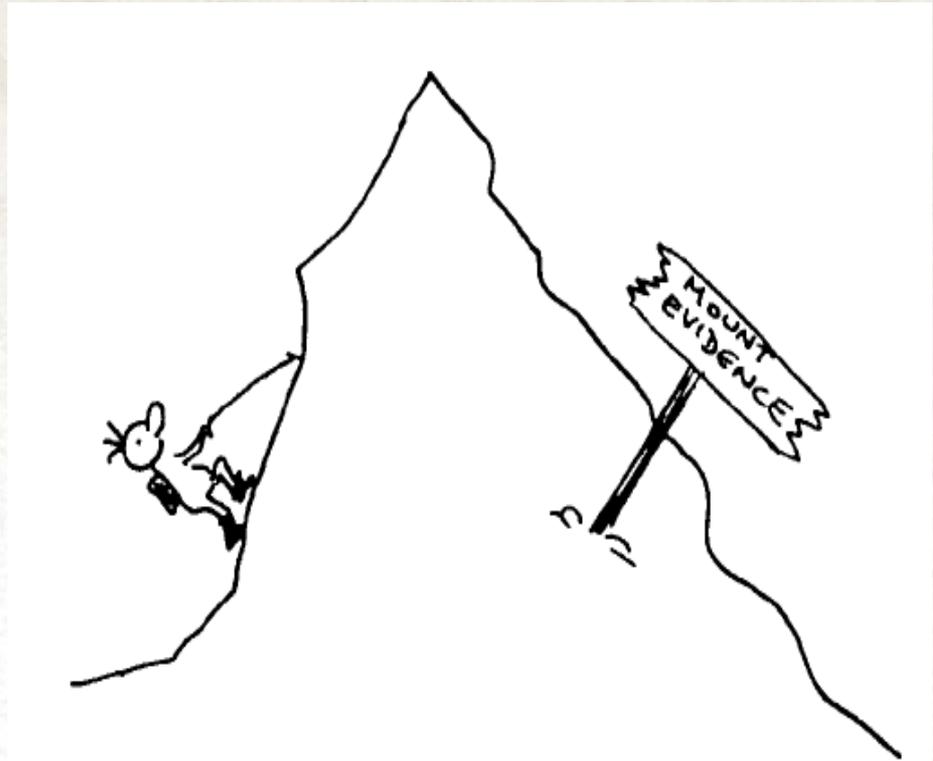
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# The Problem with Evidence

- Availability
- Access
- Analysis
- Shifting Sand
- Prioritizing



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# Where Do We Start?

The screenshot shows the top navigation bar of the NCBI website with links for 'NCBI', 'Resources', and 'How To'. The 'PubMed' logo is prominently displayed, along with the text 'US National Library of Medicine National Institutes of Health'. A search bar is present with a 'Search' button and a 'Help' link. Below the navigation bar, there is a main content area with a 'PubMed' section describing the database's 22 million citations. To the right, there is a 'PubReader' section with an image of a tablet displaying a document. Below these are three columns of links: 'Using PubMed', 'PubMed Tools', and 'More Resources'. At the bottom, there is a breadcrumb trail 'You are here: NCBI > Literature > PubMed' and a 'Write to the Help Desk' link. A footer section contains four columns of links: 'GETTING STARTED', 'RESOURCES', 'POPULAR', 'FEATURED', and 'NCBI INFORMATION'.

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- NCBI Handbook
- Training & Tutorials

**RESOURCES**

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- Data & Software
- DNA & RNA
- Domains & Structures
- Genes & Expression
- Genetics & Medicine
- Genomes & Maps

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- BLAST
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- Gene
- Bookshelf
- Protein

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- PubMed Health
- GenBank
- Reference Sequences
- Map Viewer
- Human Genome
- Mouse Genome

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<http://www.ncbi.nlm.nih.gov/pubmed/>

# What is PubMed?

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- Ran through the National Library of Medicine.
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- PubMed Central®
  - 4.4 Million Articles
  - 2016 Full Participation Journals



# Respiratory Care

## RESPIRATORY CARE



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### CURRENT ISSUE

01 Sep 2017 (Vol. 62 Issue 9) Table of Contents



### ISSUE HIGHLIGHTS

Effect of Interval Between Actuations of Albuterol Hydrofluoroalkane Pressurized Metered-Dose Inhalers on Their Aerosol Characteristics

Development and Testing of a Bubble Bi-Level Positive Airway Pressure System

Spirometry, Static Lung Volumes, and Diffusing Capacity

Pulmonary Function and Respiratory Health of Military Personnel Before Southwest Asia Deployment

Most Read

Most Cited

Airway Pressure Release Ventilation: What Do We Know?

Tracheostomy Tubes

How to Write an Abstract That Will Be Accepted for Presentation at a National Meeting

Tracheostomy: Epidemiology, Indications, Timing, Technique, and Outcomes

Classification of Ventilator Modes: Update and Proposal for Implementation

More...



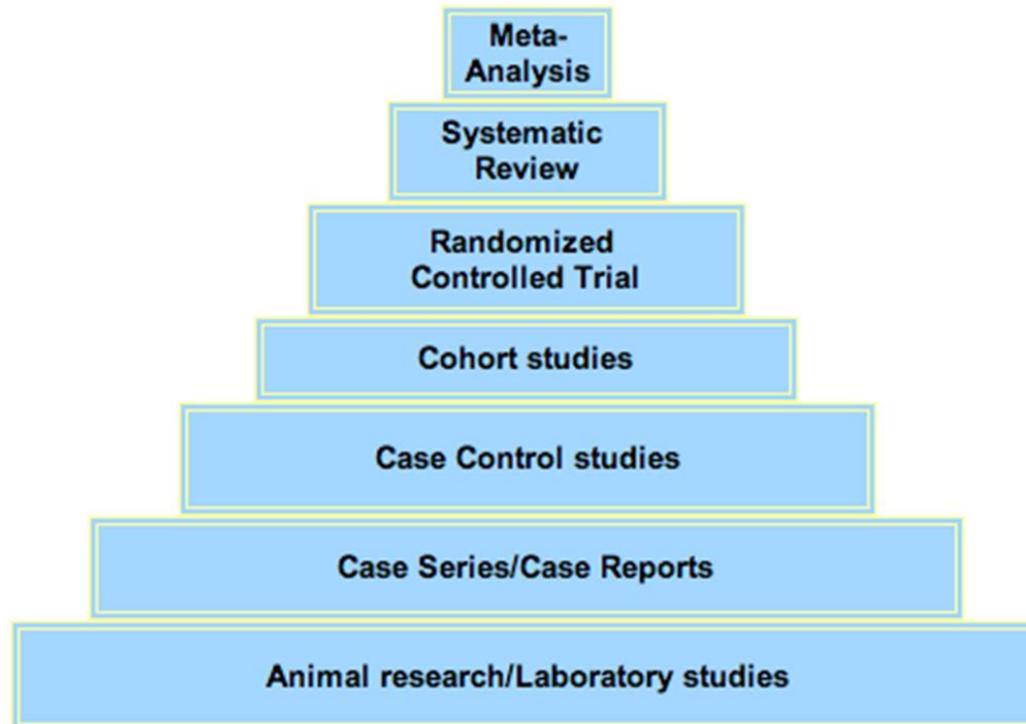
# Other Sources of Evidence

- Google Scholar
  - <http://scholar.google.com/>
- Cochrane Reviews
  - <http://www.cochrane.org/cochrane-reviews>
- AHRQ Clinical Guidelines Site
  - <http://www.guideline.gov/>



# Levels of Evidence

## Type of Study



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# Five Phases of Research

- Basic Research
- Applied Research
- Clinical Investigations
- Clinical Trials
- Demonstration and Education Research

Chatburn, R.L. (2011) *Handbook for Healthcare Research 2<sup>nd</sup> ed.* Jones and Bartlett



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# Statistically Significant or Clinically Relevant

- **Statistical significance**
  - Quantify the probability of a study's results due to chance.
  - Can use a p Value
- **Clinical significance**
  - Magnitude of the actual treatment effect.
  - Will look at treatment effect size or the difference between the intervention and control group



# Statistically Significant or Clinically Relevant

- Statistical significance ( $p < 0.05$ ) does not imply practical relevance.
- Example
  - A drug has a statically significant reduction in blood pressure.
  - It is only a reduction of 1 torr in the systolic BP.
  - It costs 100 dollars more a month for patients.



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# Now Let's Look at Some Research and Decide



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# Lung Protective Ventilation for Surgical Patients

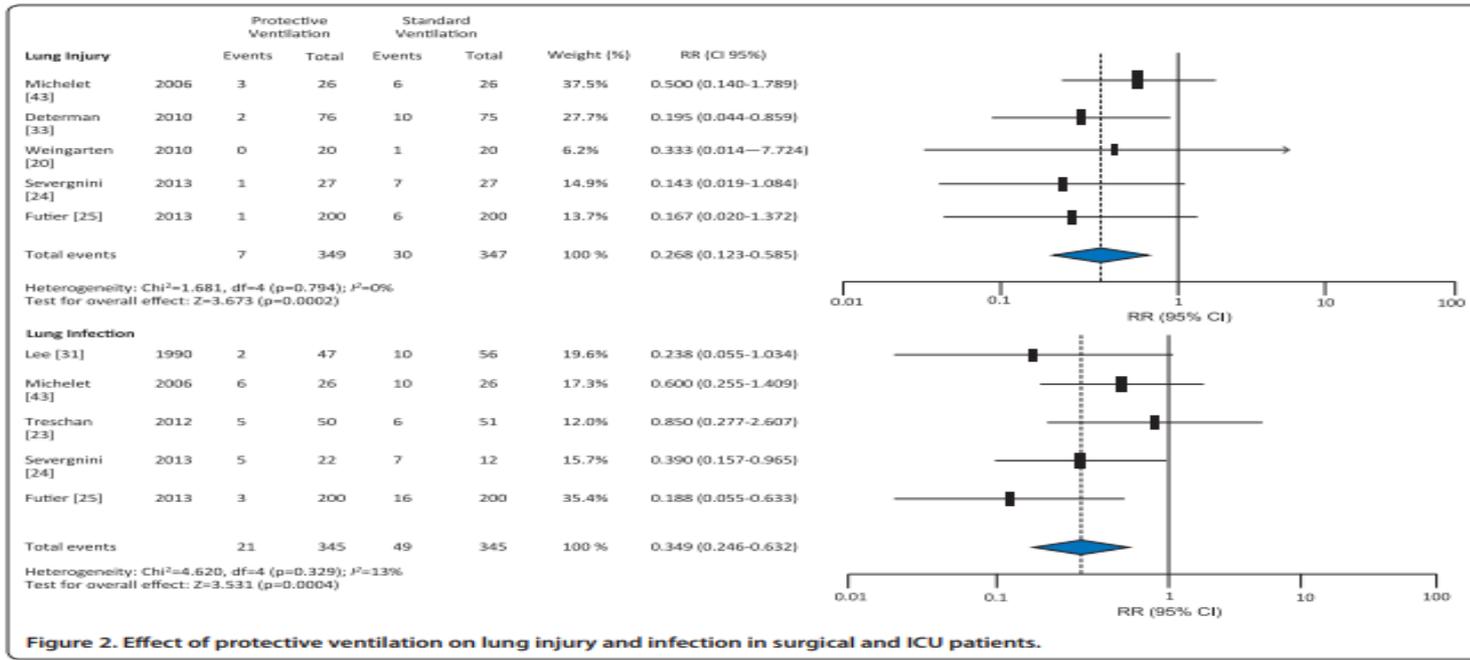


Figure 2. Effect of protective ventilation on lung injury and infection in surgical and ICU patients.

Sutherathan, Y., Vargas, M., & Pelosi, P (2014) Protective mechanical ventilation in the non injured lung: review and meta-analysis *Critical Care* 18 211, 1-12.



# Lung Protective Ventilation for Surgical Patients

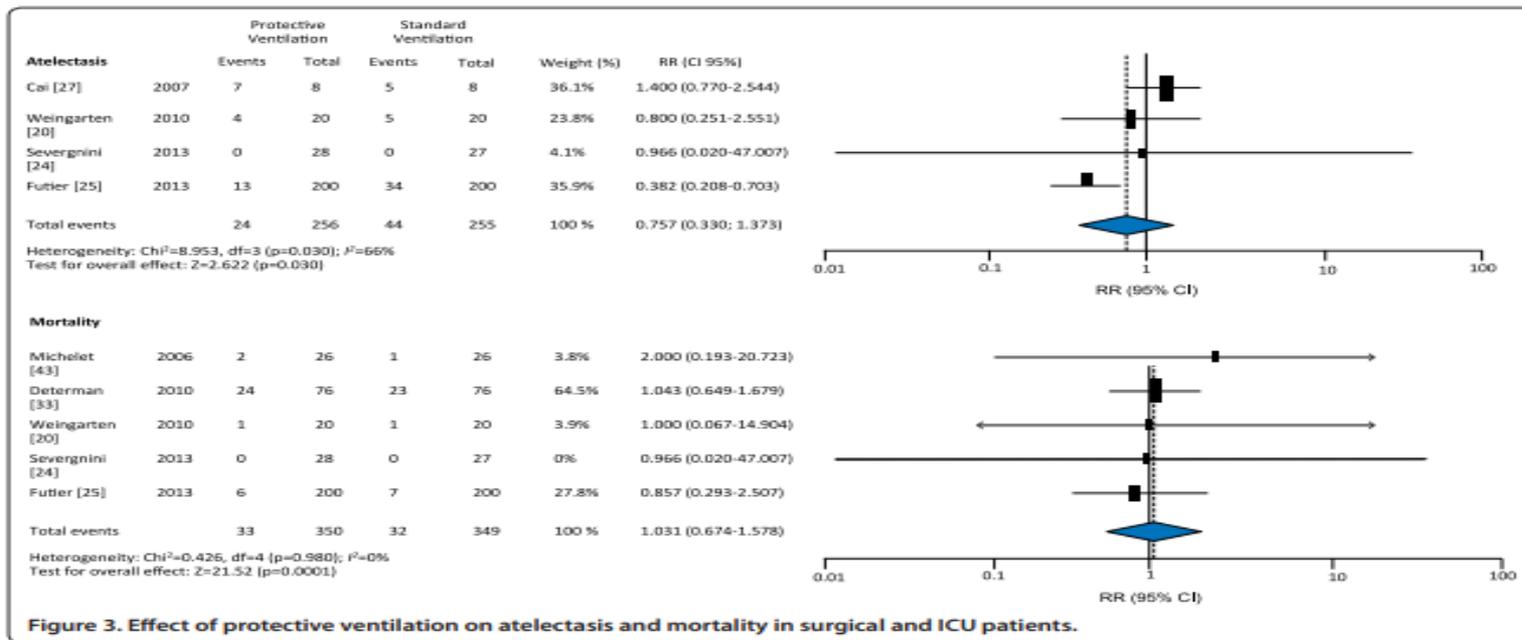
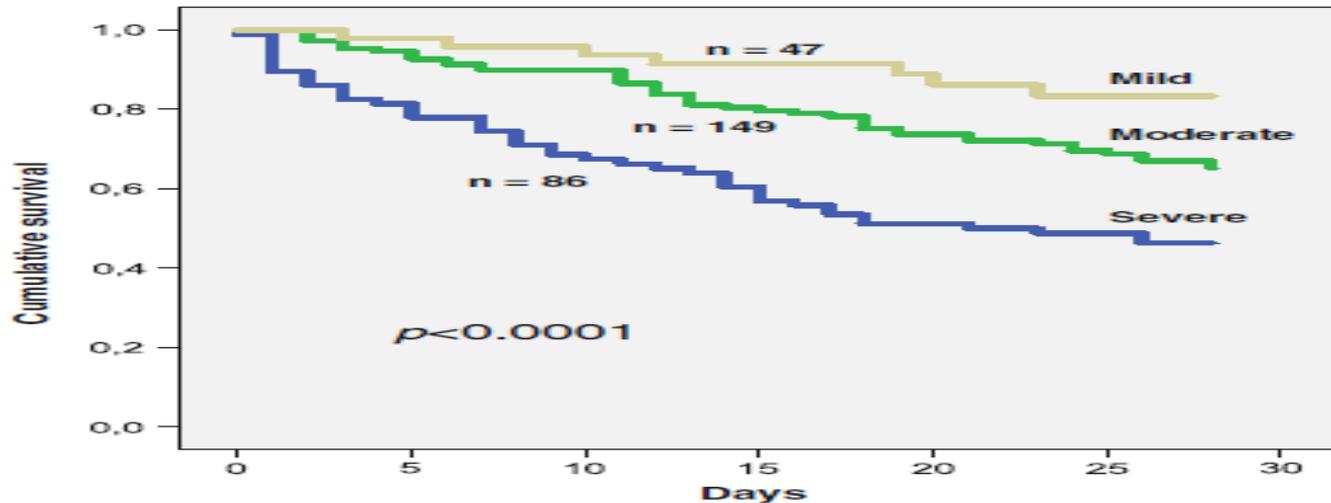


Figure 3. Effect of protective ventilation on atelectasis and mortality in surgical and ICU patients.

Sutherathan, Y., Vargas, M., & Pelosi, P (2014) Protective mechanical ventilation in the non injured lung: review and meta-analysis *Critical Care* 18 211, 1-12.

# Importance of Separating into Three Phenotypes



**Fig. 4** Kaplan-Meier 28-day probability of survival curves for the three phenotypes of 282 patients with the acute respiratory distress syndrome (ARDS) from the validation cohort classified by their response to  $\text{FiO}_2 \geq 0.5$  plus  $\text{PEEP} \geq 10$   $\text{cmH}_2\text{O}$  at 24 h of ARDS onset (see text for details). More than half of deaths (55.3 %) occurred within the first 15 days of inclusion into the study: 38 of 53 deaths (71.7 %) in the severe ARDS subgroup, 31 of 68 deaths (45.6 %) in the moderate ARDS subgroup, and 4 of 11 deaths (36.4 %) in the mild ARDS subgroup

Villar, J., et.al. (2013) A universal definition of ARDS: the  $\text{PaO}_2/\text{FiO}_2$  ratio under standard ventilatory settings-a prospective, multicenter validation study *Intensive Care Medicine* 39 583-592.



# What Helps Us Identify ARDS Phenotypes?

Variables	Mild ARDS PaO <sub>2</sub> /FiO <sub>2</sub> > 200 (n = 47)	Moderate ARDS PaO <sub>2</sub> /FiO <sub>2</sub> 101-200 (n = 149)	Severe ARDS PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 100 (n = 86)	p value
Age (years), mean ± SD	53 ± 18	56 ± 18	55 ± 17	0.594
APACHE II	20.5 ± 5.5	21 ± 6	22 ± 6	0.505
SOFA	9.0 ± 3.3	8.8 ± 3.4	9.6 ± 3.5	0.221
Lung injury score	2.8 ± 0.6	2.9 ± 0.6	3.0 ± 0.6	0.172
V <sub>T</sub> (ml/kg), PBW	7.2 ± 1.0	7.2 ± 1.1	7.3 ± 0.9	0.753
PEEP (cmH <sub>2</sub> O)	8.5 ± 2.9	9.2 ± 3.3	9.6 ± 3.8	0.205
Plateau pressure (cmH <sub>2</sub> O)	25 ± 5.7	25.7 ± 6.0	28 ± 5.6	0.003
Respiratory rate (breaths/min)	21.2 ± 6.2	21.3 ± 5.8	21.5 ± 6	0.951
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)	130 ± 41	117 ± 39.5	86.6 ± 26.9	0.00001
PaCO <sub>2</sub> (mmHg)	44.7 ± 11.7	46 ± 10.2	46.8 ± 11.3	0.558
No. organ failures	1.4 ± 1.1	1.4 ± 1.1	1.6 ± 1.3	0.646
Minute ventilation ≥ 10 (l/min), n (%)	17 (36.2)	67 (45)	42 (48.8)	0.371
Main causes of ARDS, n (%)				
Sepsis	16 (34)	46 (30.9)	29 (33.7)	0.868
Bacterial pneumonia	21 (44.7)	49 (32.9)	25 (29.1)	0.187

Villar, J., et.al. (2013) A universal definition of ARDS: the PaO<sub>2</sub>/FIO<sub>2</sub> ratio under standard ventilatory settings-a prospective, multicenter validation study *Intensive Care Medicine* 39 583-592.



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# Ventilation With Low Tidal Volumes in ARDS

## The New England Journal of Medicine

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VOLUME 342

MAY 4, 2000

NUMBER 18



**VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH  
TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY  
AND THE ACUTE RESPIRATORY DISTRESS SYNDROME**

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK\*



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# Ventilation With Low Tidal Volumes in ARDS

- The Acute Respiratory Distress Network
  - NEJM 2000;342:1301
  - Multicenter prospective randomized trial
  - 861 patients
  - Standard Group 12 cc/kg PlatP < 50
  - Low Vt Group 6 cc/kg PlatP < 30

*Mortality was 31% in low tidal volume group vs 39.8% in the standard Rx group, P = 0.007*



# Is Permissive Hypercapnea Beneficial in ARDS?

- Survival benefits are still unclear
- Has been associated with:
  - Reduced levels of protein leak
  - Reduced pulmonary edema
  - Reduced pulmonary inflammation
- Protective against free radical-mediated injury while preserving lung compliance

Marhong, J., & Fan, E. (2014) Carbon dioxide in the critically ill: too much or too little of a good thing? *Respiratory Care* (59) 10: 1597-1605



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# Corticosteroid Therapy

- Multiple trials have shown no survival benefits associated with steroid therapy.
- Marik, PE Crit Care Clin 2011: 27: 589-607
  - Did show some benefits in early severe cases and resolved cases
  - Showed improved gas exchange, shorter duration of mechanical ventilation, shorter length of stay in the ICU.
  - Only in early severe cases and unresolved ARDS



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# Neuromuscular Blockers

- Papazian, et.al. N Engl J Med 2010: 363 (12): 1107-1116
  - Reduction in mortality and no long term differences in muscle weakness
- Alhazzani, et.al. Crit Care 2013: 17
  - Follow-up meta-analysis that confirmed the findings of Papazian
- Most likely do to better patient-ventilator synchrony and reduction of early VILI.



# Neuromuscular Blockers

- Grawe, E.R, et.al. (2016) Respiratory Care 61 (6): 830-838
  - Hypothesized that the mechanism of action included:
    - Improving patient-ventilator synchrony
    - Decreasing oxygen consumption
    - Decreasing the systemic inflammatory response
  - Use of NMBAs can have a positive impact on mortality, ventilator days, and ICU length of stay.
  - Must use early
  - Sicker patients respond better



# High-Frequency Oscillatory Ventilation

- OSCAR and OSCILLATE trials
  - No reduction in mortality in adults with moderate to severe ARDS
  - Where these findings accurate?
  - How was the trial conducted?
  - How have these studies affected the use of HFOV?

Ferguson, N.D., et.al. (2013) High-frequency oscillation in early acute respiratory distress syndrome. *The New England Journal of Medicine* (368) 9: 795-805

Young, D., et.al. (2013) High-frequency oscillation for acute respiratory distress syndrome. *The New England Journal of Medicine* (368) 9: 806-813



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# Flaws in OSCAR and OSCILLATE

## OSCAR

### STUDY DESIGN

We conducted a randomized, controlled trial of HFOV, as compared with conventional mechanical ventilation. Patients were recruited from adult general intensive care units (ICUs) in 12 university hospitals, 4 university-affiliated hospitals, and 13 district general hospitals in England, Wales, and Scotland. Three hospitals had previous experience with HFOV with the use of SensorMedics 3100B ventilators (CareFusion), and the remainder had limited experience (in 6 hospitals) or no experience (in 20 hospitals) with HFOV. Details regarding HFOV training are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The full protocol is also available at NEJM.org.

Ferguson, N.D., et.al. (2013) High-frequency oscillation in early acute respiratory distress syndrome. *The New England Journal of Medicine* (368) 9: 795-805

Young, D., et.al. (2013) High-frequency oscillation for acute respiratory distress syndrome. *The New England Journal of Medicine* (368) 9: 806-813

## OSCILLATE

measured in the trachea.<sup>35-37</sup> It is possible that an HFOV protocol that uses lower mean airway pressures, a different ratio of inspiratory-to-expiratory time, or a lower oscillatory frequency might have led to different results.

Physicians prescribed fluids, sedatives, neuromuscular blockers at their discretion.



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# Should High-Frequency Ventilation in the Adult Be Abandoned?

For HFOV to be a safe and effective therapy in ARDS, it needs to be used in the right patient (severe hypoxemic respiratory failure, failing conventional ventilation), with the right expertise and device settings, and with the right hemodynamic monitoring/management strategy. Another important consideration is knowing when to stop HFOV as ineffective. In general, observational studies suggest that if HFOV is going to be effective, gas exchange improvements will occur over the first 6–12 h. If this does not occur, the likelihood of HFOV success is low, and alternative rescue strategies, such as extracorporeal membrane oxygenation, should be considered.

Nguyen, A.P., Schmidt, U.H., & MacIntyre, N.R. (2016) Should High-Frequency Ventilation in the Adult Be Abandoned? *Respiratory Care* (61) 6: 791-800



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# So Is HFOV Effective?

- Camporota, et.al. performed a retrospective observational study
  - Aimed at describing physiological predictors of survival during HFOV in severe ARDS.
  - Showed that HFOV was effective in improving oxygenation when instituted early.
  - Changes in  $\text{PaO}_2/\text{FIO}_2$  are sensitive criteria to predict survival.
  - Change in  $\text{PaCO}_2$  may identify patient with a greater proportion of recruitable lung
  - Patient who do not show improvement within 6 hours will benefit from other modalities

Camporota, L., et.al. (2013) Physiologic predictors of survival during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Critical Care* (17): 1-10



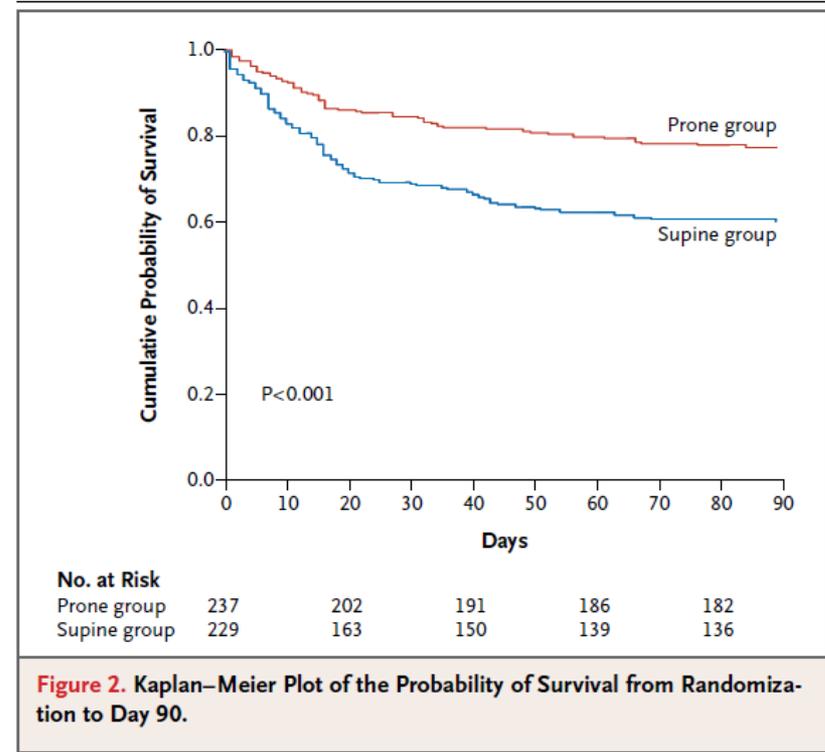
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# Prone Positioning

- PROSEVA study
  - Multicenter, prospective, randomized, controlled trial
  - Evaluate the effect of early application of prone positioning in patients with severe ARDS.
  - Significant decrease in 28-day and 90-day mortality



Guerin, C., et.al. (2013) Prone positioning in severe acute respiratory distress syndrome. *The New England Journal of Medicine* (368) 23: 2159-2168

# APRV and ARDS

- Lim, et.al. conducted a retrospective observational study
  - Patients with ARDS based on Berlin criteria
  - $\text{PaO}_2/\text{FIO}_2$  ratio was significantly improved within 24 hours
  - Low incidence of barotrauma
  - And lower incidence of need for ECMO

Lim, J. et.al. (2016) Characteristics and outcomes of patients treated with airway pressure release ventilation for acute respiratory distress syndrome: a retrospective observational study. *Journal of Critical Care* ), <http://dx.doi.org/10.1016/j.jcrc.2016.03.002>



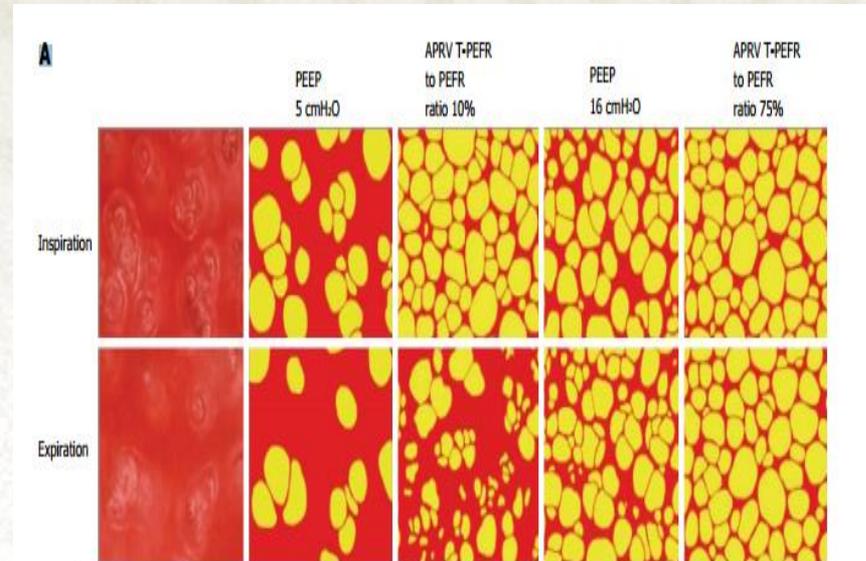
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# Preventing Acute Lung Injury using APRV

- Sadowitz, et.al., looked at early treatment of ARDS
- Looked at using APRV as a protective ventilatory strategy



Sadowitz, B., et.al. (2016) Preemptive mechanical ventilation can block progressive acute lung injury.  
*World Journal of Critical Care Medicine* (5) 1: 74-82

# Should APRV Be The Primary Mode in ARDS?

- 2016 Pro-Con article in *Respiratory Care* by Eduardo Mireles-Cabodevila and Robert Kacmariek

large tidal volumes leading to lung injury). Finally, we do not have evidence that APRV (as originally described) improves relevant clinical outcomes of patients with ARDS. For APRV to become the primary mode of ventilation for ARDS, it will require development of sound protocols and technological enhancements to ensure its performance and safety. For now, APRV does have a greater potential for adversely affecting patient outcome than improving it; unless definitive data are forthcoming demonstrating outcome benefits from the use of APRV in ARDS, there is no reason to consider this approach to ventilatory support. *Key words: Airway pressure release ventilation,*

Mireles-Cabodevila, E. & Kacmarek, R.M. (2016) Should Airway Pressure Release Ventilation Be the Primary Mode in ARDS? *Respiratory Care* (61) 6: 761-773



# Nitric Oxide and ARDS

- Adhikari, N.K.J. et.al. preformed a systematic review and meta-analysis
  - Use of inhaled nitric oxide to treat ALI/ARDS
  - No significant effect on hospital mortality
  - No effect on mean pulmonary arterial pressure
  - Increased risk of developing renal dysfunction

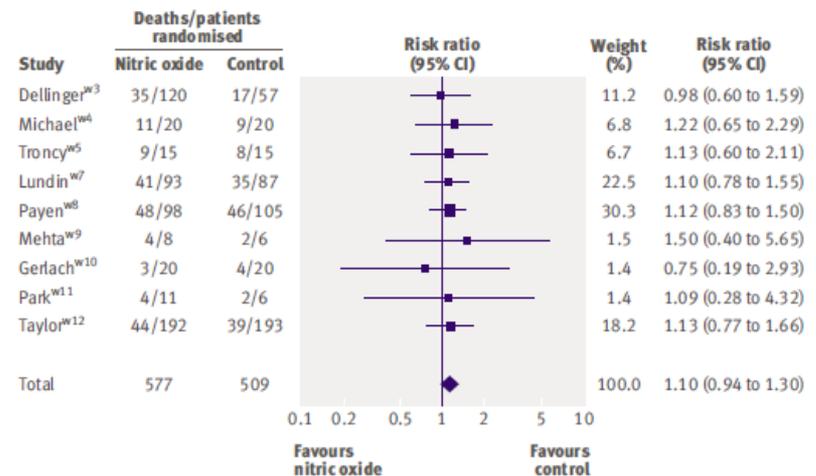


Fig 2 | Effect of nitric oxide on mortality. Weight is the relative contribution of each study to the overall estimate of treatment effect on a log scale assuming a random effects model. Two trials with  $\geq 50\%$  of control patients crossing over to nitric oxide also reported mortality data.<sup>w1,w5</sup> Inclusion of these trials did not alter summary mortality estimate (risk ratio 1.09, 0.94 to 1.27)

Adhikari, N.K.J., et.al. (2007) Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis  
*British Medical Journal* doi:10.1136/bmj.39139.716794.55

# ECMO for ARDS

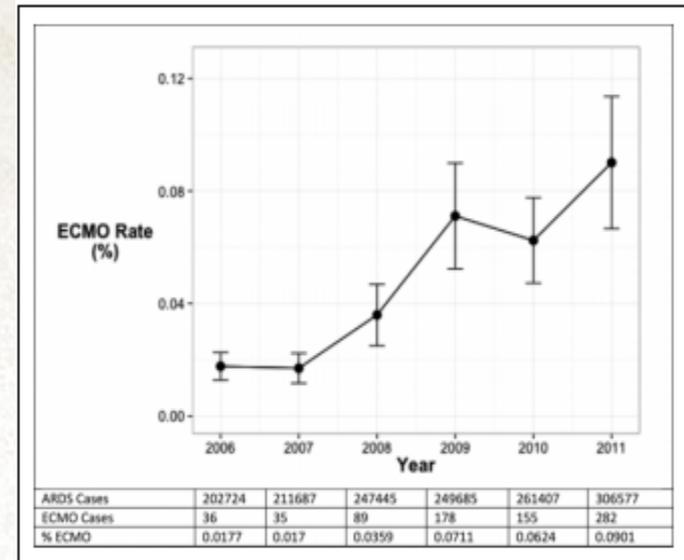
- Bosage, P.L., et.al. performed a retrospective study.
  - Study limited to trauma patients diagnosed with severe ARDS using Berlin definition.
  - Primary outcome of interest was mortality.
  - Secondary outcomes:
    - Hospital LOS
    - ICU free days
    - Ventilator free days
  - Showed an improvement in mortality

Bosage, P.L., et.al. (2016) Early initiation of extracorporeal oxygenation improves survival in adult trauma patients with severe acute respiratory distress syndrome. *Journal of Trauma Acute Care Surgery* <http://www.ncbi.nlm.nih.gov/pubmed/27032012>



# Trends in Using ECMO for ARDS

- Rush, B. et.al. used the nationwide inpatient sample to investigate trends in ECMO usage in ARDS.
- They discovered a dramatic increase in ECMO use for ARDS in the US.



**Figure 2.** Trend in the utilization of extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome (ARDS) during the study period, test for trend  $P = .0041$ .

Rush, B. et.al. (2016) Trends in extracorporeal membrane oxygenation for the treatment of acute respiratory distress syndrome in the United States.

*Journal of Intensive Care Medicine* DOI: 10.1177/0885066616631956



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# Are We Consistent in Recognition and Management of ARDS?

- Bellani, G. et.al. evaluated ICU incidence and outcomes of ARDS.
  - International multicenter, prospective cohort study
  - 459 ICUs and 50 countries
  - Primary outcome: ICU incidence of ARDS
  - Secondary outcomes:
    - Assessed clinical recognition
    - Ventilator management
    - Use of adjunctive therapies

Bellani, G. et.al. (2016) Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries  
*JAMA* 315 (8): 788-800



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# Albuterol For ALI? (ALTA Trial)

- Multicenter, randomized, placebo-controlled clinical trial
- 282 patients with ALI received 5 mg albuterol or saline placebo.

**Conclusions:** These results suggest that aerosolized albuterol does not improve clinical outcomes in patients with ALI. Routine use of  $\beta_2$ -agonist therapy in mechanically ventilated patients with ALI cannot be recommended.

Randomized, placebo-controlled clinical trial of an aerosolized beta-2 agonist for treatment Of acute lung injury (2011) *American Journal of Respiratory and Critical Care* 184 (5) 561-568



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# Blood Lactate Monitoring in Critically Ill Patients

- Should we have continuous monitoring of blood lactate levels?
- Is it cost effective to do this?
- Will this change our clinical plan?
- Results
  - Unknown whether lactate monitoring can be use as a resuscitation end-point.

Jansen, T.C., van Bommel, J., & Bakker, J. (2009) Blood lactate monitoring in critically ill patients: A systematic health technology assessment. *Critical Care Medicine* 37: 2827-2839.



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# Clearing Lactate as a Predictor of Mortality

- Dezman, et al. conducted a retrospective chart review of patients admitted for trauma.
  - 18,000 patients had initial lactate measurement
  - 3800 patients had lactate clearance monitoring
  - The mortality rate among patients with an elevated lactate that did not decline was nearly seven times higher than patients who lactate did normalize.

Dezman, Z.D.W. et.al. (2015) Failure to clear lactate predicts 24-hour mortality in trauma patients. *Journal of Acute Care Surgery* 79 (4): 580-585.

# Protocol Management for Septic Shock Management

- The ProCESS investigators
- 31 EDs in the US
- Randomly assigned patients
  - Protocol-based EGDT
  - Protocol- based standard therapy
  - Usual care
- No significant advantage, with respect to mortality or morbidity, of protocol-based resuscitation over MD judgement

The ProCESS Investigators (2014) A randomized trial of protocol-based care for early septic shock  
*The New England Journal of Medicine* 370 (18): 1683-1693.



# Comparative effectiveness of budesonide/formoterol combination and tiotropium bromide among COPD patients new to these controller treatments

This article was published in the following Dove Press journal:  
International Journal of COPD  
28 September 2015  
[Number of times this article has been viewed](#)

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**Background:** Inhaled corticosteroid/long-acting  $\beta_2$ -agonist combinations and/or long-acting muscarinic antagonists are recommended first-line therapies for preventing chronic obstructive pulmonary disease (COPD) exacerbation. Comparative effectiveness of budesonide/formoterol combination (BFC, an inhaled corticosteroid/long-acting  $\beta_2$ -agonist combination) vs tiotropium (long-acting muscarinic antagonist) in the US has not yet been studied.

**Methods:** Using US claims data from the HealthCore Integrated Research Environment, COPD patients (with or without comorbid asthma)  $\geq 40$  years old initiating BFC or tiotropium between March 1, 2009 and February 28, 2012 and at risk for exacerbation were identified and followed for 12 months. Patients were propensity score matched on demographics and COPD disease severity indicators. The primary outcome was time to first COPD exacerbation. Secondary outcomes included COPD exacerbation rate, health care resource utilization, and costs.

**Results:** The Cox proportional hazards model for time to first exacerbation yielded a hazard ratio (HR) of 0.78 (95% CI = [0.70, 0.87],  $P < 0.001$ ), indicating a 22% reduction in risk of COPD exacerbation associated with initiation of BFC versus tiotropium. A post hoc sensitivity analysis found similar effects in those who had a prior asthma diagnosis (HR = 0.72 [0.61, 0.86]) and those who did not (HR = 0.83 [0.72, 0.96]). BFC initiation was associated with lower COPD-related health care resource utilization and costs (\$4,084 per patient-year compared with \$5,656 for tiotropium patients,  $P < 0.001$ ).

**Conclusion:** In COPD patients new to controller therapies, initiating treatment with BFC was associated with improvements in health and economic outcomes compared with tiotropium.

**Keywords:** COPD, inhaled corticosteroid/long-acting  $\beta_2$ -agonist combinations, long-acting muscarinic antagonist, comparative effectiveness, administrative claims



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# Future Research Areas in Respiratory Therapy (Just My Thoughts)

- Effectiveness of RTs as pulmonary disease navigators.
  - Have outcomes improved
  - Are hospitalizations reduced
- Weaning from mechanical ventilation
  - Everyone gets an SBT or we screen patients and then do an SBT.



# Future Research Areas in Respiratory Therapy (Just My Thoughts)

- Triage RT in the ED
  - Will patients get treated faster?
  - Can we prevent hospitalizations?
  - Can we serve as an educational resource?
- RT as a discharge planner
  - How would this role affect readmission rates?
  - Another opportunity to make sure patients get the education they need?



# Future Research Areas in Respiratory Therapy (Just My Thoughts)

- RT role in managing chronic pulmonary illness as a global public health issue.
  - Identify at risk populations
  - Identifying certain socioeconomic factors that put certain patients at risk.
  - Role as a consultant to stakeholders in the community.



Questions and Thank You  
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