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.

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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
The Problem with Evidence

- Availability
- Access
- Analysis
- Shifting Sand
- Prioritizing
Where Do We Start?

What is PubMed?

• Developed and maintained by the National Center for Biotechnology Information.
• Ran through the National Library of Medicine.
• Free access to citation and abstracts in several health fields.
• PubMed Central®
  – 4.4 Million Articles
  – 2016 Full Participation Journals
Respiratory Care

CURRENT ISSUE
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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

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

- Meta-Analysis
- Systematic Review
- Randomized Controlled Trial
- Cohort studies
- Case Control studies
- Case Series/Case Reports
- Animal research/Laboratory studies

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Five Phases of Research

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

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.
Now Let’s Look at Some Research and Decide
Lung Protective Ventilation for Surgical Patients

Lung Protective Ventilation for Surgical Patients

Importance of Separating into Three Phenotypes

Villar, J., et.al. (2013) A universal definition of ARDS: the PaO$_2$/FiO$_2$ ratio under standard ventilatory settings-a prospective, multicenter validation study

What Helps Us Identify ARDS Phenotypes?

Ventilation With Low Tidal Volumes in ARDS
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

Corticosteroid Therapy

- Multiple trials have shown no survival benefits associated with steroid therapy.
  - 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
Neuromuscular Blockers

  – 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

  - 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?


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.

OSCILLATE

measured in the trachea.\textsuperscript{35-37} 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.


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.
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 PaO$_2$/FIO$_2$ are sensitive criteria to predict survival.
  - Change in 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

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

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

Preventing Acute Lung Injury using APRV

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

Should APRV Be The Primary Mode in ARDS?

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

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


*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

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
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 β₂-agonist therapy in mechanically ventilated patients with ALI cannot be recommended.

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.

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.

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

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

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) ≥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
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
Email: linabnit@uncc.edu

THANK YOU FOR YOUR TIME
BEST PRESENTATION EVER