Assessing Innovations In Respiratory Care

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Assessing Innovations In Respiratory Care

• What is an innovation?
• Approaches to assess before adoption
• Case Studies

Examples: Resp Care Innovations

• Devices
  – Ventilator features
  – Aerosol system
• Drugs
  – Inhaled
• Practices/processes
  – Ventilator protocols
  – QA systems

Clinical Assessments

• Basic constructs – Does it make sense? Does it address a specific problem/deficiency?
  – Engineering specs
  – Protocol or process design
• Phase I studies:
  – Does it work under carefully controlled conditions (beta tests, pilot studies)?
  – Are there any downsides?
• Phase II studies:
  – Does it work in real clinical situations/departments (observational trials)?
  – Are there any downsides becoming apparent?
• Phase III studies:
  – How does it behave in the "real world" compared to current standards?

Assessment End-Point Considerations Involve Cost and Risk of the Innovation

• Three tiers:
  – Engineering/design evaluation only:
    • Improved ease of use and reduced cost to operate
    • Conceptual clinical benefit with minimal costs/risks
  – Demonstration of an intermediate clinical benefit:
    • Physiologic benefit with some cost/risk attached
  – Demonstration of an improved meaningful clinical benefit:
    • Improved meaningful outcomes and/or significant risks or costs
Higher Costs/Risks Demand Greater Demonstrated Benefits

- Low risk/cost usually only requires demonstration that engineering/design claims verified
  - Tubing connectors, endotracheal tubes
- Moderate risk/costs usually require demonstration of some benefit
  - Staff time reduction, ventilator graphics design, nebulizers
- High risk/cost must come with a real clinical outcome benefit
  - Ventilator modes, ECMO

Other Considerations in Clinical Trial Design

- Patient selection
  - Does it reflect your population?
  - Beware of “dilutional” effects
- Sample size
  - Big enough to show a signal amidst the noise?
- Control group
  - Placebo vs usual care vs protocol simulating usual care
- Intervention quality
  - Intervention done right?

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Lung Protective Ventilator Strategies

Balancing need for support vs. distending pressures

Cris also better in the HIGH VT group

Long Inspiratory Time Strategies: APRV
APRV – Clinical Trials

  - 58 pts, no difference vs SIMV/PS
- J Trauma 2010; 69: 510
  - 64 pts, no differences vs ARDSnet
- Int Care Med 2010; 36:817
  - 234 pts, no differences vs “usual care”

Three RCTs: High vs Low PEEP Tables:
ARDS (n=585), Canadian (n=983) European (n=767)

<table>
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<th>Low PEEP</th>
<th>High PEEP</th>
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JAMA 2010;303:865
Table 1—Summary of Four Randomized Trials on Pressure Volumes

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<th>No. of patients</th>
<th>566 pts with P/F &lt; 150: 41 vs 24% mortality benefit</th>
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<td>Pressure</td>
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HFV in ALI/ARDS: 2010 Meta-analysis

- Key results from 6 peer reviewed studies:
  - Mortality reduced (RR 0.77, P=0.03), 5/6 trials
  - Treatment failures (RR 0.67, P=0.04), 5/6 trials
  - Barotrauma (RR 0.68, P=0.2)
  - VFDs not consistently reported – no obvious difference
- Physiology:
  - Consistently better PaO2/FiO2 but comparable OI

OSCAR and OSCILLATE Trials

- 2 large RCTs – OSCAR equivalent, OSCILLATE suggested harm
- Concerns (both):
  - HFO expertise low – HFO settings counter-intuitive
  - Concerns (OSCILLATE)
  - High Paw protocol in setting of shock/inexperience
- My take:
  - Clinician skill important – especially with high mean P and hemodynamic compromise

- Should not expose pts with adequate lung protection on CV to risks of HFO (fluid balance, NMBs)
- Still reasonable option in patients who are failing lung protective conventional ventilation
Inhaled Nitric Oxide in ALI/ARDS

- Multiple studies have demonstrated transient improvements in oxygenation with the use of inhaled nitric oxide for acute lung injury.
- But, no study has demonstrated improved survival with the administration of inhaled nitric oxide for acute lung injury.
- Also, concerns about toxic free radical development
- Could inhaled prostaglandins be a cheaper alternative?

Conventional Ventilation vs ECLS in Severe Acute Respiratory Distress Syndrome

- 180 patients with severe “potentially reversible” ARDS in UK
- Randomized to “usual care” or sent to one center for ECLS
  - Not all received ECLS – died en route, “too healthy”
- ITT survival:
  - 63% ECLS vs 46% usual care
  - P = 0.03

Late Stage Steroids in ARDS

- Concept: Steroids may reduce fibrosis in healing phase of ARDS
- 180 ARDS patients past 7 days without infection – steroids vs placebo
- Two days less on vent with steroids
- BUT most reintubated in 48 hours

Nothing is risk-free
ARDS mediator modulation—Some of the more spectacular failed clinical trials ($billions in costs)

- Anti-endotoxin antibodies
- Ibuprofen
- anti-TNF
- ketoconazole
- lypoiphyline
- PGE

ARDS -failed mediator clinical trials

- Failures due to:
  - Bad drugs/concept?
    - In vivo activity may be different than in vitro
  - Inappropriate dosing?
    - Timing issues, tissue penetration
  - Effects of co-morbidities NOT present in animals?
  - Bad study design?
    - Sample size, realistic endpoints, biologic activity
  - Wrong patients/heterogeneous “dilution”?
    - Importance of mechanistic diagnoses

Clinical Trials to Assess RC Innovations: Lessons Learned

- ARDSnet: showed “disconnect” between physiology and clinical outcome
- PEEP trials/Proning: showed importance of large sample size/meta analyses
- HFO/steroids: showed importance of proper application of innovation
- ECMO: showed importance of control group
- NO/APRV: await larger numbers before discarding
- Failed mediator trials: showed importance of patient selection

Assessing Innovations In Respiratory Care

- What is an innovation?
  - Device, drug, process
- Approaches to assess before adoption
  - Higher cost/risk demand clinical outcome benefit
- Case Studies
  - Underscore the challenges of clinical trial design