PETAL Network
Challenges and Opportunities

Critical Care Canada Forum
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Chair, PETAL Network Steering Committee
PETAL Network

- History
- Objectives, Guiding Principles
- PETAL Network Structure
- Challenges to Prevention Trials
- Current Status
PETAL Network
Relationship to ARDS Network?

1995-2013
NIH ARDS Network
Multicenter Trials of Promising Approaches for Treatment of ARDS

- Ketoconazole
- Lower Tidal Volume Ventilation
- Lisofylline
- Corticosteroids in Late Phase of ARDS
- Central Venous vs PA Catheters
- Liberal vs Conservative Fluid Management

- Albuterol
- Omega-3 Fatty Acids and Antioxidants
- Trophic vs Full Enteral Feeding
- Rosuvastatin
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An NHLBI Workshop Report

Beyond Mortality
Future Clinical Research in Acute Lung Injury

Roger G. Spragg1, Gordon R. Bernard2, William Checkley3, J. Randall Curtis4, Ognjen Gajic5, Gordon Guyatt6, Jesse Hall7, Elliott Israel8, Manu Jain9, Dale M. Needham9, Adrienne G. Randolph10, Gordon D. Rubenfeld11, David Schoenfeld12, B. Taylor Thompson13, Lorraine B. Ware2, Duncan Young14, and Andrea L. Harabin15

Am J Resp Crit Care 181: 1120, 2010

Prioritized Recommendations

1. “Highest priority” - Phase III trials to optimize ICU care and interventions
2. ARDS prevention trials – collaborate with Emergency Medicine
3. Outcomes other than mortality; composite outcomes
August, 2013

“The Network will develop and conduct randomized controlled clinical trials to prevent, treat, and/or improve the outcome of adult patients with or at risk for … ARDS.”
Differences Between PETAL and ARDSNet

- *Prevention* and Early Treatment (3-5 RCTs)
- Emergency Medicine/Acute Care/Trauma + Critical Care
- Establish and utilize a central IRB
- Dialog, Collaboration, Exchange
  - International Partnership Committee
  - Canadian Clinical Trials Group Representative on PETAL Steering Committee
  - Advisory Committee - CCCTG, ANZICS, and UK-CRN
  - Website portal for feedback and suggestions: www.petalnet.org/
12 PETAL Clinical Sites and CCC

~ 40 hospitals
LA, OR, ME, VA, MS
PETAL Network Steering Committee

• 12 Clinical Centers
  • Two PIs – Critical Care, Emergency Medicine/Acute Care/Trauma
• Clinical Coordinating Center
  • Biostatistics, trial design
  • Communications: web site, webinars, conference calls, meetings
  • Data management
• Steering Committee Chair
• Canadian Clinical Trials Group representative
• NHLBI Division of Lung Disease
PETAL Network
Standing Committees and Working Groups

• Ethics and Conflict of Interest
• Publications
• Pathogenesis
• Long-term Outcomes
• Natural History
• Institutional Support
• International Partnership
Central IRB (Vanderbilt)

- One IRB to review protocol, consent form, adverse events, ....
- Local context info provided by local IRBs
- Local IRBs cede to cIRB
- cIRB provides approval letter and consent to local IRBs
- If SAEs, cIRB works with local IRB to investigate
Prevention Trials

Challenges

• Who is at risk for ARDS?
Lung Injury Prediction Score (LIPS)

Overall Sensitivity 69%; Specificity 78%
- Positive Predictive Value only 18%
Best dichotomous cut-off >4
Area under ROC curve 0.80

Gajic, AJRCCM 2010
Prevention Trials

Challenges

• At risk for ARDS?
• Lower mortality in patients at-risk for ARDS
  – Huge enrollment necessary to demonstrate small absolute differences in mortality
  – Resources?
1995

ARDS Network Lower Tidal Volume Trial

• Assumed control group mortality = 50%
• Estimated lower tidal volume mortality = 40%
• Type 1 Error .05
• Type 2 Error .90

Sample Size: 1000 Subjects
Prevention and Early Treatment

**Challenges**

At risk for ARDS – Mortality ~15%

~4,000 subjects needed to demonstrate a 20% relative reduction in mortality (to 12%)

(PETAL Network funded to enroll 2,640 patients, total)
PETAL Network
Composite Endpoints Considered

• % ARDS after enrollment
• Ventilator-free days
• ICU-free days
• Mortality + Persistent Organ Dysfunction at 28 days
PETAL STATUS

- Funded July 2014 for 7 years
- First meeting June, 2014
- Biweekly webinars
- Many committee meetings
- Twice yearly in-person meetings
- SC developing protocols
- Begin enrollment in 2015
NIH PETAL Network Trials
October, 2015

• Enrolling
  – Neuromuscular blockade in established ARDS

• Protocol development
  – Vitamin D in at-risk patients
  – Lower tidal volume ventilation in at-risk patients
  – Fluid management in septic shock
Thank you
Designs Under Consideration

• Large pragmatic trials of interventions likely to be safe using mortality as the primary endpoint
  – Prevention of ARDS (or intubation or PPV) as main secondary endpoints
  – Evaluation of ARDS as an endpoint will guide future trial design

• Use of composite endpoints (e.g. VFDs)
  – May allow for a smaller sample size

• Cluster randomized trials
  – Most appropriate for some “process of care” interventions
  – Consider waiver of consent if applicable
Efficacy vs Effectiveness Trials

**Efficacy Trials**
Demonstrate that a new therapy works in carefully controlled experiments
- Many exclusions
- Costly
- Skeptics – efficacious therapy may not be adopted

**Effectiveness Trials**
Demonstrate that a new therapy works in “the real world”
- Few exclusions
- Lower cost/subject
- Many more subjects
- Potentially efficacious therapy may not work
Proposals Submitted

- Novel Approaches, New Applications
  KGF, GMCSF, Aerosolized rhDNAse, Stem Cells, Azithromycin, Rosuvastatin, CO, NIV, Vit C, Zinc, Anti-platelet

- Process of Care Management
  NMB, Checklist, Post discharge intervention, Extracorporeal Gas Exchange, NIV
Sample Size for Mortality

- In the LIPS Validation cohort 5,584 at-risk patients,
  - overall mortality = 5.1%
  - ARDS = 6.8%
  - fatal ARDS = 1.6%
- If New Rx prevented half the ARDS cases, overall mortality decreases 5.1 to 4.3%.
  - n = 20,000 to detect this effect
Design Considerations for Prevention Trials

• How to identify patients at risk for ARDS?
• Lower mortality in patients at-risk for ARDS
• Is development of ARDS the right endpoint?