David Ingbar, MD, is Professor of Medicine, Pediatrics and Integrative Biology & Physiology and Director of the Pulmonary Allergy, Critical Care Division at the University of Minnesota (UMN). He received his medical degree from Harvard Medical School after growing up in Boston suburbs and graduating with a BA from Reed College in Portland, Oregon. He completed his medicine residency and chief residency at the University of Washington and his Pulmonary Critical Care Fellowship at Yale University School of Medicine. He was an Assistant Professor of Medicine and Cell Biology at Yale University until his recruitment to University of Minnesota in 1991. Dr. Ingbar’s research is on the cell biology of repair of the injured lung with a specific focus on alveolar epithelial cell repair and clearance of pulmonary edema fluid and his clinical interests are ARDS, hemoptysis and respiratory failure. He has received multiple research grants from the NIH, American Lung Association and American Heart Association and is the principal investigator for a NHLBI T32 research training of predoctoral students and post-doctoral MD and PhD fellows. He is Associate Director of the NIH-funded UMN Clinical Translational Science Institute, directing the Research Education, Training and Career Development Core. He is a past president of the American Thoracic Society and of the Association of Pulmonary & Critical Care Medicine Program Directors. He served for 6 years on the ABIM Pulmonary Board.

OBJECTIVES:
Participants should be better able to:

1. Identify what is the current overall mortality from ARDS in non-ARDS network clinical reviews;
2. Identify which treatments have proven survival benefit in ARDS.
Disclosures

- Honoraria received for lectures on unrelated topics from Glaxo Smith Kline, Pfizer, Bayer & Boehringer Ingelheim
- Adverse event review board for Merck – pulmonary complications of drug for osteopenia (past)
- Prior site PI for phase I, II & III studies of recombinant human SP-C (Venticute) for ARDS - developed by Byk Gulden
CASE 1A

- 23 yo U Minnesota MD-PhD student presented to student health service with 3 days of worsening SOB, cough, fevers and chest tightness
- No prior medical illnesses
- Exam:
  - Ill appearing male with HR 94, RR 22, Temp 37.5;
  - Posterior crackles R>L
- Labs:
  - WBC 14K with left shift
  - CXR: diffuse patchy densities
- Dx: “Atypical Pneumonia”
- Rx: Azithromycin

Case 1B

- Next AM returns to ER with worsening SOB
- ER eval notable for O2 sat in low 80% range
- CXR: increased diffuse densities – becoming consolidated
- RA ABG: 7.52 / PaCO2 25 / PaO2 52
- Admitted to ICU and given iv Abx & fluids
- Within 12 hours requires intubation, mechanical ventilation with high FiO2 and PEEP 14
Case 1C

- Remains persistently hypoxemic requiring FiO2 > 0.9 to maintain O2 sat > 90% and/or PaO2 > 50
- Intermittently hypotensive
- Inhaled nitric oxide modestly improves oxygenation
- Bronchoscopy with BAL cytology reveals fungal elements (& ? Mycobacteria)
- Treated empirically with amphotericin B and anti-mycobacterial Rx
What are the Current Epidemiology & Outcomes?

Mortality
Function & Quality of Life

ARDS Epidemiology
King County c.2005

- Age adjusted incidence = 86 per 100,000 person-years
- In-hospital mortality = 38.5%
  - (60% in patients > 85 y.o.)
- 191,000 annual cases in US
- 74,500 estimated annual deaths US
- 2.1 million estimated annual ICU care days
- Cost/case ~ $160K Canadian in 2006

Rubenfeld et al NEJM 2005; 353:1685-93
Cheung et al; AJRCCM 174:542, 2006
ARDS Question 1
Which of the following ARDS causes is associated with better prognosis?

- Sepsis
- Trauma
- Pneumonia
**ARDS: Age-dependent Incidence & Mortality**  
*(King County)*

Rubenfeld et al NEJM 2005; 353:1685-93

**ARDS Mortality: Progress?**

Crude 60 day mortality of ARDS  
Net patients 1996 – 2005  (p value trend 0.19 for low Vt)  
SE Erickson et al, for the NIH NHLBI ARDS Network;  
Critical Care Medicine 3/25/09

“Conclusions: A decrease in ARDS mortality was only seen in observational studies from 1984 to 1993. Mortality did not decrease between 1994 (when a consensus definition was published) and 2006, and is lower in RCTs than observational studies.”  
Phua et al AJRCCM 2009
**ARDS – Current Standard Rx**

**Source Control**
- Treat underlying risk factors – infection, DIC, etc

**Supportive Care:**
- Maintain adequate oxygenation & gas exchange
- Minimize additional lung injury
- Minimize extravascular lung water
- Insure adequate nutrition
- Avoid other iatrogenic ICU complications (VTE, nosomial pneumonia, stress ulcers, …)

**Specific Therapy: ??**

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**ARDS Question 2**

Which of the following improves overall survival in patients with ARDS?

- Recruitment maneuvers
- High dose steroid therapy in late phase ARDS
- Prone ventilation
- N-acetyl cysteine
- Inhaled nitric oxide
Specific ARDS Therapy

<table>
<thead>
<tr>
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<td>Antioxidant vitamins</td>
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<td>Swan Ganz use</td>
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ARDS Rx

\[ \text{High Tech Babysitting} \]

**High Tech Babysitting – Mechanical Ventilation**

*Mechanical Ventilation Issues:*
- Which type of ventilator?
- What mode of ventilation?
- What tidal volume is optimal?
- How should alveoli be recruited?
- What is the optimal level of PEEP?
- Relative injury from high FiO2 vs P
**ARDS Network Vt Trial**

**Improvement:**
- 9% *absolute* reduction in mortality

**Surprises:**
- Low Vt group had normal PaCO2
- Low Vt group had worse oxygenation for first 3 days

**Controversies:**
- Which is more important: limit Vt or Plateau P?
- Must we limit both?
- What is the optimal Vt?
- What is the proper control group?
- How long to continue?
- What if pt ‘wants’ bigger Vt?

---

**ARDS Relative Risk of Hospital Death Depends on Driving P**

![Graph showing ARDS Relative Risk of Hospital Death Depends on Driving P](image)

Amato et al. NEJM 372:747, 2015
VILI – Rat Model

Peak Airway Pressure/PEEP

Tierney & Webb
Am Rev Respir Dis 1973

FUNCTIONAL OUTCOMES POST ARDS

"As you can see, we've transferred your husband from intensive to casual care."
Neurocognitive Dysfunction Post ARDS

- Neurocognitive sequellae are common
  - 73% at discharge; ~ 45% @ 1 & 2 years
- Memory difficulty and weakness are very common
- Depression (moderate – severe): 16-40%
- Anxiety: (24%)
- PTSD criteria met in ~ 25%
- Half are jobless at 1 year
- Most improvement in 1st year; stable from 1-2 years

Weinert et al, Am J Respir Crit Care Med 156:1120, 1997
Hopkins et al, AJRCCM 171:340, 2005
Mikkelsen et al Am J Respir Crit Care Med 185:1307, 2012

Dysfunction & QOL in Survivors

- Are neurocognitive and QOL problems due to:
  - ARDS per se
  - Severity of illness (in general)
  - Drugs given (sedatives, etc)
- Does care in ICU affect frequency of late pulmonary &/or CNS dysfunction?
- Can prophylactic use of anti-depressants decrease depression in survivors?
Case 1D - Outcome

- Survives > 2 week ICU admission
- Gradually recovers with period of transitional care rehab stay
- No apparent neuropsychological deficits
- Returns to medical school (but abandons MD-PhD program)
- After residency, completes Pulmonary & Critical Care fellowships
- Now Pulmonary & CC practitioner in Colorado

How Can We Improve Outcomes?

What about specific therapy targeted to the disease process?
“Specific” ARDS Therapy

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Salvage Therapies for ARDS

Definition:
- Clinical improvements in subgroup (~ 1/3)
- No overall mortality improvement
- ? Which subgroups to Rx or empiric ??

Therapies:
- Surfactant replacement
- Inhaled nitric oxide
- High frequency ventilation/oscillation
- Partial liquid ventilation
- PCV or APRV
- ECMO or ECCO2R
Moving Towards Precision Medicine in ARDS

Can we identify prognostic molecular markers for good and poor outcomes?

Will the markers and their related pathways identify new molecular targets for therapy?

Differing Biological Processes in Early ARDS Survivors vs Non-survivors

Selected Canonical Pathways with Differing Expression in Early ARDS

- Ethanol degradation II, IV
- Oxidative ethanol degradation
- Fatty acid alpha-oxidation degradation
- Lipid aldehyde metabolism

*Theme:* proteins from these pathways are involved in NRF-ARE dependent cytoprotection via phase 1 and 2 detoxification

So now where are we?
Hypothesis

- Attempts to specifically treat ARDS have failed for two reasons:
  - 1) Too many simultaneous pathophysiologic pathways are activated for a single intervention to have major impact
  - 2) Intervention directed at early pro-inflammatory events is too late when clinical Dx is apparent
- Targeting therapy at speeding repair is more likely to be beneficial

Strategies to Augment Repair

- Decrease severity of early injury
  - Decrease inflammation, oxidants, proteases
  - Cytoprotection
- Decrease secondary amplifiers of injury
  - Infection
  - Ventilator-induced lung injury and O2 toxicity
- Accelerate alveolar fluid clearance
- Promote repair of epithelial barrier
- Decrease intra-alveolar fibrosis
  - Lessen provisional matrix formation
  - Prevent mesenchymal cell in migration
- Clear intra-alveolar granulation tissue – promote apoptosis

*LB Ware & MA Matthay, NEJM 2000*
Keratinocyte Growth Factor (KGF) & ARDS

- Multiple potential benefits:
  - Increased fluid resorption, Na transporters
  - Epithelial cytoprotectant
  - Increased surfactant lipid/apoprotein secretion
  - Preserved alveolar barrier with type II hypertrophy
- Pre-injury KGF Rx improves lung injury & survival in hyperoxia, radiation, bleomycin, acid aspiration
- Low dose systemic KGF pre-BMT improves survival and lung injury in animals

ARDS Rx with Surfactant Recombinant SP-C

- Improves oxygenation
- Doesn’t improve overall mortality
- May increase survival in most severely ill sub-group

Spragg et al; NEJM 2004
Apoptosis in ARDS

**EARLY ARDS**
- Alv epithelial apoptosis
  - Seen in human lungs (p53; WAF-1; BAX)
  - Induced by human BALF
- Oxidants, TNF, Fas – Fas ligand can induce alveolar & epithelial apoptosis
- **Interpretation:** Probably contributes to early injury

**CHRONIC PHASE ARDS**
- Dying/excess apoptotic PMNs specifically cleared by macrophages
- Intralveolar granulation & fibrotic tissue may be cleared by apoptosis
- Need to clear some hyperplastic type II cells for type I cell differentiation
- **Interpretation:** Important for lung repair

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Stimulation of Edema Fluid Absorption

**Potential Benefits**
- Improved gas exchange
- Lower airway pressures
- Less ventilator-induced lung injury
- Less oxygen toxicity

**Agents:**
- Beta Adrenergic Agonists
  - Intravenous salbutamol trial (BALTI)
  - ARDS Net trial
- Other approaches
  - Increase transporters – gene Rx
  - Thyroid hormone
Is it worth stimulating fluid transport in the face of an injured, leaky lung?

Diffuse severe injury with very high permeability

Ability to “Bail” out the boat likely is important

Mild - moderate injury with increased permeability

Clinical Trials of Beta Agonists in ARDS/ALI

- BALTI (Scotland)
  - iv salbutamol
  - initially positive results in 36 patients with improved oxygenation and lower EVLW
  - unpublished larger trial stopped due to harm

- ARDS Network
  - 282 pts in multicenter RDBPCT
  - albuterol/placebo nebulization q 4H
  - no difference in ventilator free days or mortality
  - shock subgroup had higher VFD but not less mortality
  - no measure of physiologic effect
Potential Problems with Using Beta Adrenergic Agonists to Increase AFC

- Downregulation &/or Desensitization of beta-adrenergic receptors
- Pre-existing high level of circulating endogenous catecholamines
- Side effects – cardiac, etc

GOAL

- Identify alternate pathways to stimulate alveolar fluid clearance, beyond beta adrenergic agonists
- Preference for working with drugs that already have been proven safe and are FDA approved
Why an Interest in T3 & the Lung?

- Alveolar type II epithelial cells have T3 receptor
- Thyroid hormone increases # and size of alveolar epithelial type II (AT2) cells
- Thyroid hormone increases surfactant synthesis & release by AT2 cells
- TRH may promote lung maturation
- Neonatal thyroid deficiency may be assoc with increased risk of RDS and TTNB
- T3 stimulates Na,K-ATPase gene transcription and/or activity in many cells and organs

Thyroid Hormone Stimulates AT2 Cell Na,K-ATPase and Alveolar Fluid Absorption

- T3 increases Na,K-ATPase gene transcription in many tissues
- In AT2 cells, T3 rapidly increases Na,K-ATPase activity by translocating cytoplasmic protein to plasma membrane
- Signaling Pathways
  - Src Kinase - PI3K – Akt Pathway
  - ERK (MAP Kinase pathway)
- IP T3 increases rat AT2 cell Na,K-ATPase activity in vivo

Lei et al. Am J Physiol (Lung) and J Biol Chem; Bhargava et al. AJRCCM 2008
T3 Stimulates AFC in Normal & Hyperoxic Lung

[T3] in Human ARDS Lung Tissue
Thyroid Hormone Metabolism

Deiodinase-3 inactivates both T4 and T3
Deiodinase-1 & 2 can increase T3

Deiodinase-3 Activity in Human ARDS Lung

![Bar chart showing velocity (fmol/mg/min) for Normal, Early ARDS, and Late ARDS phases, with significance markers for comparisons.](chart.png)
Clinical Trial of Instilled T3 in ARDS

- Goals - for instilled T3 assess:
  - Primary endpoint = Safety & tolerability
  - Secondary endpoints = EVLW; PaO2/FiO2 ratio
- Number of Subjects = 68 (34 Rx; 34 control)
- Main Inclusion Criteria
  - Clinical diagnosis of ARDS
  - Adult (≥18 years of age) and non-pregnant
  - Mechanical ventilation; arterial and central venous lines
- Intervention: instilled T3 (Liothyronine or Triostat) for 96 hours with dose escalation
- Statistical methodology: Non-inferiority analysis

ARDS: Why have almost all interventions failed thus far?

- Wrong targets
- Treatments ineffective on specific target
- Studies not well designed
- Treatment initiated too late
- Treating one aspect is too little to alter clinical outcome
Conclusions

- Stimulating repair is likely to be useful alternate to early intervention with single agents
- Clinically approved, safe agents are available that stimulate repair in animal models
  - T3 for fluid resorption
  - Recombinant human KGF – multifactorial
  - Pro-fibrinolytic therapies – APC, TFPI, ATIII
- Prior to human trials we need to:
  - Understand mechanisms
  - Prove efficacy in large animal trials

ARDS Rx: My Biases

- Successful intervention will require combination therapy a la combination chemoRx
- Don’t discard potential of a treatment just because it doesn’t work in isolation
- Need to have both supportive interventions and those that alter the disease process.
ARDS Treatment of 2020?

**Supportive Treatments:**
- Optimize mechanical ventilation
- Supplement antioxidants & antiproteases

**Specific Therapies**
- Cytoprotection – KGF
- Promote resolution of inflammation –
  - induce PMN apoptosis
- Pro-epithelialization therapy
- Pro-fibrinolytic therapy
- Pro-apoptotic therapy late

**Mixed Approaches**
- Surfactant replacement
- Increased alveolar fluid resorption

The Molecular Intensivist
2020 (?)

Pass me an endotracheal tube and start the KGF, T3, surfactant and Apo-Neb please
Co-Investigators

**Univ Minnesota**
- Scott O'Grady, Ph.D.
- O. Douglas Wangensteen, Ph.D.
- Timothy Rich, MD
- Grant Anderson, PhD
- Christine Wendt, M.D.
- Hyun Kim, M.D.
- Craig Henke, MD
- Peter Bitterman, MD
- Howard Towele, Ph.D.

**Elsewhere:**
- Cary Mariash, M.D., U Indiana
- John Shannon, Ph.D., U. Cincinnati
- Michael Caplan, M.D., Ph.D., Yale
- Edward Benz, M.D., Harvard
- Greg Gick, Ph.D. SUNY Brooklyn
- Kiyoshi Kawakami, Ph.D., Jichi U
- Stephen Huang, Ph.D. Harvard

**Present**
- Jianxun Lei, Ph.D.
- Maneesh Bhargava, M.D.
- Bing Zhou, Ph.D.
- Polly Hergert
- Tommy Bastian
- Tom Groppoli

**Past:**
- Xinpo Jiang, Ph.D.
- Ethan Carter, Ph.D.
- Hong Hao, Ph.D.
- Sogol Nowbar, M.D.
- Zhong Zhao, M.D., Ph.D.
- Kent Tegtmeyr, M.D.
- Gun Sandhu, M.D., Ph.D.
- Marie Runyon
- Patricia Jung
- Richard Rhodes, M.S.
- Robert Bair
- John Podobienski
The Big Picture

- Thyroid hormone plays significant role in regulation of alveolar fluid clearance
- In ARDS, increased lung deiodinase 3 activity may create a local deficiency of T3
- Does the sick euthyroid syndrome have potential adverse consequences, at least in specific organs?
- Local treatment of alveolar epithelium with T3 has potential to stimulate edema fluid absorption (and other beneficial effects – surfactant, etc)
- In vivo, T3 supplementation of rats decreases the lung inflammatory response to hyperoxia

Lung Repair in Chronic Phase ARDS

Observations:
- Variable clinical course of patients
- After 2 weeks relatively little ongoing mortality
- Most surviving patients recover much of their pulmonary function, even with severe prolonged injury

Questions:
- How do some patients recover rapidly after weeks/months of little progress?
- Why the wide dispersion in rates of recovery?
- How is recovery possible from severe injury?
- What is the role of genetic predisposition?
Differing Early vs Late Biological Processes in ARDS Survivors

- Early: Leukocyte, Lymphocyte immune response, Cellular di,tri-valent inorganic cation homeostasis, Iron ion homeostasis
- Late: Cell Migration, Actin filament based processes


BALF Proteome Differences in ARDS Survivors compared to Non-survivors

- High Survivors, 122
- High Non-Survivors, 52
- No difference, 1015

Inverse variance weighted t-test, FDR ≤5%

Shedding Some Light On the Subject

Why is ARDS Important?

- Residual high mortality (25-50%)
- Relatively common: 22–85 cases/100K person yrs
  - 200,000 cases per year in US
- Occurs in individuals with little underlying chronic disease
- Very expensive to treat
- Most survivors recover to relatively normal lung function, but often neuropsychologic sequellae
- Model to understand paradigms of injury and repair of the lung
Recovery of Pulmonary Function Post ARDS

- **PFTs**
  - FEV1 & FVC recover over 1st 6 - 12 months
  - DLCO recovers more slowly & less completely
  - Overall at 1 Yr:
    - 1/3 Normal;
    - 1/3 mildly abnl;
    - 1/3 mod or severely abnormal
- Exercise limitation is common for at least 2 yrs

### ARDS Network Low Vt Trial

- Randomized pts to conventional ventilation (Vt 12 ml/kg IBW) vs: {low tidal volume AND lower plateau airway pressure}
- Similar demographics: age (51-52); APACHE III (81-84); Non-lung organ failure (1.8); etiologies
- Low Vt group had:
  - Lower Vt (6.2 vs 11.8 mls/kg PBW)
  - Higher PEEP & FiO2, lower PaO2/FiO2 at days 1 & 3
  - Lower PEEP & FiO2 at day 7
  - Lower mortality rate (31 vs 40%)
  - Higher # Vent Free Days & days without NLOF
  - Greater fall in plasma IL-6 from day 0 to 3

*ARDS Network  NEJM 342:1301-8, 2000*
**BALF Proteomic Studies to Identify Molecular Pathways in ARDS**

**Pooled BALF of ARDS SCOR Patients**
- Samples collected 1988 – 1993
- Cell free supernatants
- Pooled as early (< 7 days) or late phase ARDS

**BALF from Contemporary ARDS Patients**
- Prospectively collected
- 20 Survivors and 16 non-survivors
- Median ages: 42 & 59
- Gender: 60% & 43% male
- Median 2 days post ARDS Dx (both groups)
- Median P/F ratios: 95 & 76

**Surfactant in ARDS**
- Reduced surface tension lowering function
- Change in composition – proteins and lipids
- Replacement therapy:
  - Exosurf: Aerosolized lipids only – no benefit
  - Beef extract with SPB, SPC – suggestive
  - Venticute – human recombinant SPC + PL
  - Surfaxin (KL4) – 21 AA SPB analog
- Immunomodulatory properties of SP-A
  - Decreases lung injury after mouse BMT
Cytoprotection & Antioxidant Defenses

- Cytoprotectants
  - Heat shock proteins
  - Keratinocyte growth factor
- Antioxidants
  - Extracellular superoxide dismutase
  - Antioxidant vitamins
  - ? Antioxidant cocktails

IM T3 & Dexamethasone Additively Stimulate Rat Lung AFC

Folkesson JAP 2000
Deiodinases & Lung Injury

- Lung injury increases D2 gene and protein expression in murine models
- Mice with reduced lung D2 levels (siRNA) have more severe lung injury (increased BAL protein and PMNs)
- In mice with VILI, D2 knockout mice have greater pro-inflammatory cytokine & chemokine levels. Changes are reversed by supplemental T3
- In humans the D2 G(Ala) allele of the Thr92Ala coding SNP (rs225014) was protective in severe sepsis and sepsis-associated ALI after adjustments for age, gender and genetic ancestry in European Americans
- D3 KO mice have impaired pneumococcal clearance

Ma, Garcia et al, AJRCMB 2011
Barca-Mayo, Weiss et al PNAS 2011

Trends in Mortality of Acute Lung Injury:
ARDS Network 1996-2005

Crude 60 day mortality of ARDS Net patients 1996 – 2005 (p value trend 0.19 for low Vt)

SE Erickson et al, for the NIH NHLBI ARDS Network;
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