ARDS – Endotypes and Phenotypes

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Disclosures

No relevant commercial interests

My work is funded by NIH R01HL087115, R01HL081619, R01HL096845, R01HL114626, R01HL113252, K24HL115354, and MaPGen: U01-HL108636

I have also received Institutional Grant Funding from GSK to study ARDS and critical illness.
Outline

• Definitions
• “ARDS” Endotypes
  – Clinical Pattern
  – Molecules
Definitions

• “Phenotype”
  – the composite of an organism's observable characteristics or traits
  – Genotype-phenotype distinction
    • 1911 Wilhelm Johannsen
    • Phenotype is the expression of the genotype
Definitions

• “Phenotype”
  – the composite of an organism's observable characteristics or traits
  – Genotype-phenotype distinction
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Definitions

• “Endotype”
  – A subtype of a condition defined by a distinct functional/pathobiological mechanism
  – Inherent in the process of syndrome evolution
    • MI → NSTEMI
  – A “functional paradigm”
    • Extrinsic asthma → IgE
    • Crohn’s → IL23R
Paradigm

- Paradigm
  - “collection of beliefs shared by scientists, a set of agreements about how problems are to be understood”
    - Kuhn: The Structure of Scientific Revolutions
  - Utility

- Can we shift the ARDS phenotype paradigm according to biology?
Why I care about ARDS phenotype

• TRANSLATIONAL GOALS

1) Understand genetic, genomic and protein risk factors for ARDS in human studies
2) Predict ARDS and identify mechanism-defined subgroups of ARDS
3) Prevent ARDS through targeted therapies and pharmacogenomic studies (PETAL)
Why I care about ARDS phenotype

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1) Understand genetic, genomic and protein risk factors for ARDS in human studies
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Predict, treat, and prevent what, exactly?
ARDS Definition

• 1994 Consensus Definition (Bernard)
  – PaO2/FiO2 <300
  – Chest x-ray c/w bilateral pulmonary edema
  – Absence of congestive heart failure
  – Used in ARMA

• 2011 Berlin Definition
  – Similar criteria, different semantics
# Predictive Validity of Berlin Definition

<table>
<thead>
<tr>
<th>Table 5. Predictive Validity of ARDS Definitions in the Physiologic Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified AECC Definition^a</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>No. (%) [95% CI] of patients</strong></td>
</tr>
<tr>
<td><strong>Mortality, No. (%) [95% CI]^b</strong></td>
</tr>
<tr>
<td>13 (20) [11-31]</td>
</tr>
<tr>
<td><strong>Ventilator-free days Median (IQR)</strong></td>
</tr>
<tr>
<td>8.5 (0-23.5)</td>
</tr>
<tr>
<td><strong>Missing, No.</strong></td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td><strong>Duration of mechanical ventilation in survivors, median (IQR), d</strong></td>
</tr>
<tr>
<td>6.0 (3.3-20.8)</td>
</tr>
<tr>
<td><strong>Lung weight, mg^c</strong></td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Missing, No.</strong></td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td><strong>Shunt, mean (SD), %^c,d</strong></td>
</tr>
<tr>
<td>21 (21)</td>
</tr>
</tbody>
</table>

Rubenfeld, JAMA 2012
Specificity of the *STAT4* Genetic Association for Severe Disease Manifestations of Systemic Lupus Erythematosus

Kimberly E. Taylor¹, Elaine F. Remmers², Annette T. Lee³, Ward A. Ortmann⁴, Robert M. Plenge⁵, Chao Tian⁷, Sharon A. Chung¹, Joanne Nititham¹, Geoffrey Hom⁴, Amy H. Kao⁸, F. Yesim Demirci⁸, M. Ilyas Kamboh⁸, Michelle Petri⁹, Susan Manzi⁸, Daniel L. Kastner², Michael F. Seldin⁷, Peter K. Gregersen³, Timothy W. Behrens⁴, Lindsey A. Criswell¹

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**Table 5.** rs7574865 association with phenotype status of cases in homogeneous analyses**

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Homogeneous OR*</th>
<th>Homogeneous p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe nephritis†</td>
<td>1.79 (1.20–2.67)</td>
<td>0.0039</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>1.48 (1.16–1.88)</td>
<td>0.0016</td>
</tr>
<tr>
<td>First PC†&gt;0</td>
<td>1.42 (1.12–1.79)</td>
<td>0.0033</td>
</tr>
<tr>
<td>Anti-dsDNA autoantibodies</td>
<td>1.40 (1.12–1.76)</td>
<td>0.0037</td>
</tr>
<tr>
<td>Diagnosis &lt;30 years</td>
<td>1.35 (1.07–1.70)</td>
<td>0.012</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>1.19 (0.94–1.52)</td>
<td>0.15</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>0.62 (0.49–0.79)</td>
<td>0.00010</td>
</tr>
</tbody>
</table>
Outline

• Definitions

• “ARDS” Endotypes
  – Clinical Pattern
  – Molecules
Is ARDS more than one syndrome?

• Are there patterns of ARDS following injury?
ARDS patterns based on timing of onset

• Severe Trauma Cohort
• Latent class models
  – timing and certainty of ARDS
  – 2 readers adjudication, all P/F
    • “Equivocal” for missing data, quality, disagreement
• Tested for discrimination of clinical variables
• Divergence of biological markers of injury
  – Lorraine Ware – VALID study

Reilly, AATS 2014
LATENT CLASS 1 – Early Onset (n=98, 52%)

- **Definite ARDS**
- **Equivocal**
- **Not ARDS**

Estimated Probability

Study Day

- Day 1
- Day 2
- Day 3
- Day 4
- Day 5
LATENT CLASS 2 – Late Onset (n=76, 40%)
LATENT CLASS 3 – Latest Onset (n=15, 8%)

- **Definite ARDS**
- **Equivocal**
- **Not ARDS**

Estimated Probability vs. Study Day

- Study Day 1: Definite ARDS - 0, Not ARDS - 0, Equivocal - 0.2
- Study Day 2: Definite ARDS - 0.5, Not ARDS - 0, Equivocal - 0.7
- Study Day 3: Definite ARDS - 1, Not ARDS - 0, Equivocal - 0
- Study Day 4: Definite ARDS - 0, Not ARDS - 0, Equivocal - 0.2
- Study Day 5: Definite ARDS - 0, Not ARDS - 0, Equivocal - 0.5
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Class 1 (n=98) Early Onset</th>
<th>Class 2 (n=76) Late Onset</th>
<th>Class 3 (n=15) Latest Onset</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>38 (22-50)</td>
<td>34 (23-48)</td>
<td>38 (21-53)</td>
<td>0.986</td>
</tr>
<tr>
<td>Male</td>
<td>79%</td>
<td>76%</td>
<td>80%</td>
<td>0.926</td>
</tr>
<tr>
<td>Race: African American</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>55%</td>
<td>47%</td>
<td>47%</td>
<td>0.567</td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2%</td>
<td>2%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>25 (20-32)</td>
<td>25 (19-29)</td>
<td>21 (18-29)</td>
<td>0.419</td>
</tr>
<tr>
<td>AIS Thorax (0-5)</td>
<td>4 (3-4)</td>
<td>3 (0-4)</td>
<td>2 (0-3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>APACHE III w/o ABG</td>
<td>59 (50-71)</td>
<td>58 (47-73)</td>
<td>58 (48-74)</td>
<td>0.821</td>
</tr>
<tr>
<td>Blunt Injury</td>
<td>74%</td>
<td>74%</td>
<td>67%</td>
<td>0.846</td>
</tr>
<tr>
<td>Pulmonary Contusion</td>
<td>40%</td>
<td>32%</td>
<td>20%</td>
<td>0.276</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td>16%</td>
<td>15%</td>
<td>21%</td>
<td>0.846</td>
</tr>
<tr>
<td>Lowest SBP – ED or OR, mm Hg</td>
<td>78 (68-98)</td>
<td>90 (80-104)</td>
<td>90 (80-102)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Initial Creatinine, mg/dL</td>
<td>1.1 (0.9-1.3)</td>
<td>1.1 (0.9-1.3)</td>
<td>1.0 (0.9-1.3)</td>
<td>0.756</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>36%</td>
<td>42%</td>
<td>20%</td>
<td>0.255</td>
</tr>
<tr>
<td>IV Fluids – ED or OR, Liters</td>
<td>5.0 (2.3-8.0)</td>
<td>3.5 (2.0-7.5)</td>
<td>5.9 (3.0-8.1)</td>
<td>0.384</td>
</tr>
<tr>
<td>PRBC – ED or OR, units*</td>
<td>4 (0-9)</td>
<td>1 (0-6)</td>
<td>1 (0-6)</td>
<td>0.030*</td>
</tr>
<tr>
<td>PRBC transfusion*</td>
<td>73%</td>
<td>54%</td>
<td>57%</td>
<td>0.049*</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>24%</td>
<td>25%</td>
<td>20%</td>
<td>0.966</td>
</tr>
</tbody>
</table>
Derivation Trauma Cohort: n=636

ARDS Case n=189 (30%)
Not ARDS n=447 (70%)

Early Onset <48 hrs n=108 (57%)
Late Onset >48 hrs n=81 (43%)

Validation Trauma Cohort: n=609

ARDS Case N=205 (34%)
Not ARDS n=404 (66%)

Early Onset <48 hrs n=115 (56%)
Late Onset >48 hrs n=90 (44%)

PENN

VANDY
Derivation Trauma Cohort: n=636

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PENN

VANDY

AIS thorax p<0.001
Shock p=0.006
## Biomarker Validation - VALID

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Class 1 (Early Onset)</th>
<th>Class 2 (Late Onset)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=46 (55%)</td>
<td>N=38 (45%)</td>
<td></td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>15.6 (15.6-71.2)</td>
<td>15.6 (15.6-65.35)</td>
<td>0.756</td>
</tr>
<tr>
<td>VWF (% control)</td>
<td>263 (192-355)</td>
<td>243 (155-353)</td>
<td>0.199</td>
</tr>
<tr>
<td>SP-D (ng/ml)</td>
<td>55 (35-82)</td>
<td>59 (43-90)</td>
<td>0.689</td>
</tr>
<tr>
<td>PAI-1 (ng/ml)</td>
<td>139 (40-266)</td>
<td>78 (40-214)</td>
<td>0.445</td>
</tr>
<tr>
<td>CC16 (ng/ml)</td>
<td>5.7 (3.5-9.0)</td>
<td>5.7 (4.0-9.8)</td>
<td>0.608</td>
</tr>
<tr>
<td>sRAGE (pg/ml)</td>
<td>1,994 (949-3,340)</td>
<td>1,298 (834-1,982)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Ang2 (pg/ml)</td>
<td>6,212 (4,300-8,581)</td>
<td>4,667 (3,193-5,942)</td>
<td>0.014*</td>
</tr>
<tr>
<td>BNP (ng/ml)</td>
<td>0.36 (0.30-0.56)</td>
<td>0.33 (0.27-0.54)</td>
<td>0.506</td>
</tr>
<tr>
<td>PCP III (ng/ml)</td>
<td>3.5 (2.6-4.9)</td>
<td>3.5 (2.7-4.3)</td>
<td>0.683</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td>22 (12-102)</td>
<td>27 (11-89)</td>
<td>0.986</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>1.77 (0.69-4.79)</td>
<td>0.8 (0.61-6.12)</td>
<td>0.240</td>
</tr>
</tbody>
</table>

Reilly, AATS 2014
Timing of Injury Endotype

• Early ARDS is associated with shock, and PRBC resuscitation

• Higher levels of Angpt-2 (sRAGE)
  – “Endothelial Injury” phenotype?
  – Targeted therapies - timing
Genetic Endotypes?

• Hypothesis
  – Evolutionary pressures select on mechanisms important to risk/outcome of ICU syndromes
    • Bleeding/injury
    • Plagues/endemic infections
    • Dehydration
    • Starvation
    • Temperature extremes
Using Convergent GWAS to guide biology

• ABO Gene
  – Evolutionary Selection
    • Malaria, cholera, E. Coli
  – GWAS ABO Gene associations
    • MI - Group A higher risk
    • VTE- Group A higher risk
    • vWF, ICAM-1 Level, E & P-selectins
      – Pathways and molecules implicated in ALI
**ABO Gene**

- Encodes a family of glycotransferases that catalyze antigen modifications on various glycans and glycoproteins.

- Determine ABO blood type
  - Proteins
  - Platelets, ECs

- Associated with various infections/vascular diseases
ABO Blood Types and ARDS

• Hypotheses:

  - “A” Transferase Blood Type A
  - Absent Transferase Blood Type O
  - ARDS Risk

• Study Populations: Penn Trauma and Sepsis (MESSI) Cohorts
Unadjusted ARDS Risk in Trauma

Unadjusted ARDS Risk by ABO Blood Type:

- A: 37% (n=138)
- AB: 26% (n=19)
- B: 15% (n=34)
- O: 26% (n=144)

Statistical significance: p=0.039

Unadjusted ARDS Risk in Sepsis

<table>
<thead>
<tr>
<th>Blood Type</th>
<th>% ARDS</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>31%</td>
<td>213</td>
</tr>
<tr>
<td>AB</td>
<td>28%</td>
<td>29</td>
</tr>
<tr>
<td>B</td>
<td>19%</td>
<td>63</td>
</tr>
<tr>
<td>O</td>
<td>20%</td>
<td>239</td>
</tr>
</tbody>
</table>

\[ p = 0.049 \]

## Multivariable Adjusted ARDS Risk

<table>
<thead>
<tr>
<th>Population</th>
<th>% ARDS Type A</th>
<th>% ARDS Non-A</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted* OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma* (n=370)</td>
<td>37%</td>
<td>24%</td>
<td>1.87</td>
<td>0.010</td>
<td>1.88</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.16, 3.01)</td>
<td></td>
<td>(1.14, 3.13)</td>
<td></td>
</tr>
<tr>
<td>Sepsis # (n=544)</td>
<td>31%</td>
<td>21%</td>
<td>1.70</td>
<td>0.009</td>
<td>1.67</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.14, 2.52)</td>
<td></td>
<td>(1.08, 2.59)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, ISS, mechanism of injury, history of diabetes, and units of red blood cells

#Adjusted for age, sex, APACHE III, history of diabetes, units of red blood cells, and pulmonary vs extra-pulmonary infection

Trauma - AKI

Adjusted AKI Risk

- O (n=95)
- A (n=94)
- B (n=28)
- AB (n=12)

p=0.01

ABO Blood Type
Sepsis - AKI

Adjusted AKI Risk

p=0.02

ABO Blood Type

O (n=190)
A (n=188)
B (n=40)
AB (n=19)
Blood Group A Endotype

• May be shared across multiple phenotypes
  – VTE
  – MI
  – ARDS
  – AKI
Blood Group A Endotype

- vWF, ICAM-1 and other mediators may be modified by A transferase leading to ARDS
  - Assess causal pathway in mediation analyses
  - Ongoing studies to identify novel protein modifications in MAPGen

- Platelet sheddome – enriched in glycoproteins
- TSP-1 most abundant glycoprotein in sheddome
  - N-linked sialylation modifications
    - A antigen
Obesity Endotype in AKI

Shashaty, CCM, 2014
Other Potential Endotypes

• **IL1RA** – Inflammasome activation
  • Meyer, AJRCCM 2013, 2014

• **mtDNA - DAMP**
  • Nakahira, Choi, PloS Med 2013

• **ANGTP2** – vascular injury/inflammation
  • Meyer, AJRCCM 2011

• **PEEP responsive** -
  • Calfee, Lancet Resp medicine 2014

• **Ongoing Studies**
  – Galaxy ALI, iSPAAR
Summary

• “ARDS” is a paradigm, like AKI
  – Useful for some clinical trials

• Biology-driven endotypes may lead to precision therapies
  – Predisposing factor
  – Timing of onset
  – Blood group
  – Inflammatory markers, shock
  – Genotype
Acknowledgements

• Paul Lanken, MD
• Barry Fuchs, MD
• Sandra Kaplan, MSN
• Nuala Meyer MD
• John Reilly, MD
• Rupal Shah, MD
• Josh Diamond, MD
• Rui Feng, PhD
• Hakon Hakonarson, MD, PhD
• Scarlett Bellamy, ScD
• Bob Gallop, PhD
• Russell Localio, PhD

• TASC Investigators
• LTOG Investigators
  – Lorraine Ware
  – David Lederer
• Melanie Doran, BS
• Carly Dericco, BS
• Richard Aplenc MD, MSCE

• Funded by NIH:
  – HL079063 (Fisher - JC)
  – HL042423 (JC)
  – HL087115 (JC)
  – HL081619 (JC)
  – HL096845 (JC)
  – HL115354 (JC)
  – HL114626 (LC)