ARDS Subphenotypes: Differential Treatment Responses, and Where Do We Go From Here?

Carolyn S. Calfee, MD MAS
Associate Professor of Medicine and Anesthesia
University of California, San Francisco
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Are Pharmacotherapy Trials in ARDS Doomed?

Decades of negative pharmacotherapy trials for ARDS,* despite promising mechanisms and preclinical data

- Corticosteroids
- Surfactant
- Prostaglandin E1
- Anti-endotoxins
- Anti-cytokines
- Procysteine
- Ketoconazole
- Lisofylline
- Activated protein C
- Beta-agonists
- Omega-3 fatty acids
- Neutrophil elastase inhibitor
- Statins
- Nitric oxide
- Ibuprofen

* A partial list
“Enrichment”: Focus on patient population in which detection of drug effect is more likely than in unselected population

* **Prognostic Enrichment**: Focus on patients at highest risk for disease-related endpoint (i.e. death due to ARDS)
  * Increase absolute effect size, not relative effect

* **Predictive Enrichment**: Focus on patients most likely to respond to a particular treatment
  * Enrich for a specific endotype relevant to mechanism
ARDS is a syndrome defined by non-specific criteria
- Clinical, biological, pathologic heterogeneity
- If we split rather than lump, can we find a treatment-responsive group?
Prognostic Enrichment in ARDS: Some Successes

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, PI Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Per- Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.I Claude Guérin, M.D., Ph.D., Gwenael Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph for the ACURASYS Study Investigators

Prone Positioning in Severe Acute Respiratory Distress Syndrome

Claude Guérin, M.D., Ph.D., Jean Reignier, M.D., Ph.D., Jean-Christophe Richard, M.D., Ph.D., Pascal Beuret, M.D., Arnaud Gacouin, M.D., Thierry Boulain, M.D., Emmanuelle Mercier, M.D., Michel Badet, M.D., Alain Mercat, M.D., Ph.D., Olivier Baudin, M.D., Marc Clavel, M.D., Delphine Chatellier, M.D., Samir Jaber, M.D., Ph.D., Sylvène Rosselli, M.D., Jordi Mancebo, M.D., Ph.D., Michel Sirodot, M.D., Gilles Hilbert, M.D., Ph.D., Christian Bengler, M.D., Jack Richecoeur, M.D., Marc Gainnier, M.D., Ph.D., Frédérique Bayle, M.D., Gael Bourdin, M.D., Véronique Leray, M.D., Raphaële Girard, M.D., Loredana Baboi, Ph.D., and Louis Ayzac, M.D., for the PROSEVA Study Group
Asthma: Not Just a Single Disease

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

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VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

One Approach To Finding Subtypes: Latent Class Analysis (LCA)

* Based on hypothesis that there are distinct sub-classes within a broader group of patients
  * Does data distribution better fit with 1 class or 2 (3, 4, …)?
  * Tests hypothesis re: fit of number of classes
Latent Class Analysis Finds Two Subphenotypes of ARDS in RCT’s
Comparison of Two ARDS Subphenotypes

“Hyper-inflammatory”

“Hypo-inflammatory”

Famous et al, AJRCCM 2017
Subphenotype Membership is Stable Over Several Days

- In both ARMA (low TV) and ALVEOLI (low vs high PEEP), two classes present on Study Day 3
- In both studies, 94% patients stayed in same class from Day 0 to 3

<table>
<thead>
<tr>
<th>In ALVEOLI, Probability of Class Transition (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
</tr>
<tr>
<td>Day 0</td>
</tr>
<tr>
<td></td>
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Delucchi et al, Thorax 2018
ARDS Subphenotypes Are Similar At Days 0 And 3

Delucchi et al, Thorax 2018
90d Mortality Much Worse in Hyper-inflammatory Subphenotype

<table>
<thead>
<tr>
<th>Trial</th>
<th>Hypo-inflammatory</th>
<th>Hyper-inflammatory</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARMA (low TV)</td>
<td>23%</td>
<td>44%</td>
<td>0.006</td>
</tr>
<tr>
<td>ALVEOLI (PEEP)</td>
<td>19%</td>
<td>51%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FACTT (fluids)</td>
<td>22%</td>
<td>45%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HARP2 (simvastatin)</td>
<td>22%</td>
<td>47%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAILS (rosuvastatin)</td>
<td>21%</td>
<td>38%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
In secondary analyses of RCT’s, two subphenotypes responded differentially to:

- **Mechanical ventilation**: High vs low PEEP
- **Fluids**: Conservative vs. liberal
- **Pharmacotherapy**: Simvastatin
  - NOT rosuvastatin
Original trial of Simvastatin: HARP-2

Hazard ratio, 1.25 (95% CI, 0.88–1.76)
P=0.20

McAuley NEJM 2014
Hyperinflammatory Subphenotype: Survival Benefit from Simvastatin

28 Day Survival

- Hypoinflammatory subphenotype, placebo
- Hypoinflammatory subphenotype, simvastatin
- Hyperinflammatory subphenotype, simvastatin
- Hyperinflammatory subphenotype, placebo

Overall p<0.0001
Hyperinflammatory subphenotype patients treated with simvastatin vs placebo p=0.008

* Secondary analysis: Needs prospective validation

Calfee Lancet Resp 2018
No Evidence of Benefit From Rosuvastatin

Sinha et al, ICM 2018
Simvastatin vs. Rosuvastatin

- Dose-related?
- Lipophilic vs. hydrophilic?

Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury

Simvastatin ameliorates injury in an experimental model of lung ischemia-reperfusion

Babu V. Naidu, FRCS
Steven M. Woolley, MBBS

Simvastatin attenuates ventilator-induced lung injury in mice

Holger C Müller, Katharina Helwig, Simone Rosseau, Thomas Tschering, Andreas Schmiedl, Birgit Gutknecht, Bernd Schneick, Stefan

Protective Role of Simvastatin on Lung Damage Caused by Burn and Cotton Smoke Inhalation in Rats

Ilias I. Siempos, MD; Nikolaos A. Maniatis, MD; Petros Kopterides, MD; Christina Megkou, MD; Constantinos

Simvastatin Decreases Lipopolysaccharide-induced Pulmonary Inflammation in Healthy Volunteers

Murali Shyamsunder, Scott T. W. McKeown, Cecilia M. O’Kane, Thelma R. Craig, Vanessa Brown, David R. Thickett, Michael A. Matthey, Clifford C. Taggart, Janne T. Backman, J. Stuart Elborn, and Daniel E. McAuley
Diffuse vs. Focal ARDS: Might Different Ventilatory Strategies Work?

- Lung Imaging for Ventilatory Setting in ARDS (LIVE) trial
- 420 patients
- Randomized to control (low TV ventilation) vs. MV tailored to radiographic pattern:
  - Focal: Early proning, low PEEP
  - Diffuse: Recruitment maneuver, high PEEP
- Completed enrollment
  - No results available

Mrozek et al, CHEST 2016; clinicaltrials.gov
Aspirations for ARDS: Targeting Specific Subgroups

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group

Hazard ratio, 0.37; 95% CI, 0.26 to 0.55; P<0.001

Chapman et al, NEJM 2011
A Cautionary Tale: Recombinant IL1RA in Sepsis

Recombinant Human Interleukin 1 Receptor Antagonist in the Treatment of Patients With Sepsis Syndrome

Results From a Randomized, Double-blind, Placebo-Controlled Trial

Charles J. Fisher, Jr, MD; Jean-Francois A. Dhainaut, MD, PhD; Steven M. Opal, MD; John P. Pribble, PharmD;

Mortality Benefit of Recombinant Human Interleukin-1 Receptor Antagonist for Sepsis Varies by Initial Interleukin-1 Receptor Antagonist Plasma Concentration*

Nuala J. Meyer, MD, MS1; John P. Reilly, MD, MSCE1; Brian J. Anderson, MD, MSCE1; Jessica A. Palakkappa, MD1; Tiffanie K. Jones, MD, MPH1; Thomas G. Dunn, BA1; Michael G. S. Shashaty, MD, MSCE1; Rui Feng, PhD1; Jason D. Christie, MD, MSCE1;2; Steven M. Opal, MD1

Fisher C et al, JAMA 1994; Meyer N, CCM 2018
A Cautionary Tale: Recombinant IL1RA in Sepsis

Meyer N, CCM 2018
Targeted Clinical Trials: How To Get There From Here?

Identification of subgroups; retrospective analysis of differential treatment response in RCTs

Targeted clinical trials
Identification of subgroups; retrospective analysis of differential treatment response in RCTs

Prospective identification

Understanding of mechanistic drivers

More populations, more subgroups?

Genes? Environment? Host vs. insult

Adaptive clinical trials?

Targeted clinical trials
Conclusions

* Prognostic and/or predictive enrichment may help find the responsive subset
* First steps: Understanding that there is heterogeneity in ARDS and it may affect treatment response
  * Retrospective identification of treatment-responsive subgroups
  * Survival benefit in hyper-inflammatory subphenotype with simvastatin but not rosuvastatin
* Next steps:
  * Prospective studies are required
  * Understanding mechanisms will be fundamental