



King's Research Portal

DOI:

[10.1164/rccm.201608-1729ED](https://doi.org/10.1164/rccm.201608-1729ED)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Shankar-Hari, M., & McAuley, D. F. (2017). Acute Respiratory Distress Syndrome Phenotypes and Identifying Treatable Traits. The Dawn of Personalized Medicine for ARDS. *American Journal of Respiratory and Critical Care Medicine*, 195(3), 280-281. <https://doi.org/10.1164/rccm.201608-1729ED>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

**ARDS phenotypes and response to therapy: the dawn of personalised medicine for
ARDS**

Manu Shankar-Hari^{1,2} and Daniel F. McAuley^{3,4#}

Manu Shankar-Hari^{1,2} M.Sc., Ph.D.

¹Department of Critical Care Medicine, Guy's and St Thomas' NHS Foundation Trust,
Westminster Bridge Rd, London SE17EH, United Kingdom; ²Division of Asthma, Allergy and
Lung Biology, King's College London, United Kingdom
email: manu.shankar-hari@kcl.ac.uk

³Centre for Experimental Medicine, Wellcome-Wolfson Institute for Experimental Medicine,
Queen's University of Belfast, Belfast, Northern Ireland; ⁴Regional Intensive Care Unit, Royal
Victoria Hospital, Grosvenor Road, Belfast, Northern Ireland
email: d.f.mcauley@qub.ac.uk

#corresponding author

Key words: ARDS, Humans, Phenotypes, Endotypes, Treatment Response

Acute respiratory distress syndrome is a heterogeneous clinical condition characterised by complex pathophysiological mechanisms such as dysregulated pulmonary and systemic inflammation, diffuse alveolar epithelial and endothelial cell injury and altered alveolar membrane permeability (1, 2). ARDS remains common (3) with high mortality of 48% (45% - 51%) in observational studies and 37% (34% - 41%) in clinical trials (4). There are no pathognomonic signs or diagnostic tests for ARDS (5). For diagnosis at the bedside, the ARDS definition identifies clinical phenotypes with predictive validity categories based on the severity of hypoxaemia to supplement clinical judgement and radiological findings. However due to the underlying biological differences within the overall clinical phenotype, these categories do not necessarily equate to generic treatment responses and interventions may only be effective in a sub-population of the overall cohort of patients with ARDS in a randomised clinical trial (RCT) (1). Therefore whether it is possible to identify these ARDS treatment response groups is an important question.

ARDS phenotype subsets (subphenotypes) represent patient groups within a heterogeneous ARDS cohort with a similar set of observable clinical, radiological, biological and/or outcome characteristics. ARDS endo-phenotypes (endotypes) represent patient subsets of ARDS defined either by a biologically restricted molecular pathway/mechanisms or by differences in treatment response or rarely both. Our current understanding of *causal* determinants (6) of clinical, radiological and biological manifestations, treatment responses, outcomes and their inter relationships is incomplete. ARDS literature like the sepsis literature is replete with RCTs where there are no differences in the average treatment effect between the intervention and control arms. Identifying *ARDS subgroups* with either an improved average treatment effect or a decreased variation in treatment response or a greater event rate or combinations thereof, may make it possible to reduce the probability of trials that show no statistically significant difference in average treatment effect (7). Reanalysis of data from completed RCTs with an emphasis on identifying these subgroups within the ARDS phenotype-endotype continuum represents a novel approach.

Latent class analysis (LCA), highlighted Lazarsfeld by in the 1950s (8), is one approach to identify clustering within cohorts, by testing the hypothesis that two or more unobserved categories (latent classes) explain the relationships between observed variables

in the cohort. The primary goal of LCA is to identify the most parsimonious set of predictor variables and latent classes that explain the cohort data. LCA assumes that all data points have conditional independence and come from one of these unobserved categories. The granularity of data is reduced to standard normal distribution for analysis. The choice of variables, the model characteristics and the number of latent classes are dependent on the methods used (9-11). Therefore LCA could potentially identify these *ARDS subgroups*.

Using LCA of data from the ARMA and ALVEOLI RCTs in ARDS, Calfee and colleagues previously reported two ARDS subgroups with distinct clinical, biological and outcome characteristics with one subgroup characterised by a higher prevalence of shock, greater inflammation and endothelial injury and higher mortality (12). Significant interaction between the subphenotype and response to PEEP was also identified. In this issue, Famous K et al replicate these findings using data from the FACTT trial(13). They show that the two-class LCA model, with one group again characterized by hypotension, inflammation and mortality still holds true. Significant interaction between the subphenotypes and fluid regimen was also observed.

This important body of work represents the beginning of personalised medicine for ARDS by improving our understanding of disease mechanisms, treatment response characteristics, and outcome determinants. This work could allow researchers to delineate causal mechanistic pathways in the development of ARDS, which could help tailor treatment accounting for individual heterogeneity. The ability to identify patient cohorts who are more likely to respond to a specific therapy (predictive enrichment)(14) could represent a major advance in clinical trial design in ARDS. Several additional questions remain. First, data to support these *ARDS subgroups* are limited to the specific population recruited into ARDSnet RCTs. Thus it would be useful to replicate and validate these findings in ARDS population from other international RCTs and whether these *ARDS subgroups* could be identified within unselected observational cohorts. Second, it is important to know if a patient's *ARDS subgroup* allocation changes over time as this could have implications for the timing of interventions. Finally it is important to highlight that caution is required with *causal* and *treatment response* inferences as the premise of randomisation may no longer be valid in these analyses. This last point that is perhaps the most fundamental challenge, is best

addressed in clinical trials designed to specifically test the hypothesis that these ARDS endotypes can be identified prior to randomisation and are associated with an increased likelihood of a positive treatment response (statistically significant average treatment effect). Such trials will be enabled by the development of point of care assays for recognition of ARDS endotypes in real-time. In terms of the current work, these data also raise the potential the need to re-visit fluid therapy in ARDS patients.

What are the implications of this research going forward? The authors have shown unequivocally that there is an urgent need for further research to understand these *ARDS subgroups* within the complex phenotype-endotype continuum and to establish uniform reporting standards. Calfee and colleagues(12, 13) have done an excellent service to our speciality by highlighting a fresh approach to study patient heterogeneity, which is likely to both improve our understanding of the pathophysiology of ARDS as well as inform future trials in ARDS as a new era of personalised medicine for ARDS emerges.

References

1. Ards Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; 307: 2526-2533.
2. Sweeney RM, McAuley DF. Acute respiratory distress syndrome. *Lancet* 2016.
3. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, Investigators LS, Group ET. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016; 315: 788-800.
4. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, Gattas DJ, Hallett D, Tomlinson G, Stewart TE, Ferguson ND. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. *Am J Respir Crit Care Med* 2009; 179: 220-227.
5. Rubenfeld GD, Caldwell E, Granton J, Hudson LD, Matthay MA. Interobserver variability in applying a radiographic definition for ARDS. *Chest* 1999; 116: 1347-1353.
6. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. *Annu Rev Public Health* 2000; 21: 121-145.
7. Rubenfeld GD. Confronting the frustrations of negative clinical trials in acute respiratory distress syndrome. *Ann Am Thorac Soc* 2015; 12 Suppl 1: S58-63.
8. Lazarsfeld, P. F., Henry, N. W. (1968). Latent structure analysis. Boston: Houghton Mifflin.
9. Dean N, Raftery AE. Latent Class Analysis Variable Selection. *Ann Inst Stat Math* 2010; 62: 11-35.
10. van Smeden M, Naaktgeboren CA, Reitsma JB, Moons KG, de Groot JA. Latent class models in diagnostic studies when there is no reference standard--a systematic review. *Am J Epidemiol* 2014; 179: 423-431.
11. Rindskopf D, Rindskopf W. The value of latent class analysis in medical diagnosis. *Stat Med* 1986; 5: 21-27.
12. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA, Network NA. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *The Lancet Respiratory medicine* 2014; 2: 611-620.
13. Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, Calfee CS. ARDS Subphenotypes Respond Differently to Randomized Fluid Management Strategy. *Am J Respir Crit Care Med* 2016.
14. Prescott HC, Calfee CS, Thompson BT, Angus DC, Liu VX. Toward Smarter Lumping and Smarter Splitting: Rethinking Strategies for Sepsis and Acute Respiratory Distress Syndrome Clinical Trial Design. *Am J Respir Crit Care Med* 2016; 194: 147-155.