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EDITORIAL

Is it time to integrate treatable traits into the syndromic definition of ARDS to personalize care?

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Ashbaugh and colleagues first described Acute Respiratory Distress Syndrome (ARDS) in 1967 as new onset hypoxemia refractory to supplemental oxygen and bilateral lung infiltrates in chest x-ray with reduced respiratory system compliance.[1] However, a tangible definition of ARDS came only on 1994 as the American European Consensus Conference (AECC) criteria.[2] The AECC criteria defined ARDS as acute onset severe hypoxemia with a PaO_2/FiO_2 (P/F ratio) of less than 200 and bilateral lung infiltrates in chest X-ray, not due to left heart failure. It also added a new terminology called acute lung injury (ALI) which used the same variables but had less stringent criteria for hypoxemia with a P/F ratio of <300. And although, AECC was a huge leap in our understanding of ARDS, it left a lot of holes unplugged. And so, the AECC criteria was improvised in 2012 by the Berlin definition[3] which mentioned that ARDS has an incubation period of up to 7 days from the time of clinical insult to the appearance of signs and symptoms of ARDS and also that positive end-expiratory pressure (PEEP) can affect the reliability and specificity of ARDS. It added a minimum PEEP of 5cm of H_2O to define ARDS, but most importantly, it categorized ARDS into three mutually exclusive groups for prognostication and treatment selection. Now, as the Berlin definition may not allow identification of ARDS in resource limited setup without PEEP, and as arterial blood gas (ABG) may not be easily available, the Kigali Modification criteria of the Berlin definition in 2015 used hypoxia with a cut off SpO_2/FiO_2 (S/F ratio) of less than or equal to 315 with bilateral lung opacities on lung ultrasound or chest radiograph for resource limited setting.[4] The New Global definition in 2023, expanded on the Berlin definition and its Kigali Modification, and added high flow nasal oxygen (HFNO) criteria with a minimum flow rate of ≥ 30 L/min for the non-intubated ARDS.[5]

Now, what we currently have, the Berlin definition and the New Global definition of ARDS, are syndromic definitions which are all inclusive and non-specific. But what we need is a precise and specific biologic definition of ARDS. However, biologic definition of ARDS is out of reach at present because of constraints in data availability and granularity, and also due to our limitations in understanding of the mechanism underlying the development of ARDS. Nevertheless, what we can do is to integrate biologic treatable traits into the syndromic definition of ARDS, to help us guide treatment.

So, what are treatable traits? These are consistent biological features that will respond to therapy. ARDS is a heterogenous syndrome and could have heterogeneity of treatment effect (HTE). Secondary analysis of various trials has shown that there are treatment responder subtypes (or treatable

traits) in ARDS. Latent class analysis (LCA) of ARMA and ALVEOLI trials identified two sub-phenotypes of ARDS based on the plasma concentration of inflammatory biomarkers – phenotype 2 (hyper-inflammatory) and phenotype 1 (hypo-inflammatory), and also that phenotype 2 had higher mortality and fewer ventilator free days (VFD).[6] Latent class analysis of SAILS trial showed 40% of the patients with hyper-inflammatory ARDS and 60% had hypo-inflammatory ARDS.[7] A greater proportion of hyper-inflammatory ARDS had non-pulmonary sepsis and hypo-inflammatory ARDS had trauma and pneumonia. Cluster analysis of HARP-2 trial showed that hyper-inflammatory sub-phenotype had higher 28-day survival when treated with simvastatin whereas simvastatin had no effect on survival in hypo-inflammatory subtype[8] indicating that ARDS could have heterogeneity of treatment effect (HTE).

Again, we may be inclined to ask, biomarker-based treatment in ARDS sounds elegant, but, what about the "method", the "cut-off", the "cost" and "availability"? The PHIND trial of UK is underway which aims to prospectively define hyper-inflammatory and hypo-inflammatory ARDS using point-of-care (POC) bedside assay (plasma IL-6 and soluble TNF receptor-1).[9] Also, the PANTHER trial of European Respiratory Society (ERS), which is an Adaptive Platform Trial (International Precision Medicine Platform Trial) is underway and is evaluating several pharmacological interventions (simvastatin and baricitinib to begin with) in hyper-inflammatory and hypo-inflammatory ARDS and will enroll patients of both hyper-inflammatory and hypo-inflammatory ARDS stratifying patients in real-time to assess HTE.[10]

Now, the heterogeneity of ARDS and its HTE could extend beyond hyper-inflammatory and hypo-inflammatory endotypes. But even for hyper-inflammatory and hypo-inflammatory ARDS, the latent class analysis of ARMA, ALVEOLI and FACTT trials have shown that hyper-inflammatory ARDS responds better to the effect of higher PEEP and fluid liberal strategy whereas the contrary is true for hypo-inflammatory ARDS (which responds better to lower PEEP and fluid restrictive strategy) indicating that HTE in ARDS could well extend beyond pharmacotherapy.[11,12]

Also based on the type of lung injury, whether direct or indirect, ARDS may be classified as pulmonary ARDS and extra-pulmonary ARDS. The primary injury in pulmonary ARDS is the injury to the alveolar epithelium (and alveolar epithelial injury markers like Surfactant Protein-D and soluble Receptor for Advanced Glycated End-products, sRAGE, are higher in Pulmonary ARDS) whereas the primary injury in extra-pulmonary ARDS is the injury to the vascular endothelium (and vascular endothelial injury marker like Angiopoietin 2 is higher in extra-pulmonary ARDS) and extra-pulmonary ARDS typically respond better to the effects of PEEP, proning and recruitment maneuver (RM) as compared to pulmonary ARDS.

Not only that, also based on the distribution and extent of lung parenchymal involvement, ARDS may be sub-classified as focal and non-focal ARDS, and non-focal ARDS respond better to the effects of lower tidal volume and higher PEEP strategy as compared to focal ARDS. And the case in point here was the LIVE study of 2019 which recruited patients with moderate-severe ARDS, the control group receiving lung protective ventilation (LPV) with a tidal volume of 6ml/kg and average PEEP of 10 cm of H_2O (based on lower PEEP strategy of PEEP/FiO_2 table of the ARDSnet, and where proning was encouraged and RM was used as rescue therapy) and in the interventional arm the focal ARDS group received tidal volume of 8ml/kg and lower PEEP around 5-9 cm of H_2O (where proning was mandated and RM was used as rescue therapy) and the non-focal cohorts received tidal volume of 6ml/kg and higher PEEP around 14-16 cm of H_2O (where PEEP was pushed up till plateau pressure (Pplat) was 30 cm of H_2O and RM was mandated and proning was used as rescue therapy).[13] Although, this study showed that there was no difference in mortality between these groups, the sub-group analysis of the study showed that there was misclassification of 21% in the personalized or the interventional arm and when corrected for misclassification there was survival benefit for the personalized arm.[13] This trial made it abundantly clear to us that although personalized mechanical ventilation may be beneficial but prospective phenotyping based on lung morphology is a difficult thing to do and is fraught with the dangers of misclassification which in turn could lead to increase in mortality.

And finally, regarding the subtypes, since there are many ways to classify ARDS into subgroups, and therefore, one patient can belong to many different subtypes simultaneously, each of which could be a treatable trait, for example, a patient with hyper-inflammatory ARDS could also have extra-pulmonary and non-focal ARDS (each of which could be a treatable trait) and could possibly respond well to higher PEEP, fluid liberal strategy and simvastatin therapy, and conversely, a patient with hypo-inflammatory ARDS could also have pulmonary and focal ARDS and could respond well to lower PEEP and fluid restrictive strategy.

To summarize, there are treatable trait ideas that cross over and de-emphasize syndromic definition mindset in ARDS, and identifying these treatable traits and treating them with appropriate therapy could reduce mortality in ARDS in the future. This could herald the beginning of Precision Medicine in Critical Care in general and ARDS in particular. But as for now, we will have to wait for the results of the PHIND and the PANTHER trials first, and then move on from there. Those being said, it is also worth noting that we are nowhere near cancer as far as Precision Medicine is concerned and that critically ill patients are entirely different from cancer patients and there will not be a golden bullet to block a single molecule in ARDS. And although, our current approach to Precision Medicine is too simplistic, and yet, I would say it is a way forward.

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