Precision medicine in acute respiratory distress syndrome: workshop report and recommendations for future research

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Acute respiratory distress syndrome (ARDS) shows variation on three distinct levels: aetiological, physiological and biological. The lack of a common presentation implies that intervention studies in patients with ARDS need to be phenotype aware and apply a precision medicine approach. https://bit.ly/36XZWcP

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ABSTRACT Acute respiratory distress syndrome (ARDS) is a devastating critical illness that can be triggered by a wide range of insults and remains associated with a high mortality of around 40%. The search for targeted treatment for ARDS has been disappointing, possibly due to the enormous heterogeneity within the syndrome. In this perspective from the European Respiratory Society research seminar on "Precision medicine in ARDS", we will summarise the current evidence for heterogeneity, explore the evidence in favour of precision medicine and provide a roadmap for further research in ARDS. There is evident variation in the presentation of ARDS on three distinct levels: 1) aetiological; 2) physiological and 3) biological, which leads us to the conclusion that there is no typical ARDS. The lack of a common presentation implies that intervention studies in patients with ARDS need to be phenotype aware and apply a precision medicine approach in order to avoid the lack of success in therapeutic trials that we faced in recent decades. Deeper phenotyping and integrative analysis of the sources of variation might result in identification of additional treatable traits that represent specific pathobiological mechanisms, or so-called endotypes.

Introduction

Acute respiratory distress syndrome (ARDS) is a devastating critical illness that can be triggered by a wide range of insults. It is characterised by leukocyte infiltration, local immune activation and alveolar endothelial and epithelial injury associated with increased pulmonary vascular permeability, acute pulmonary oedema, and loss of aerated lung tissue [1]. The diagnosis of ARDS is based on the development of bilateral opacities on chest radiography indicative of pulmonary oedema within 1 week of known clinical insult, in combination with impaired oxygenation as measured by the ratio of arterial to inspired oxygen (P_{aO_2}/F_{IO_2}) despite the application of at least 5 cm H_2O of positive end-expiratory pressure (PEEP) [2]. Cardiac failure does not fully explain the radiographic and clinical abnormalities.

No specific aetiological, physiological or biological criteria are required for ARDS diagnosis, inherently resulting in heterogeneity on these three levels. The in-hospital mortality of ARDS remains around 30–40% [3]. Treatment of ARDS is limited to the prevention of harm induced by ventilatory support

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(ventilator-induced lung injury (VILI)) through lung protective mechanical ventilation strategies [4]. Recent interventional studies targeting the pathophysiological principles underlying ARDS, such as inflammation, coagulation, oxidative stress and endothelial injury, have failed to show benefit and, therefore, the therapy for ARDS remains supportive [5]. We hypothesise that these treatments failed partly due to insufficient understanding of the heterogeneity of ARDS.

Precision medicine has been defined as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics (a subphenotype) that distinguish a given patient from other patients with similar clinical presentations (the phenotype)" [6]. Precision medicine aims to provide a treatment to those patients who will benefit and withhold that same treatment from those who will not benefit or will be harmed. When does precision medicine provide additional information on top of the Oslerian paradigm of syndromic pattern recognition? This added value is more likely when the clinical diagnostic criteria do not capture a single pathophysiological process because only some of the patients will benefit from a treatment targeting a specific pathophysiological process. Simultaneously, other patients may experience side-effects without the potential for benefit. The profit from a precision medicine approach will increase when those side-effects have larger consequences, as is likely the case in critically ill patients. We acknowledge that "all models are wrong" and that any subphenotype can be further split into smaller units [7]. Therefore, we do not seek excessive elaboration to explain the pathophysiology of ARDS but rather seek a simple description of subphenotypes that are evaluated on their predictive accuracy for treatment response in the hope to find "models that are useful" and applicable in clinical practice [7].

In this perspective from the European Respiratory Society research seminar on "Precision medicine in ARDS", we will summarise the current evidence for heterogeneity, explore the evidence in favour of precision medicine and provide a roadmap for further research in ARDS. The basic assumption of the seminar was that there are challenges in heterogeneity of ARDS on three distinct levels: 1) aetiological, 2) physiological and 3) biological [8]. The experts attending the research seminars provided literature reviews, and researchers presented their latest paper in the form of abstracts. Focus groups worked on statements for each of the three domains, which were discussed in a round table format at the conference.

Aetiology

When ARDS was described in 1967 by Ashbaugh *et al.* [9], it was noted that patients with different risk factors showed similar clinical characteristics, and *post mortem* pathological evaluation revealed diffuse alveolar damage (DAD) in all. ARDS is now known to be a frequent cause of acute respiratory failure, and subsequent definitions have become more and more inclusive, lumping patients with increasingly heterogeneous conditions together [2, 9, 10]. With the current definition, only a minority of patients who fulfil the criteria for ARDS actually have findings of DAD at *post mortem* pathological evaluation [11]. Aetiological factors may play role in the heterogeneity of ARDS at three levels: risk factors for lung injury, factors that further induce pulmonary oedema, and clinical states that stand in the way of reparative processes of lung injury [1].

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Evidence for heterogeneity and precision approaches

Treatment targeted at specific aetiological causes for ARDS

Other aetiologies under the umbrella of "diffuse interstitial acute lung diseases", "diffuse pulmonary infections" and "drug/chemical-induced diffuse lung disease" can present with similar characteristics as ARDS and fall within the syndrome definition. These diagnoses are sometimes referred to as ARDS-mimics because they show a known and distinct pathophysiology and require specific treatment. These patients may be included in clinical trials if no additional diagnostic tests are performed to distinguish between ARDS and ARDS-mimics [12]. This issue may be important for clinical practice and trial design, as some of these ARDS-mimics can be effectively treated with immunosuppressants such as corticosteroids, antimicrobial drugs or withholding the drug that caused the lung injury. There is no consistent diagnostic approach that takes the probabilities of ARDS-mimics into account [13].

The specific causes for infectious and drug/chemical-induced diffuse lung disease may differ between institutions and can change over time, as is exemplified by the recent rise of vaping-induced lung injury [14] and the SARS-CoV-2-2019 pandemic [15]. Recognition of the underlying cause is essential because one of the fundamentals of ARDS care is the adequate treatment of the underlying disease, when possible. The rapid discovery of dexamethasone as effective treatment for severe COVID-19 pneumonia shows the importance of recognition of the underlying aetiology and the potential for phenotype-aware clinical trials [16].

Aggravation of lung injury

We also recognise that there are patients with risk factors for ARDS in whom pulmonary oedema is caused or aggravated *via* the administration of fluids, transfusions or injurious mechanical ventilation [17–20]. This iatrogenic injury should be considered a second hit after the first insult and adds additional complexity to the syndrome.

ARDS rapidly resolves in some patients, while it does not in others [1, 21, 22]. Super-imposed nosocomial infection and inadequate or suboptimal treatment of the primary insult may contribute to the persistence of lung injury. In some patients, fibroproliferation might contribute to the unfavourable evolution of ARDS, and there currently is no proven therapy to counteract this process. Some evidence suggests that corticosteroid therapy might be beneficial specifically in patients with fibroproliferation [23].

Attributable mortality

The attributable mortality of ARDS on top of chronic comorbidities and the underlying aetiological factors is unknown [24]. The attributable mortality may be different between patients with different risk factors. Trauma and sepsis patients with ARDS required more resources and died more frequently than patients with similar injuries but no ARDS [25, 26]. However, in patients with severe community-acquired pneumonia, ARDS was not a risk factor for mortality [27].

Research agenda

1) Establish and apply a diagnostic protocol to identify treatable diseases within the syndrome diagnosis of ARDS.
2) Evaluate the contribution of second hits such as mechanical ventilation, excess fluid administration and blood product transfusions, to specific aetiological phenotypes.
3) In patients with unresolved ARDS, identify those patients who have fibroproliferation/nosocomial infection, or persistence of the primary cause of ARDS.
4) In patients with evidence for fibroproliferation, test treatments such as steroids or anti-fibrotic treatments in clinical trials.
5) Quantify the attributable mortality of ARDS in the setting of different aetiologies.
6) When performing randomised controlled trials (RCTs), particular care needs to be taken to identify and, depending on the intervention of choice, possibly exclude patients with ARDS-mimic diagnoses.

Physiology and morphology

The aim of mechanical ventilation in ARDS is to improve gas exchange and thereby buy time for treatment of the underlying cause, resolution of pulmonary oedema, and repair of injured lung epithelium and endothelium [28]. The main challenge is to prevent further damage to the lungs due to VILI. Low tidal volume ventilation was shown to be protective in all patients with ARDS, sparking interest in the application of other strategies that were considered "lung protective" in an unselected cohort of patients such as recruitment manoeuvres, high PEEP and prone positioning [29]. "Protective" ventilator strategies other than low tidal volume ventilation are likely to work in some subsets of patients, while they could be ineffective or even harmful in others [30, 31].

Evidence for heterogeneity and precision approaches

Noninvasive support of ventilation and oxygenation

Around 16% of patients with ARDS may not require invasive mechanical ventilation but could be managed by noninvasive mechanical ventilation (NIV) or high-flow nasal oxygen (HFNO) therapy [32]. High tidal volumes and strongly negative intrathoracic pressures during NIV are speculated to contribute to failure of this approach *via* aggravation of lung injury through large pulmonary pressure swings, sometimes referred to as patient self-inflicted lung injury (P-SILI) [33, 34] and might be more frequent in patients with moderate or severe hypoxaemia (P_{aO_2}/F_{IO_2} <200 mmHg). The helmet interface is suggested to be most effective in patients with acute respiratory failure, many of whom have ARDS [35]. HFNO might, however, be more beneficial in patients with moderate or severe hypoxaemia [36]. Patients managed with NIV or HFNO whose clinical conditions do not stabilise with this treatment and who require intubation have worse outcomes [37]. Since the COVID-19 pandemic, there is increasing interest in combining HFNO or helmet NIV with prone positioning [38].

Persistence of hypoxaemia

The degree of hypoxaemia indicated by the P_{aO_2}/F_{IO_2} and PEEP at the moment of diagnosis may be less predictive for mortality than a reclassification on the following day [39–41]. There seems to be a phenotype of ARDS that resolves rapidly [42]. It is unclear what underlying physiology explains this phenotype, and mortality in this population is still high [39].

Recruitment response

There is a preferential treatment response to higher PEEP, prone positioning and early neuromuscular blockade in patients with lower P_{aO_2}/F_{IO_2} ratios [43–46]. However, despite these data, enrichment based on severe hypoxaemia has proven insufficiently effective for an "open lung approach" with high PEEP and aggressive recruitment manoeuvres, and for neuromuscular blockade in recent years [47, 48].

There is considerable variation in the amount of recruitable lung tissue between patients with ARDS. Predictors for a recruitable lung include: nonpulmonary ARDS, nonfocal ARDS [51] and lower P_{aO_2}/F_{IO_2} ratios [52]. Thus, there is heterogeneity in response to an open lung approach between patients with different phenotypes. A recent RCT assigned patients to a "standard" lung protective mechanical ventilation protocol or to a personalised approach based on a focal or nonfocal morphology of consolidations on computed tomography (CT)-imaging of the lung [53]. The intention to treat analysis did not show a difference between the arms, possibly because of the misclassification of morphological patterns in 20% of cases. In the per protocol analysis excluding misclassified patients, patients in the personalised mechanical ventilation protocol group showed a lower mortality (hazard ratio 0.6, 95% CI 0.36–0.99). Interestingly, patients who were misclassified had a significantly higher mortality when receiving the inappropriate treatment, suggesting harm of these interventions when applied to the wrong population and highlighting the importance of precision therapy.

Studies have failed to address the interactions between tidal volume, PEEP, driving pressure and respiratory rate and, rather, evaluated each variable in isolation. The establishment of the concept of mechanical power may serve as a way to stratify the amount of damage inflicted by mechanical ventilation [49, 50].

Research agenda

1) Identify phenotypes that are predictive for a positive response to HFNO or NIV.
2) Identify patients who benefit from specific NIV settings (flow, inspiratory pressure and PEEP), interface, sedation and analgesia to limit p-SILI.
3) Improve reclassification of patients after the first period of treatment to better identify rapid resolvers who may not need further lung-focused therapy.
4) Develop alternative (imaging) modalities that can accurately identify focal and nonfocal ARDS morphology.
5) When performing RCTs, collect data on the physiological and morphological phenotype of patients in the study and evaluate differential treatment effects.

Biology

Lung injury in ARDS is a consequence of a complex interaction between cellular and biochemical pathways resulting in lung epithelial and endothelial damage that is clinically characterised by protein-rich pulmonary oedema [54]. Many underlying biochemical processes have been targeted with drugs that effectively reverse the molecular mechanism of interest, but none of the studied drugs were effective in lowering mortality [5]. Heterogeneity in the biological mechanisms responsible for lung injury may explain these results. Even if patients with ARDS *on average* have an increased concentration of a certain cell or

molecule, indicative for a specific mechanistic contribution to the development of lung injury, it does not necessarily mean that *every* ARDS patient would benefit from targeting the underlying pathway. In fact, targeting a pathway that is not activated in a specific patient might lead to harm. Therefore, a personal assessment of systemic and pulmonary host response could help identifying homogenous patient groups and guide treatment decisions.

Evidence for heterogeneity and precision approaches

Pre-clinical research

In an ideal world, an experimental model of ARDS would fully reflect the mechanisms of injury, the clinical evolution, and the outcomes; in this sense, no experimental model of acute lung injury comes close [55]. No experimental model can hope to replicate the complexity of human ARDS, but some models will reflect well some aspect(s) of the syndrome [56]. More recently, comparison of biological heterogeneity between septic humans and mice has resulted in the validation of subphenotypes across species [57].

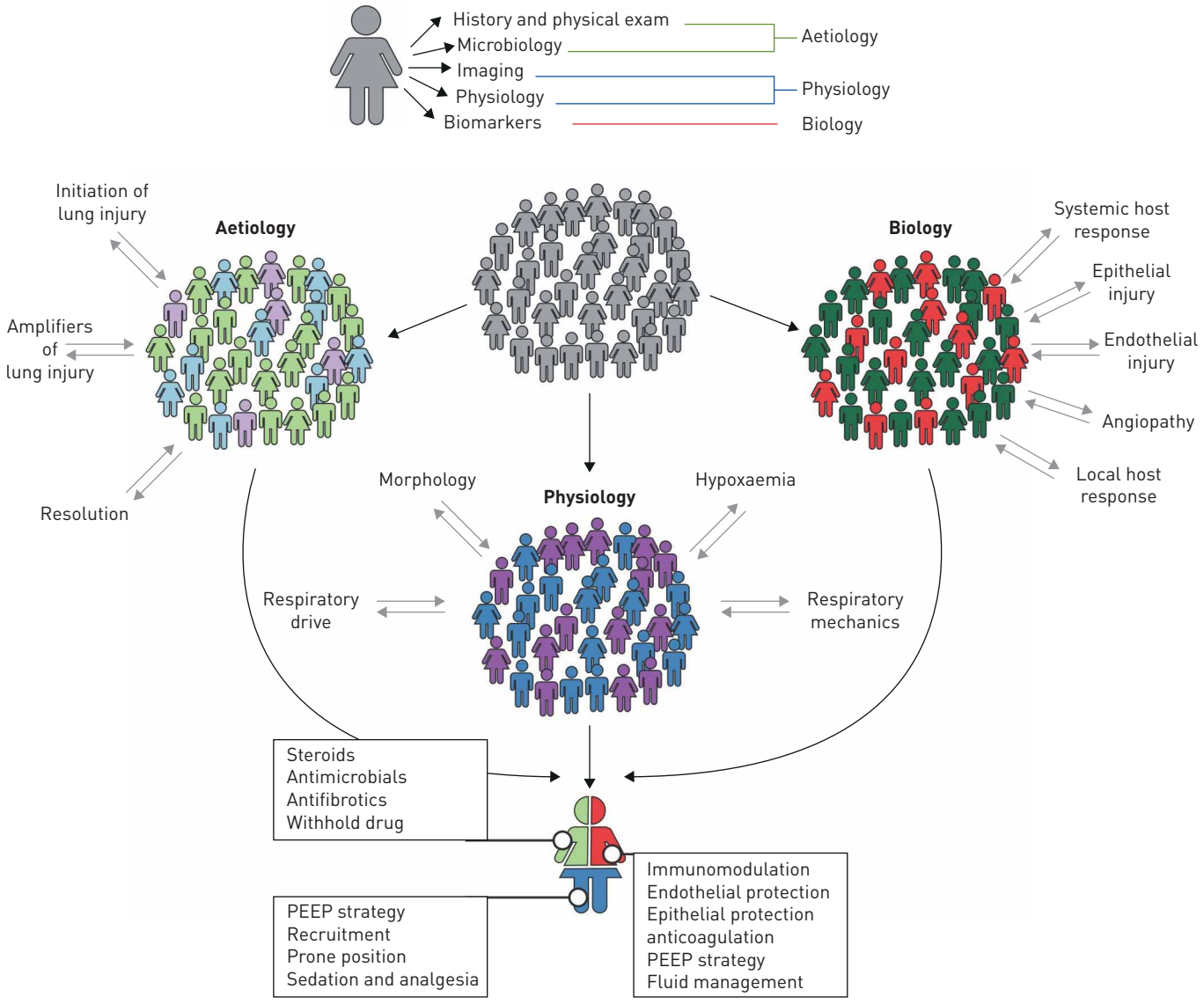

FIGURE 1 ARDS can be phenotyped based on information in three domains: aetiology, physiology and biology. Multiple phenotypes can coexist between and within a domain (within domain coexistence not shown). We recognise that there is a complex interaction between phenotypes and that true endotypes might capture phenotypic presentations within multiple domains. Traits are potentially treatable based on phenotypic recognition and subsequent empirical evidence for effectivity of intervention or on deep understanding of the critical causal pathways. ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure.

TABLE 1 Potential treatable traits in ARDS across aetiology, physiology and morphology, and biology

Domain	Subdomain	Trait	Test	Evidence	Interventions to be tested	Challenges
Aetiology	Causal pathogen	COVID-19	PCR for virus	[16]	Dexamethasone	
	ARDS-mimic	Diffuse acute interstitial lung diseases	History Imaging Immunological analysis	[75–77]	Immunosuppression	Relatively rare and requires systematic investigation to identify
		Diffuse pulmonary infections	History Serology Imaging Culture Metabolic products Metagenomics	[78]	Antimicrobials	
		Drug-induced diffuse lung disease	History	www.pneumotox.com	Withhold drug	
	Amplifiers of lung injury	Fluid overload	History Clinical examination Ultrasound Extravascular lung water	[79]	Diuretics Vasopressors	Diagnosis of fluid overload can be challenging
		Ventilator-induced lung injury	Tidal volume Driving pressure Mechanical power	[80]	Lower tidal volumes	No direct test for the actual development of VILI
	Nonresolving lung injury	Fibroproliferation	Markers of fibroproliferation in bronchoalveolar lavage fluid	[27]	Corticosteroids Antifibrotics	Biomarker test not routinely available
		Secondary infection	Imaging Culture Metagenomics	[81]	Antimicrobials	Identify ventilator-associated pneumonia in patient with ARDS
Physiology	Shunt	P_{aO_2}/F_{IO_2}	Blood gas	[43, 44]	Prone positioning Adjust PEEP Lung recruitment	Various thresholds proposed in different studies Influence of PEEP on P_{aO_2}/F_{IO_2}
	Ventilation	Dead space ventilation	Dead space calculation Ventilatory ratio	[82]	Adjust PEEP	Volumetric capnography not widely available
	Drive	High respiratory drive on NIV	Oesophageal pressure	[34]	Analgesia and sedation	Balance between high drive and too low drive
	Mechanics	High mechanical power	Formula based	[49]	Adjust PEEP, tidal volume and/or respiratory rate	Various thresholds proposed and unclear how to adjust settings based on value
		Driving pressure	Ventilator settings Oesophageal pressure	[83]	Adjust PEEP	Various thresholds proposed in different studies
Morphology	Imaging	Focal	Imaging	[53, 84, 85]	Prone positioning Low PEEP	Misclassification of morphology common and associated with worse outcome
		Nonfocal	Imaging	[53, 84, 85]	Lung recruitment High PEEP	
Biology	Systemic host response	Hyperinflammatory (or Reactive)	IL-8, bicarbonate and protein C IL-6, bicarbonate and TNFRI	[31, 60, 62, 63, 86]	High PEEP Restrictive fluid Simvastatin Immunomodulation	No routine test available Frequently unknown if cause or effect of lung injury
	Epithelial injury	Damaged epithelium	Biomarkers *e.g.* sRAGE	[87]	Epithelial protection	
	Endothelial injury	Vascular permeability and endothelial injury	Biomarkers *e.g.* angiopoietin 1 and 2	[88]	Endothelial protection Immunomodulation	
	Angiopathy	Microthrombosis	Biomarkers *e.g.* D-dimers, PAI-1 Perfusion imaging	[89, 90]	Anticoagulation Immunomodulation	
	Local host response	Pulmonary hyper-inflammation	Biomarkers in bronchoalveolar lavage fluid	[91]	Immunomodulation	

There are a wide range of clinical conditions, ARDS severities and mediators in lung injury pathogenesis that may be targetable for treatment. Most interventions listed are speculative and should not yet be applied. The list is also not exhaustive. For all these interventions, we emphasise the need for phenotype-aware randomised controlled trials. COVID-19: coronavirus disease 2019; ARDS: acute respiratory distress syndrome; VILI: ventilator-induced lung injury; PaO_2: arterial oxygen tension; FIO_2: inspiratory oxygen fraction; PEEP: positive end-expiratory pressure; NIV: noninvasive mechanical ventilation; IL: interleukin; TNFRI: tumour necrosis factor receptor 1; sRAGE: soluble receptor for advanced glycation endproducts; PAI-1: plasminogen activator inhibitor-1.

Identification of biological phenotypes

Using latent class analysis (LCA) of a panel of plasma biomarkers of inflammation, endothelial injury and coagulopathy in combination with routinely available clinical variables revealed two phenotypes across five RCTs [31, 58–60]. The so-called hyperinflammatory phenotype consistently had a higher mortality than the hypoinflammatory phenotype. These phenotypes seem to be stable at least up to 3 days after intensive care unit (ICU) admission [61].

Cluster analysis of a set of 20 biomarkers of inflammation, endothelial injury and coagulopathy *without* consideration of routinely available clinical variables in an observational study also revealed two phenotypes with consistent differences in mortality [62]. The gene expression of leukocytes in peripheral blood at admission to the ICU was profoundly different between phenotypes particularly in pathways involved in neutrophil activation, cholesterol metabolism and oxidative phosphorylation [63].

Differential treatment responses between biological phenotypes

Post hoc analysis of several RCTs showed that patients with the hyperinflammatory phenotype had a differential response to PEEP, fluid management and simvastatin treatment compared with patients with a hypoinflammatory phenotype [31, 58–60].

A parsimonious model of different combinations of three or four biomarkers (interleukin (IL)-6 or IL-8, bicarbonate, tumour necrosis factor receptor 1 or protein C, possibly in combination with vasopressor use) as well as a machine learning algorithm that used readily available clinical data was able to accurately identify the LCA phenotypes and showed adequate predictive enrichment in *post hoc* analysis of the above described RCTs [64, 65].

Endotyping

Despite these promising findings, the currently available data is insufficient to endotype because subphenotypes have not been related to specific pathobiological mechanisms [66, 67]. True endotyping would reliably identify and measure the critical biochemical pathways within patients and inform treatment based on a deep and highly predictive understanding of the underlying pathophysiology.

Research agenda

1) Translate biological variation in humans to animal models of acute lung injury by matching animal models to phenotypes rather than assuming that the model is representative of all human ARDS.
2) Embrace heterogeneity within animal models by introducing variation through experimentation in different laboratories, across (sub-)species, ages and comorbidities.
3) Validate the identified biological phenotypes in prospective clinical studies.
4) Determine the evolution of biological phenotypes throughout the course of ARDS and evaluate the influence of interventions on phenotype assignment.
5) Explore the generalizability of biological phenotypes of ARDS to other populations such as patients with acute respiratory failure, sepsis and unselected ICU patients.
6) Compare phenotypes based on plasma biomarkers to the pulmonary biological response by obtaining simultaneous samples from the lung and systemic compartments.
7) Further increase our understanding of heterogeneity within ARDS by deeper phenotyping and better understanding the immunology through functional assays, possibly resulting in the identification of endotypes.
8) Develop surrogate outcomes that reflect effectiveness of treatment within the target pathway of intervention.
9) Ideally, all ARDS RCTs should collect biological samples in order to consider the biological phenotype of patients in the study and evaluate differential treatment effects.

Integrating heterogeneity in aetiology, physiology and biology

One of the major challenges of precision medicine is to split patients into homogenous groups that are adequately enriched for positive treatment effects, while lumping a sufficient proportion of patients together to test interventions on clinically relevant outcomes, which frequently require large sample sizes. For this purpose, it is pivotal to understand the links between the three sources of heterogeneity (figure 1). We recognise that any subdivision in domains, including ours in aetiology, physiology and biology, is arbitrary. If a phenotype translates from one domain to another, the more easily evaluated phenotype can be used as a surrogate for the other. For example, the plasma concentration of the soluble form of the receptor for advanced glycation end products (sRAGE), a marker for lung epithelial injury, is strongly associated with the presence of nonfocal ARDS [68]. This finding is in line with the hypothesis that widespread pulmonary permeability is more profound in nonfocal ARDS and that an open lung approach

may benefit these patients. Furthermore, sRAGE or another surrogate may substitute for CT scanning to identify this morphological phenotype. However, biomarkers of endothelial injury and lung epithelial damage were significantly different between patients with pulmonary and nonpulmonary causes of lung injury, but still showed so much overlap that we cannot equate the aetiological factor with a particular biological phenotype [69, 70]. We recognise these are only the first steps into integrating information from the different domains and acknowledge the need for more collaboration between experts in all aspects of the quantification of heterogeneity and integration of the generated information in the near future.

Research agenda

1) Define the relationship between aetiological, physiological and biological phenotypes, with deeper phenotyping on all three levels.
2) A better treatment of ARDS requires open sharing of data, expertise and integration of multiple data streams.
3) Apply techniques used to integrate phenotypic data in other complex syndromes, such as chronic airway diseases or heart failure, in ARDS [71].

Towards treatable traits

One approach that has gained considerable attention in chronic airway diseases is the concept of treatable traits [72]. To cite: "these traits can be *treatable* based on *phenotypic* recognition (and thereby probabilistic evidence based on positive and negative predictive values) or on deep understanding of the critical causal pathways (*e.g.* true *endotypes*)" [72]. These treatable traits may be independent of the traditional syndromic diagnosis and may change over time. For ARDS, we propose to take a similar approach in which a patient can fulfil multiple treatable traits and thereby require multiple treatments. Furthermore, as treatable traits are, per definition, *label-free* they might generalise outside of ARDS, to acute respiratory failure [73], sepsis [74] or even unselected critically ill ICU patients. We can already start to recognise some potential treatable traits within the ARDS syndrome (table 1), although we emphasise that prospective validation of these approaches is pivotal. Using a treatable traits framework, we can rethink the concept of "ARDS-mimickers" and consider them as examples of treatable traits within the larger syndrome of ARDS (see table 1).

Implications of the research agenda

The evidence for aetiological, physiological and biological heterogeneity in ARDS has important implications for clinical, translational and basic scientists. We presented a list of research priorities that will require elaborate collaboration between researchers across continents, disciplines and expertise. We invite researchers and clinicians from around the world to join us in these efforts. One of the major challenges is that funding agencies incentivise solo projects in radical new directions rather than the highly collaborative, descriptive and iterative studies that are needed to better define phenotypes and validate previous findings [92]. This paper will require novel initiatives of international and intercontinental collaboration.

Perhaps the most important implication of the observed heterogeneity in ARDS is that future RCTs in an unselected population of patients with ARDS should make efforts to thoroughly phenotype the included patients, so as to try to identify phenotypes that are predictive of a positive response in *post hoc* analysis. Ultimately, we believe that RCTs should include a phenotype-based allocation strategy in order to have a chance of showing benefit of the intervention, though it is premature at this point to proceed in this direction without prospective validation of phenotypes. Furthermore, it is of utmost importance to select the end-point based on the attributable effect of ARDS on the outcome within the specific phenotype.

Conclusions

The search for targeted treatment for ARDS has been disappointing, possibly due to the enormous heterogeneity within the syndrome. We propose to systematically address the variations in aetiology, physiology and biology in order to identify treatable traits that can be targeted in future clinical trials. We have established a research agenda and a list of potential treatable traits that may serve as a basis for future studies. Deeper phenotyping and integrative analysis of the sources of variation might result in identification of additional treatable traits that represent specific pathobiological mechanisms, or so-called endotypes.

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