Toward Precision Medicine in Respiratory Failure

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Acute hypoxemic respiratory failure (AHRF) is one of the leading causes for admission to the ICU (1). Acute respiratory failure (ARF) is defined as the inability of the respiratory system to meet the oxygenation and ventilation requirements of the patient. Respiratory support for oxygenation, for example, with high-flow nasal cannula (HFNC), and of ventilation, with mechanical ventilation is required to sustain effective gas exchange while treatment for the underlying condition is initiated.

Critically ill patients with AHRF frequently fulfill the criteria for acute respiratory distress syndrome (ARDS) (2). Patients with ARDS exhibit exudative pulmonary edema due to increased permeability of the alveolar-capillary membrane due to injury. The pathophysiology of ARDS involves a local or systemic inflammatory response, endothelial dysfunction, and epithelial injury (3). These processes are not captured in the clinical definition of the syndrome, and there is poor agreement between the clinical criteria and histopathological evaluation postmortem (4). In recent years, the clinical criteria for ARDS have been broadened, and the recently published global definition allows patients supported with HFNC alone to be classified as having ARDS (5). In effect, this will result in an even larger proportion of patients with AHRF who fulfill the criteria of ARDS (6).

Simultaneous with the trend to broaden the diagnostic criteria for ARDS, there has also been a redirected focus on the further development of precision medicine strategies for ARF in general and ARDS in particular (3). This review aims to answer three questions related to precision medicine in ARF: 1) why do we need it; 2) what has been done so far; and 3) what is the agenda going forward?

WHY DO WE NEED PRECISION MEDICINE IN ACUTE RESPIRATORY FAILURE?

Patients with ARF are inherently heterogeneous. Respiratory failure has a broad differential diagnosis and can be traced to dysfunction of respiratory drive or muscles, filled pleural space, vascular obstruction, alveolar filling, or airway narrowing. Even when only conditions that affect the alveolar space are considered, the between-patient differences are obvious at the bedside. For ARDS specifically, the debate regarding lumping or splitting of these patients has been ongoing for at least 50 years (7, 8).

Irrespective of such heterogeneity, most interventional studies have included unselected populations of patients with ARDS. Advances in lung protective mechanical ventilation strategies have been gained in recent decades

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and guidelines now recommend the use of low tidal volume ventilation in all ARDS patients, and prone positioning and eventually venovenous extracorporeal membrane oxygenation (ECMO) in select patients with persistent severe hypoxemia (9). The inclusion of all-comers with ARDS without further stringent selection based on other criteria has been important for the inclusion of sufficiently large patient populations and has supported the development of national, regional, and even global recruitment. In contrast to the identification of lung protective strategies, almost all pharmacological interventions failed to show a consistent improvement in outcomes (10, 11).

It is not due to lack of trying that no effective pharmacological intervention for ARDS has been identified so far. More than 50 randomized controlled trials (RCTs) have studied a wide variety of interventions with good preclinical and early-stage clinical evidence to support their benefit in patients with ARDS (10, 11). Some interventions have shown signals for benefit in early trials, but these signals could not be reproduced in validation studies. This is an additional argument for inherent heterogeneity of the population, where the patient sample might drive differential treatment effects between studies.

The ICU is the ultimate data rich environment. In AHRF, in particular, we have access to rich and longitudinal data related to physiological, imaging, and biological changes. In clinical practice, physicians use data from all of these sources to guide decision-making. This is largely based on clinical training, experience, and physiological understanding. For a long time, we have failed to utilize the available data and improve trial design to address the sources of heterogeneity and improve trial design.

WHAT HAS BEEN DONE SO FAR?

AHRF and ARDS can be considered clinical phenotypes; a set of traits that result from an interaction of the genotype and environmental exposures. With precision medicine, we aim to move beyond the clinical phenotype alone. Traditionally, subsets based on arbitrary cutoffs of clinically relevant variables have been identified. The reliance on such univariable approaches has the major disadvantage that many patients will fall just on either side of the cutoff, resulting in frequent switching between subgroups. Subphenotypes have been described as "subgroups that can be reliably discriminated from other subgroups based on a data-driven assessment of a multidimensional assessment of traits" (3, 9). **Table 1** provides an overview of important concepts related to precision medicine in AHRF. Valuable advances have been made in the identification of subgroups and subphenotypes related to respiratory physiology, lung imaging, and biological

TABLE 1.
Important Concepts in Precision Medicine for Acute Hypoxemic Respiratory Failure

Concept	Definition
Phenotype	Clinically observable set of traits resulting from an interaction of genotype and environmental exposures
Subgroup	A subset of patients in a phenotype, based on any cutoff in any variable; this cutoff can be arbitrary and frequently patients fall just on either side of it resulting in patients switching subgroups
Subphenotype	Subgroup that can be reliably discriminated from other subgroups based on a data-driven assessment of a multidimensional assessment of traits
Endotype	Subphenotype with distinct functional or pathobiological mechanism, which preferably responds differently to a targeted therapy
Treatable trait	A subgroup that shows beneficial treatment effect toward a relevant clinical outcomes
Heterogeneity of treatment effect	Nonrandom variability in the direction or magnitude of a treatment effect toward a clinical outcomes
Predictive enrichment	Selection of a subgroup of patients who are more likely to show beneficial heterogeneity of treatment effect
Prognostic enrichment	Selection of a subgroup of patients who are more likely to experience the primary endpoint of the study

response through retrospective analyses of observational cohorts and RCTs.

Respiratory Physiology

Respiratory physiology has been used for decades to guide selection of patients for whom an intervention could be beneficial, predict responsiveness to a therapy if evaluated after its application, or inform prognosis at a static moment or over time. This has led to some "precision" in our approach to patients with AHRF.

Hypoxemia thresholds have been a historic example of physiologic cut points that have been used to discriminate subgroups who may benefit from an intervention vs. those who may not. Invasive mechanical ventilation in the prone position was initially hypothesized to benefit all patients with ARF and the initial RCTs evaluated this intervention across all severities of ARF. While these RCTs did not demonstrate a mortality benefit, it was noted that the most hypoxemic subgroup seemed to derive the greatest benefit (12). This informed the design of the landmark Proning Severe ARDS Patients (PROSEVA) trial that restricted inclusion to patients with ARDS and a Pao_2/Fio_2 less than 150 mm Hg on at least positive end-expiratory pressure (PEEP) of 5 cm H_2O with an Fio_2 of at least 60% after a 12–24 hours stabilization period (13). When prone positioning was applied to this higher severity subgroup, a 28-day mortality benefit was seen. One of the keys to success in PROSEVA may have been the exclusion of patients who respond well to optimization of the ventilator or recover in the stabilization period, as they are unlikely to benefit from the intervention. Similar hypoxemia cut points—learned over time—combined with other evidence of injurious ventilator settings have demonstrated the ability to discriminate subsets of patients who may benefit venovenous ECMO vs. those who may not (14).

Despite the success of prone positioning and venovenous ECMO for the most severe hypoxemic ARDS patients, we should not only rely on hypoxemia for the identification of physiological subgroups. Furthermore, traditional subgroup analyses with arbitrary cutoffs may not be the most efficient way to detect heterogeneity of treatment effect (HTE; a nonrandom variation in the direction or magnitude of the treatment effect; Table 1). Using individual patient meta-analysis of patients randomized in a lower vs. higher tidal volume trial, HTE based on elastance (inverse of compliance) of the respiratory system was studied (15). Elastance was adjusted for predicted body weight (PBW) to account for the size of the normal lung and modeled as a continuous variable in a Bayesian framework. Based on this analysis, the benefit of low tidal volume ventilation was attributable to patients with an elastance of 2 cm H_2O/(mL/kg) or more. A similar approach was taken in a secondary analysis of the REST trial, in which extracorporeal Co_2 removal was studied in patients with moderate/severe ARDS. HTE was observed for ventilatory ratio and Pao_2/Fio_2, with a higher likelihood for benefit in patients with a higher ventilatory ratio or a higher Pao_2/Fio_2 at baseline (16).

Heterogeneity of treatment may not only be restricted to subgroups across entry criteria but also subgroups defined by a physiologic response after the application of an intervention. The Lung Open Ventilation Strategy (LOVS) and Expiratory Pressure (ExPRESS) trials evaluated a high vs. low PEEP strategy in patients with ARDS and found no difference in mortality (17). In a post hoc analysis, the subgroup of patients that had improvement in their Pao_2/Fio_2 following the application of the high PEEP strategy derived a mortality benefit (18). Oxygenation response is, however, a poor predictor of success across interventions as it was not associated with benefit for prone positioning and tidal volume selection. Driving pressure has been postulated as a mediator of lung protective mechanical ventilation in a meta-analysis of RCT focused on PEEP and/or tidal volume strategy, but a driving pressure targeted approach has not yet shown to be beneficial in prospective studies (19).

Lung Imaging

There is a widely variable effect of an increase in PEEP on reaeration of poorly and nonaerated lung tissue in patients with ARDS (20–22). The extent of nonaerated lung tissue on CT has consistently been shown to be associated with reaeration after recruitment (20–22) and was one of the most important parameters in latent class analysis (LCA) derived subphenotypes of lung recruitment (23, 24). Based on qualitative analysis of CT scans at low PEEP, three morphology patterns were identified: focal with predominant dorsal-inferior consolidations, patchy distribution, and diffuse lung involvement (25). Patients with focal morphology on CT were highly unlikely to respond to recruitment, while the nonfocal morphologies, both diffuse and patchy, showed a better response (26). Patients that show limited reaeration

after recruitment generally suffer from potentially harmful hyperinflation of the lung (26).

Mechanical ventilation personalized to focal or nonfocal lung morphology has been studied in the Lung Imaging Ventilation (LIVE) study where patients with nonfocal lung morphology received higher PEEP and routine recruitment maneuvres and patients with focal lung morphology received lower PEEP and daily prone positioning (27). The primary intention-to-treat analysis revealed no mortality benefit. Yet, the authors acknowledged that roughly 20% of patients had misclassified lung morphology, likely resulting from the dominant use of limited-quality chest radiography for classification as CT scans are logistically impractical. In accurately classified patients, personalized ventilation demonstrated a 10% reduction in mortality, whereas misaligned ventilation in misclassified patients proved harmful. Therefore, personalized ventilation based on morphology is promising but accurate bedside classification is crucial.

An alternative to CT and chest radiography could be lung ultrasound (LUS), which is a bedside, radiation-free and easy to learn imaging modality (28). Focal and nonfocal lung morphology can be assessed with LUS based on the presence and the distribution of artifacts and nonaerated lung tissue in multiple lung regions (29, 30). These LUS methods have shown to be accurate compared with gold standard CT (29).

Biological Response

Systemic inflammatory subphenotypes have been identified in patients with ARDS using LCA and cluster analysis (31, 32). The LCA-derived classes were later called hypoinflammatory and hyperinflammatory subphenotypes. Across various intervention and observational studies, the hypoinflammatory and hyperinflammatory subphenotypes have conserved prevalence (67–74% vs. 26–33%, respectively) and mortality rates (19–23% vs. 44–51%, respectively) demonstrating utility for prognostic enrichment (33–35). These subphenotypes may also provide predictive enrichment, although more evidence is needed. The hyperinflammatory subphenotype is characterized by higher circulating plasma levels of inflammatory markers (interleukin [IL]-6, IL-8, soluble tumor necrosis factor 1 [sTNFR1], and plasminogen activator inactivator-1), more use of vasopressors, more metabolic acidosis, and a greater prevalence of sepsis as compared with the hypoinflammatory subphenotype. These subphenotypes are extensible to ARF (36), COVID-19 (37, 38), pediatric ARDS (39), sepsis (40), and a generalized population of intensive care patients on mechanical ventilation (41).

In post hoc analyses of interventional trials, ARDS subphenotypes responded differently to multiple treatments (HTE) (31, 33, 34). Simvastatin showed no overall benefit in the Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction (HARP-2) RCT (42), but in post hoc analysis, the hyperinflammatory subphenotype seemed to benefit selectively (34). These data highlight the need to test pharmacotherapeutic agents prospectively in a subphenotype stratified trial. In the past, however, ARDS subphenotypes were impossible to identify prospectively due to the need for large, normalized datasets that include a broad set of inflammatory biomarkers for LCA. Now, systemic inflammatory subphenotypes can be identified on an individual patient basis using a parsimonious logistic regression model (43) that incorporates the rapid measurement of a limited number of biomarkers (Clinical Evaluation of a Point of Care [POC] assay to identify PHenotypes IN the Acute Respiratory Distress Syndrome [PHNID] study; NCT04009330). Identification is also possible using an eXtreme Gradient Boosting "clinical classifier" model that incorporates 24 routinely collected clinical data points (44).

WHAT IS THE AGENDA GOING FORWARD?

One of the key challenges of the next decade is to evaluate the effect of the precision medicine approaches outlined above in prospective RCTs. There are various initiatives that will evaluate ventilation strategies and pharmacotherapy in a precision framework. We will discuss three that align most closely with the heterogeneity that has been described (**Fig. 1**).

Respiratory Physiology

Platform of Randomized Adaptive Clinical Trials in Critical Illness (PRACTICAL) is a Bayesian adaptive randomized platform trial evaluating multiple interventions for patients with ARF. Precision is integrated through the use of respiratory physiology to explore HTE according to respiratory system elastance

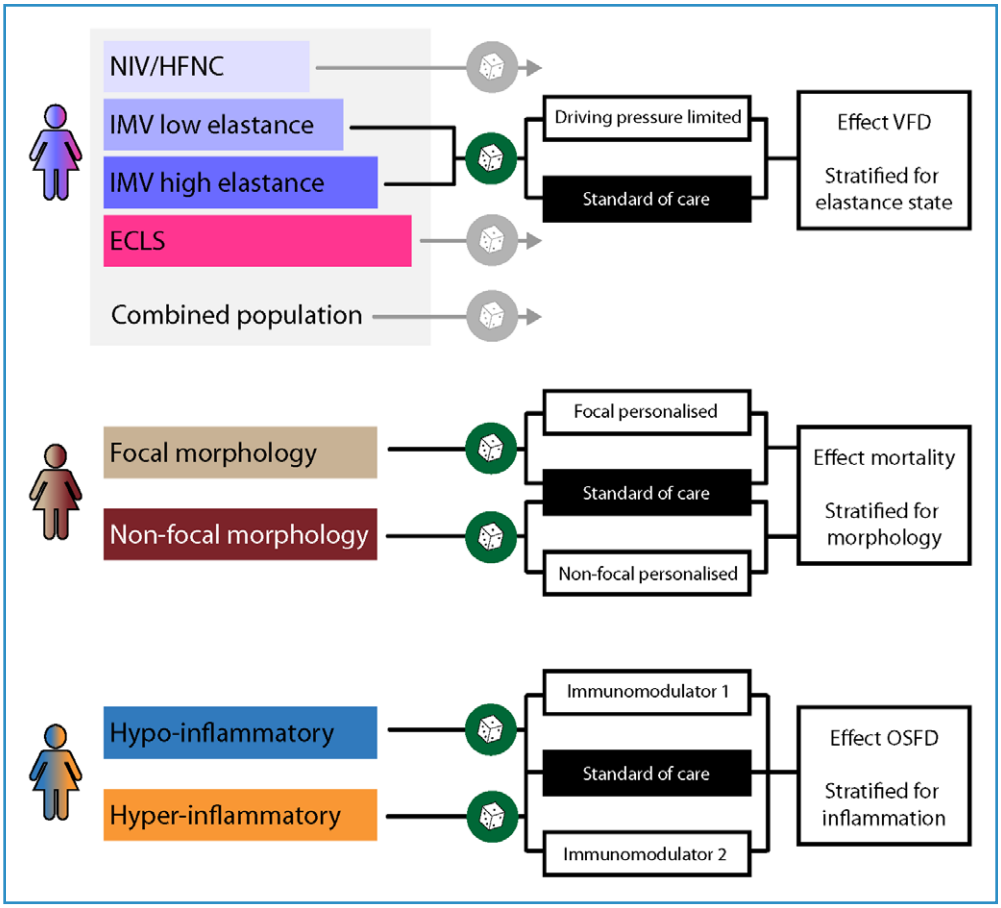

Figure 1. Precision medicine trial design: three examples. **Top**, Design of select domains of the Platform of Randomized Adaptive Clinical Trials in Critical Illness (PRACTICAL) platform that considers different disease states of acute respiratory failure. Four mutually exclusive disease states are identified: 1) nonintubated, 2) patients undergoing invasive mechanical ventilation (IMV) with low elastance of the respiratory system, 3) IMV with high elastance of the respiratory system, and 4) patients undergoing extracorporeal life support (ECLS). Each disease state has a series of different trial domains. Patient in disease state 2–3 undergo randomization in the DRIVing PrEssure Limited Ventilation in Hypoxemic Respiratory Failure (DRIVE) trial. They receive driving pressure limited mechanical ventilation or standard of care. The primary endpoint is the effect on ventilator-free days (VFDs) at day 28. A priori stratification for baseline elastance allow for testing of the explicit hypothesis that a driving pressure limited strategy is more beneficial in patients with low elastance than in patients with high elastance. Multiple other trials are run in PRACTICAL including the evaluation of Helmet noninvasive ventilation (NIV) with high-flow nasal cannula (HFNC) vs. HFNC in the nonintubated disease state and various mechanical ventilation strategies with ECLS in the ECLS disease state. Further details available at: https://practicalplatform.org/. **Middle**, Design of the Personalized Mechanical Ventilation Guided by UltraSound in Patients with Acute Respiratory Distress Syndrome (PEGASUS) trial. Two mutually exclusive disease states are identified based on lung ultrasound: 1) focal morphology and 2) nonfocal morphology. Patients are randomized within each subphenotype between personalized treatment strategy and standard of care. In contrast to the other studies, the personalized strategy is different for each subphenotype. The primary endpoint is mortality at day 90. The trials allows for causal inference regarding the effect of personalized treatment strategies per morphology subphenotype. **Bottom**, Design of the Precision Medicine Adaptive Network Platform Trial in Hypoxemic Acute Respiratory Failure (PANTHER) platform. Two mutually exclusive disease states are identified based on plasma biomarkers: 1) hypoinflammatory and 2) hyperinflammatory subphenotype. Patients are randomized within each subphenotype to one of two drugs on top of standard of care, or standard of care alone. The primary endpoint is organ support-free days (OSFDs). Adaptive analyses with stopping rules for effectiveness and futility are a priori stratified per inflammatory subphenotype, assuming differential treatment effects between subphenotypes. *Dice indicate randomization.

to estimate strata-specific treatment effects in these trials. The severity of respiratory support (HFNC or noninvasive ventilation, invasive ventilation, and ECMO) and respiratory system elastance are used to guide patient-level strata evaluations within these trials. The platform is organized in domains such as noninvasive respiratory support strategies, invasive mechanical ventilation and sedation, extracorporeal life support, and the use of corticosteroids among others. The platform biosampling and biobanking strategy together with embedded physiological studies will facilitate translational science to understand mechanism and HTE. One of the advantages of this platform trial is the creation of a standardized research ecosystem to facilitate coenrollment and shared control groups to maximize the contribution of each individually enrolled patient.

In the PRACTICAL DRIVing PrEssure Limited Ventilation in Hypoxemic Respiratory Failure trial, ARDS patients undergoing invasive mechanical ventilation are randomized to driving pressure-limited mechanical ventilation or guideline-based conventional mechanical ventilation. In the intervention arm, tidal volume and PEEP are adjusted to maintain static airway driving

pressure less than 15 cm H_2O (during passive ventilation) and dynamic transpulmonary driving pressure less than 23 cm H_2O (during assisted ventilation). As patients are stratified based on respiratory system elastance, this allows for prospective evaluation of two previous predictions using secondary analyses of already performed RCTs: 1) is driving pressure guided mechanical ventilation superior to a one-size-fits-all strategy and 2) is it safe to increase tidal volumes in ARDS patients with low elastance. Ventilator-free days at day 28 will serve as the primary endpoint.

Lung Imaging

The Personalized Mechanical Ventilation Guided by UltraSound in Patients with Acute Respiratory Distress Syndrome (PEGASUS) study (27) is currently recruiting and aims to overcome the limitations of the LIVE study by adopting a LUS method that showed to be accurate in morphology classification (29, 45). The study designs of these two trials are similar by intention. Patients are randomized to an intervention and control arm, where the intervention arm receives mechanical ventilation aligned with either focal or nonfocal morphology and the control arm receives conventional ventilation according to European Society for Intensive Care Medicine (ESICM) ARDS guidelines (9). The benefit of this design is that it is relatively simple to comprehend and execute. The intervention tested in these trials is personalized ventilation rather than a specific ventilator strategy for one subphenotype. The assumption in this design is that the personalized ventilation strategy benefits focal and nonfocal ARDS patients to the same extent. This assumption proved to be reasonable in the LIVE study and will be confirmed in a preplanned secondary stratified analysis in PEGASUS.

Correct classification of lung morphology is crucial for successful personalized ventilation and is challenging, especially in imaging subphenotypes where the allocation is done either visually on CT and chest radiography or semiquantitatively with LUS. Extensive training of all study staff and monitoring correct classification during the trial is therefore a prerequisite for performing morphology-guided interventions.

The dynamic changes in lung morphology over time remain unknown. Arguably, lung injury could progress in patients who initially present with focal abnormalities resulting in a nonfocal lung morphology, and thus are more likely to benefit from higher PEEP and recruitment. In PEGASUS, due to the low PEEP strategy in the focal subphenotype randomized to the personalized arm, morphology classification can be repeated over time, and the personalized ventilation strategy can be adapted. For patients with an initial nonfocal injury pattern, such an approach may not be feasible due to the high PEEP strategy and is probably unwanted. Recruitment of ventral lung regions due to a beneficial response to high PEEP in the personalized treatment arm could result in a switch of lung morphology to a focal pattern but would not warrant a change in ventilation strategy.

Biological Response

The Precision Medicine Adaptive Network Platform Trial in Hypoxemic Acute Respiratory Failure (PANTHER) trial is planned to commence recruitment in 2024 (46). PANTHER is an international phase II trial in ARDS that will use a Bayesian adaptive multiarm trial design, with parallel arms for the hyperinflammatory and hypoinflammatory biological subphenotypes and simultaneous testing of multiple pharmacological interventions, using a primary outcome measure of organ support-free days. Precision is integrated into the trial from the outset, with participants being stratified by subphenotype at the point of care using a parsimonious model incorporating IL-6, sTNFR1, and bicarbonate (43). IL-6 and sTNFR1 are rapidly quantified using a bedside chemiluminescence analyzer and integrated into the model with bicarbonate from an arterial blood gas, which generates a probability of allocation to the hyperinflammatory subphenotype. Based on a threshold probability, participants are assigned to either the hyperinflammatory or hypoinflammatory subphenotype and subsequently randomized in 1:1:1 ratio between two intervention arms or control per inflammatory subphenotype strata.

The design of PANTHER has multiple potential benefits that facilitate early matching of treatment to biological subphenotype, trial efficiency, and ongoing translation research. The adaptive design allows efficacy or futility to be declared in an arm at adaptive analyses based on prespecified stopping criteria, facilitating the earlier recognition of beneficial or futile treatments with a reduced number of participants

recruited. The design also allows the simultaneous evaluation of multiple therapies in both the hyperinflammatory and hypoinflammatory subphenotypes. The platform design allows for the addition of new treatment arms when a previous treatment either "graduates" to a subphenotype-specific evaluation in a definitive phase III trial or is declared futile. The process of deciding which new treatments to evaluate will be undertaken in a transparent fashion by an independent therapeutics prioritization committee, which can evaluate treatments proposed by platform members, industry, or independent academic investigators (47).

In addition to the integration of new treatments, the flexibility of PANTHER's design allows the rapid integration of new methods to subphenotype patients with ARDS. The refinement or addition of subphenotyping methods and insights into new potential treatments will be supported by ongoing embedded translational research. From the outset, PANTHER will collect a breadth of biosamples from participants, including plasma, peripheral blood mononuclear cell isolates, and respiratory samples from the upper and lower airways. This will allow comparison of subphenotypes between the systemic and alveolar compartment, an important knowledge gap that needs to be addressed. These samples will facilitate the understanding of biological subphenotypes of ARF and how they interact with treatment. As such, PANTHER will not only be an engine for efficacy evaluation but will also drive an increased understanding of ARF biology and putative underpinning mechanisms linked to subphenotype development and recovery.

SUBPHENOTYPE INTEGRATION

A foreseeable future challenge is the integration of different subphenotyping approaches in clinical practice. In general, we envision that subphenotypes be interpreted in a multidimensional space and will serve as treatable traits: identifiable and modifiable factors that can be targeted by an intervention that improves patient outcomes. A single patient may, for example, present with a focal ARDS requiring a low PEEP strategy with early application of prone positioning and a hyperinflammatory state that requires immunomodulatory treatment. Yet, when interventions are mutually exclusive problems occur. For example, if an ARDS patient with nonfocal lung morphology also has a low driving pressure, personalized treatment strategies may recommend a tidal volume strategy of 4–6 mL/kg PBW based on morphology criteria, but a more liberal approach based on the driving pressure. Guidelines will have to carefully evaluate overlap between subphenotype-targeted interventions, a currently underdeveloped science. Two precision medicine platform trials, PRACTICAL and PANTHER, have therefore set out to coordinate data and sample collection, in order to make meaningful inferences regarding subphenotype overlap.

CONCLUSIONS

A step toward precision medicine is critical in improving outcomes of patients with ARF in general and ARDS in particular. Subphenotype-targeted RCTs are the only way toward broadly impacting patient care. Substantial steps have been taken to understand HTE based on physiology, imaging, and biological data. Novel international and collaborative trials are now recruiting patients and will test if our predictions regarding the benefit of precision medicine for ARF are correct.

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