



Acute Respiratory Distress Syndrome Subphenotypes beyond the Syndrome: A Step toward Treatable Traits?

Few trials of pharmacological interventions in critical care show benefit despite decades of laboratory-based and translational research dedicated to identifying mechanisms responsible for critical illness (1). This reality has prompted us to consider the limitations of our current definitions of critical illness syndromes. Syndromes such as acute respiratory distress syndrome (ARDS) and sepsis are defined based on clinical criteria that yield little insight into their underlying biology. This syndromic approach to disease classification has led to trial designs that target heterogeneous populations, which may explain why treatments have been unsuccessful.

The identification of biologically distinct subphenotypes in ARDS (2, 3), sepsis, and acute kidney injury, which have divergent outcomes and may respond differently to randomly allocated therapies (2, 4–7), may point toward an alternative approach to testing pharmacological therapies. These subphenotypes tend to be defined by biomarkers that are agnostic to syndromic diagnosis within critical illness, suggesting mechanistic pathways may be conserved across these syndromes. Interestingly, similarities between subphenotypes identified using varying methods for phenotype allocation and in different syndromes have emerged (7, 8). Indeed, ARDS subphenotypes with distinct clinical trajectories have also been identified in patients with coronavirus disease (COVID-19) (9). These findings led to the hypothesis that there may be host-response subphenotypes of critical illness, which might also be termed “treatable traits,” that are independent of syndromic definitions (Figure 1). If this hypothesis is correct, our approach to clinical trials premised on those syndromic definitions should be reevaluated.

In this issue of the *Journal*, Heijnen and colleagues (pp. 1503–1511) provide the most compelling evidence to date supporting the concept that treatable traits in critical illness are independent of syndromic diagnosis (10). In a retrospective analysis of a large cohort of mechanically ventilated patients ($n = 2,499$), they used previously described parsimonious models for subphenotype allocation for their reactive and uninflamed ARDS subphenotypes (cluster-derived, using IL-6, IFN- γ , ANG1/2, and PAI-1) (3) and for the hyperinflammatory and hypoinflammatory subphenotypes (latent class analysis [LCA]-derived, using IL-8, protein C, and bicarbonate) (11) to demonstrate that these classifier methods also provide prognostic enrichment in a non-ARDS population ($n = 1,825$). Regardless of ARDS diagnosis, the reactive and hyperinflammatory subphenotypes retained their associations with increased ICU mortality, increased 30-day mortality, and lower probability of successful extubation. In keeping with previous ARDS

studies, this study demonstrates that in univariable analysis, the reactive and hyperinflammatory subphenotypes were the strongest predictors of ICU mortality in patients without ARDS (hazard ratio, 2.43; 95% confidence interval [CI], 1.90–3.11; $P < 0.001$; and hazard ratio, 2.54; 95% CI, 2.00–3.24; $P < 0.001$, respectively). These subphenotypes retained their association with mortality even when adjusted for APACHEIV score, demonstrating prognostic value independent of severity of illness.

A subset of patients ($n = 719$) had leukocyte gene expression profiles examined by microarray. Principal component analysis revealed that members of the same cluster-derived and LCA-derived subphenotypes grouped together regardless of the presence of ARDS, suggesting that the transcriptome is conserved within these subgroups across syndromic definitions and providing further evidence that the biology of these subphenotypes is fundamentally distinct.

These data have important implications. First, they suggest that the subphenotypes identified in ARDS to date (e.g., reactive vs. uninflamed and hyper- vs. hypoinflammatory) may be translatable to patients without ARDS. Furthermore, independently described subphenotypes have significant overlap, and analogous cluster- and LCA-derived subphenotypes (hyperinflammatory and reactive; hypoinflammatory and uninflamed) demonstrated similar blood leukocyte gene expression profiles. This latter finding suggests convergence at a common biological signal, further increasing confidence that these subphenotypes represent a generalizable and reproducible finding.

Despite the strength of this data, some limitations should be considered. The study population consisted solely of mechanically ventilated patients, and there was a bias in biomarker data availability toward those patients with definite or probable infection, who have a high risk of developing ARDS. Subphenotyping methods developed in ARDS may therefore be more translatable to this population rather than a broader population. Furthermore, classification was accomplished using parsimonious models rather than the gold-standard cluster analysis or LCA. Despite the strong concordance of these models with gold standard (AUC = 0.94; 95% CI, 0.92–0.95 for LCA-derived subphenotypes; AUC = 0.98; 95% CI, 0.97–0.99 for cluster-derived subphenotypes) (3, 11), without *de novo* cluster analysis or LCA, these results cannot provide statistical evidence that a two subphenotype approach is the most robust approach to subdivision in patients without ARDS.

These results imply that treatments that are found to work in ARDS-specific subphenotypes might be translatable to a broader population of patients. In a *post hoc* analysis of the HARP-2 clinical trial of simvastatin in ARDS, which showed no overall benefit, the LCA-derived hyperinflammatory subphenotype had improved 28-day survival with simvastatin versus placebo (5). Although prospective validation is needed, the results presented here suggest that “hyperinflammatory” patients without ARDS might also benefit from simvastatin. Unfortunately, the ability to prospectively phenotype critically ill patients on ICU admission remains a

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Supported by NIH-NHLBI grant R35 HL140026 (C.S.C.).

Originally Published in Press as DOI: 10.1164/rccm.202101-0218ED on February 10, 2021

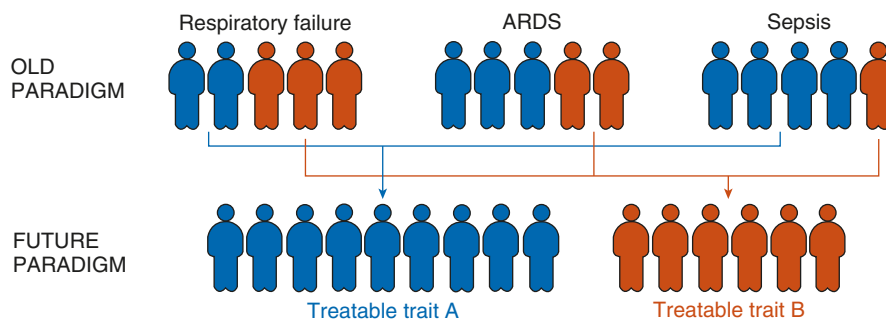


Figure 1. The impending transformation in critical care syndrome classification. In the old paradigm, we classify syndromes such as respiratory failure, acute respiratory distress syndrome, and sepsis based on clinical criteria that poorly inform treatments. In the future paradigm, we identify more biologically meaningful subgroup characteristics that inform disease-modifying treatment options (treatable traits). As pictured above, the data presented by Heijnen and colleagues (10) in this issue of the *Journal* brings us closer to identifying treatable traits. ARDS = acute respiratory distress syndrome.

limitation to the translation of these subphenotypes into clinical trials and, ultimately, practice. Allocation of ARDS subphenotypes requires the measurement of biomarkers that are not available in routine care, limiting their clinical utility at present. A prospective multicenter study (NCT04009330) that employs a point-of-care assay for allocation of the subphenotypes is in progress and aims to address this challenge. Alternatively, a clinical variable-only classifier has recently been developed for the LCA-based subphenotypes, though prospective validation of this approach is also needed (12). Of note, Heijnen and colleagues demonstrate incomplete overlap between cluster-derived and LCA-derived subphenotypes. Notably, only 56% of patients assigned to the reactive subphenotype were also assigned to the hyperinflammatory subphenotype, whereas 44% were assigned to the hypoinflammatory group (10). Further studies of the reasons for the divergence in these two approaches are needed.

Once we can consistently and prospectively identify subphenotypes, we need a better understanding of the underlying biology to identify which therapies might be appropriate to test in each subphenotype. Leukocyte expression profiles presented here and previously (13) point toward neutrophil activation, oxidative phosphorylation, and mitochondrial dysfunction in the reactive subphenotype, with upregulation of MAPK pathways in the uninflamed group. As more advanced techniques that allow detection of novel transcripts and modifications (RNA sequencing) and transcriptomic mapping of individual cell types (single-cell RNA sequencing) become increasingly available, we hope to further advance our understanding (14, 15). Other key unanswered mechanistic questions include how the biology of subphenotypes differs beyond the circulating plasma (e.g., for lung or kidney injury), whether metagenomic sequencing can identify differences in either pathogens or the microbiome between subphenotypes, and which experimental models are best suited to test novel interventions for each subphenotype.

The novel findings presented in this issue of the *Journal* (10) represent important evidence in support of a new ontology of critical illness—identifying treatable traits in critical care that are independent of clinical diagnosis (Figure 1). Whether such a sea change will ultimately be usefully translated to clinical trials and clinical care remains unknown, but other fields such as oncology have

embraced this possibility. Heijnen and colleagues have helped bring us one step closer to this new frontier. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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⊗ The Intersection of Health and Critical Illness: Preservation and Restoration

Health is a state of “physical, mental, and social well-being” (1). Critical illness, by its nature, is a threat to all domains of health. Envision the innumerable patients laying in ICU beds across the world. As they fight serious illness, and their care teams rally to battle with them, their muscles atrophy. Their cognition falters. The fabric of their social well-being is torn apart.

Days (or weeks) later, those who survive will emerge from the hospital, in varied states of disability, to continue their recovery. What is the long-term fate of these survivors? Will their health—their physical, mental, and social well-being—be restored to live and thrive? Does long-term recovery vary by the type of serious illness that warrants ICU admission?

These and other fundamental questions have troubled us since Dr. Ramona Hopkins and colleagues published the experience of 55 acute respiratory distress syndrome survivors in 1999 (2). At 1 year, 78% exhibited impaired attention, concentration, memory, and/or mental processing speed, together with impairments in physical health, pain, and general health. Nearly half were unable to resume usual activities or return to work.

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Author Contributions: Conception and design of manuscript: J.H.M. and M.E.M. Drafting and revision: J.H.M. and M.E.M.

Originally Published in Press as DOI: 10.1164/rccm.202102-0306ED on February 26, 2021

In the decades after this wake-up call, an expansive body of literature has substantiated impairments in three domains—physical function, mental health, and cognition—after sepsis, respiratory failure, and other critical illnesses (3–5). Termed post-intensive care syndrome (PICS), this constellation of impairments after critical illness is remarkably common, and often severe and enduring (6, 7).

However, the epidemiology of PICS often lacked insight into patients’ baseline health before ICU admission. Given that “asteroid strikes are rare events in our medical ICUs,” accounting for pre-ICU health trajectory is vital to our understanding of long-term impairments (8). Furthermore, to personalize post-ICU care, a more mature understanding of impairments for the surgical population was warranted.

In this issue of the *Journal*, Geense and colleagues (pp. 1512–1521) provide important new insights into the trajectory of health in the year after critical illness (9). The investigators conducted a multicenter, longitudinal, prospective cohort study. The study enrolled adults admitted to medical and surgical ICUs from four hospitals in the Netherlands. Patients, or their proxies, completed baseline health questionnaires before elective surgery or during urgent surgical or medical ICU admissions. The investigators then obtained follow-up measures 1 year after ICU admission.

Assessments obtained in the pre-ICU and post-ICU period included measurement of frailty, fatigue, anxiety, depression, cognition, and quality of life. New or worsened physical function and post-traumatic stress symptoms were assessed at 1-year follow-up.

Of 3,320 patients who completed the baseline questionnaire, 2,345 (71%) completed the 1-year questionnaire. Most patients had an elective surgical admission (60%), whereas the remainder experienced medical (28%) or urgent surgical (12%) admissions.