Toward Smarter Lumping and Smarter Splitting: Rethinking Strategies for Sepsis and Acute Respiratory Distress Syndrome Clinical Trial Design

Hallie C. Prescott[1,2], Carolyn S. Calfee[3,4], B. Taylor Thompson[5], Derek C. Angus[6], and Vincent X. Liu[7]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Michigan, Ann Arbor, Michigan; [2]Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan; [3]Division of Pulmonary and Critical Care Medicine, Department of Medicine, and [4]Department of Anesthesia, University of California, San Francisco, San Francisco, California; [5]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Massachusetts General Hospital, Harvard School of Medicine, Boston, Massachusetts; [6]Clinical Research, Investigation, and Systems Modeling of Acute Illness Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and [7]Division of Research, Kaiser Permanente, Oakland, California

ORCID ID: 0000-0002-8442-6724 (H.C.P.).

Abstract

Both quality improvement and clinical research efforts over the past few decades have focused on consensus definition of sepsis and acute respiratory distress syndrome (ARDS). Although clinical definitions based on readily available clinical data have advanced recognition and timely use of broad supportive treatments, they likely hinder the identification of more targeted therapies that manipulate select biological mechanisms underlying critical illness. Sepsis and ARDS are by definition heterogeneous, and patients vary in both their underlying biology and their severity of illness. We have long been able to identify subtypes of sepsis and ARDS that confer different prognoses. The key is that we are now on the verge of identifying subtypes that may confer different response to therapy. In this perspective, inspired by a 2015 American Thoracic Society International Conference Symposium entitled "Lumpers and Splitters: Phenotyping in Critical Illness," we highlight promising approaches to uncovering patient subtypes that may predict treatment responsiveness and not just differences in prognosis. We then discuss how this information can be leveraged to improve the success and translatability of clinical trials by using predictive enrichment and other design strategies. Last, we discuss the challenges and limitations to identifying biomarkers and endotypes and incorporating them into routine clinical practice.

Keywords: sepsis; acute respiratory distress syndrome; endotype; prognostic enrichment; predictive enrichment

Critical illnesses such as sepsis and acute respiratory distress syndrome (ARDS) are costly (1, 2) and deadly (3, 4). Unfortunately, despite decades of dedicated research efforts, we have yet to identify a single targeted pharmacological therapy effective in sepsis or ARDS (5, 6). Hundreds of immunomodulatory therapies (e.g., tumor necrosis factor, endotoxin, and IL-1 antagonists) have shown promise in animal sepsis models, but none have translated into improved outcomes in human studies (5). In ARDS, although the field has advanced in terms of limiting mechanical injury from ventilation (positive studies for lower tidal volume ventilation [7], neuromuscular blockade [8], and high positive end-expiratory pressure [PEEP] [9]), there have been many negative trials for pharmacological agents, including corticosteroids, neutrophil elastase inhibitors, anticoagulants, prostacyclin, and surfactant replacement, among others (6).

Certainly, several factors may explain our failure to identify targeted pharmacologic therapies in sepsis (5) and ARDS (6). Many of the treatments tested may simply not have been efficacious. For other treatments, such as corticosteroids for persistent ARDS, the side effects of treatment (e.g., hyperglycemia, neuromyopathy) may always outweigh the benefits (e.g., reduced

(Received in original form December 31, 2015; accepted in final form May 26, 2016)

Supported by National Institutes of Health grants K08 GM115859 (H.C.P.), HL131621 (C.S.C.), GM107650 (D.C.A.), K23 GM112018 (V.X.L.), and U01 HL 123009-01 (D.C.A. and B.T.T.).

Author Contributions: H.C.P. drafted the manuscript; C.S.C., B.T.T., D.C.A., and V.X.L. revised it critically for important intellectual content.

Correspondence and requests for reprints should be addressed to Hallie C. Prescott, M.D., M.Sc., NCRC Building 16, 341E, 2800 Plymouth Road, Ann Arbor, MI 48109-2800. E-mail: hprescot@med.umich.edu

Am J Respir Crit Care Med Vol 194, Iss 2, pp 147–155, Jul 15, 2016
Copyright © 2016 by the American Thoracic Society
Originally Published in Press as DOI: 10.1164/rccm.201512-2544CP on May 31, 2016
Internet address: www.atsjournals.org

inflammation) (10). However, the large number of studies that have shown benefit in preclinical studies, but failed to translate to improved outcomes in randomized clinical trials (RCTs), suggests that either (*1*) the animal models poorly represent the human condition, or (*2*) we are failing to identify the appropriate subset of humans to target with novel therapies (5, 6, 11). Although efforts proceed to improve preclinical models, this Perspective explores the second avenue: efforts to better identify patients in whom specific biologic processes are most linked to their subsequent clinical outcomes.

In this perspective, we summarize ideas for identifying meaningful subtypes (*see* Table 1 for nomenclature) of patients to improve clinical trial design and advance patient care. This perspective is motivated by the 2015 American Thoracic Society International Conference Symposium entitled "Lumpers and Splitters: Phenotyping in Critical Illness" and conversations over the ensuing months. Although we focus on sepsis and ARDS, the ideas in this perspective are also applicable to other critical illness syndromes.

Why Lump?

For centuries, physicians have tried to align the signs and symptoms of disease (and later anatomic and biological phenomena) into groupings that would result in better therapeutic management. The decision to "lump" heterogeneous critically ill patients together has served an important function in advancing critical care by promoting early recognition using simple and relatively nonspecific criteria. The key elements of current sepsis treatment—antibiotics, source control, and resuscitation—all require timely delivery to be effective. Likewise, low tidal volume ventilation must be initiated early in the course of ARDS to prevent ventilator-induced lung injury. Yet, many cases of sepsis and ARDS are recognized late, resulting in delayed and inconsistently applied treatment (4, 12).

The 2001 and 2016 consensus sepsis definitions (13, 14) and the 1994 American-European and 2012 Berlin ARDS definitions (15, 16) all rely on clinical criteria. These syndrome definitions are reliable and timely, with good construct validity, predictive validity, and low measurement burden. These clinical definitions have facilitated earlier recognition and timely treatment of both sepsis (17) and ARDS (18), likely contributing to the observed declines in mortality from these syndromes (18–20). But, although useful, these consensus definitions do not identify patients with a high likelihood of an explicit disease process, such as dysregulation of a particular immune pathway in sepsis or the presence of diffuse alveolar damage in ARDS.

A positive consequence of these clinical definitions has been the identification of intensive care unit practices that are effective for the broader critically ill population, such as sedation and ventilator liberation practices (21), lower tidal volume ventilation (7), and early mobility (22). For many of these therapies, the clinically defined syndrome may even be too narrow a target population, as patients without the syndrome may still benefit. For example, all ventilated patients may do better with a lower tidal volume ventilation strategy, not just those with ARDS (23).

Why Split?

Just as physicians have lumped similar patients together for centuries, they have also observed that the traits of individual patients affect both predisposition to disease and response to treatment. The principles of personalized medicine—finding the right treatment for the right patient—date back to the fifth century B.C. writings of Hippocrates (24). And, with the recent failure of many highly anticipated trials of novel therapies for sepsis and ARDS, there is renewed interest in identifying meaningful subtypes to match the right treatment to the right patients (5, 6, 11). For patients who meet the clinical definitions for sepsis or ARDS, there will always be subgroups of patients who are more or less likely to benefit from a particular therapy. In the case of sepsis, this variability may exist because:

Table 1. Nomenclature for Describing Subsets of Patients with Critical Illness

Term	Synonyms	Definition
Subtype	Subgroup; subset	Generic terms for subset of patients. These terms do not imply differences in function, biology, or observable characteristics.
Endotype		A subset of patients defined by a distinct functional or pathobiological mechanism. Endotypes often confer both a differential risk of disease-related outcome and a differential response to a therapy. Thus, such markers may enable both predictive and prognostic enrichment.
Biomarker for treatment responsiveness	Predictive marker; biomarker for therapeutic responsiveness; theranostic marker	A measureable indicator that predicts likelihood of responding to a particular therapy. Such a marker enables predictive enrichment. The biomarker may also have prognostic enrichment potential if it also predicts higher disease severity and worse clinical outcomes.
Phenotype*		A clinical entity defined by observable characteristics that are produced by interactions of the genotype and the environment. The term is often used to describe subsets on the basis of clinical or biochemical variables, natural history, manifestations of disease, and/or response to treatment without any implication about mechanism.

*Because phenotype is used inconsistently in practice, we avoid this term in the Perspective for the sake of clarity.

1. Some patients meeting the clinical definition of sepsis (suspected infection plus acute change in Sequential Organ Failure Assessment score ≥ 2) do not actually have sepsis—for example, if the organ failure is not actually caused by a dysregulated host response to the infection;
2. Even among patients with sepsis, differences in the infection (25), the host inflammatory response (26), or other differences in the underlying biology may render certain therapies more or less beneficial;
3. Even among patients with more homogenous disease (e.g., pulmonary sepsis due to pneumococcus), the severity and time course of illness may still render certain therapies more or less beneficial.

Clinicians inherently recognize that sepsis in a young, healthy patient with pneumococcal pneumonia is different than sepsis in an immunosuppressed transplant recipient with fungal infection. Yet, despite this clinical intuition, our existing treatment paradigms and bundles recommend the same approach for both patients. For some treatments, such as supportive care, this may be optimal. However, for other treatments, such as immune-modulating agents, it is likely better to target specific subtypes of septic patients.

Endotypes distinguish subtypes of patients on the basis of differences in function or biology, such as differences in genotype, gene expression profile, or biomarker concentrations. The identification of distinct endotypes of breast cancer, for example as defined by hormone receptor status, has advanced the management of this disease. Of course, subtypes of complex diseases are rarely defined by a single mechanistic pathway. For example, in "*BRAF*-positive melanoma," after eradicating melanoma cells that are *BRAF* positive, slower-growing melanoma cells with different mutations may be left to grow unchecked. Nonetheless, just as *BRAF* positivity is a useful predictor of responsiveness to a *BRAF* inhibitor (27), endotypes defined by a single mechanism can be valuable, even if they do not fully explain disease pathogenesis.

Lacking insight into underlying mechanisms in critical care, or being unable to measure mechanisms in real time, we have settled for studying novel therapies among all-comers with sepsis or ARDS in most clinical trials or in subgroups not tightly linked to underlying biological mechanisms. It is possible that certain therapies—effective for only a subset of patients with sepsis or ARDS—have been discarded or gone undiscovered because we have not identified the optimal patient population in which to test them.

Another barrier to identifying effective therapies in clinical trials is that subgroups of patients at different likelihood of benefit from disease-modifying therapy (e.g., those with mild vs. severe sepsis) end up having different net relative risk reductions (RRRs) if the therapies also pose fixed harms that are independent of the magnitude of disease (e.g., risk of intracranial hemorrhage from a therapy for sepsis with anticoagulant properties)—a concept known as heterogeneity of treatment effect (28). A recent simulation study suggests that clinically relevant heterogeneity of treatment effect may well exist within critical care trial populations, such that some groups of patients benefit a lot, whereas other groups experience negligible benefits or may even be harmed from treatment (29). Without assessing for heterogeneity of treatment effect, we may mistakenly conclude that a therapy efficacious for some patients is never efficacious because the average treatment effect (the overall result of the clinical trial) is negative.

Potential Solutions

To identify novel pharmacological therapies for sepsis, ARDS, or any syndrome, we must enroll patients who are most likely to benefit. Although pragmatic clinical definitions promote broader recognition and implementation of first-line therapies, they may not be the optimal criteria by which to enroll patients into all RCTs (30), particularly for trials that examine therapies anticipated to work for only a subset of patients (e.g., septic patients with specific bacterial infection or patients with ARDS with diffuse alveolar damage). Clinical trials definitions require high reliability and construct validity but can also tolerate greater measurement and time burdens (31). Yet, despite the contrasting goals of clinical care and trial definitions, the majority of critical care trials over the past few decades have used clinical definitions for study entry criteria (32).

Clinical Trial Enrichment

The United States Food and Drug Administration has recently published a guidance for clinical trial enrichment strategies—"the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be an in unselected population" (33). These strategies fall into three broad categories: (*1*) practical enrichment—decreasing "noise"; (*2*) prognostic enrichment—identifying high-risk patients; and (*3*) predictive enrichment—selecting patients who are likely to respond to treatment.

Practical enrichment is a feature in nearly all early phase efficacy trials. A few of the many examples include selecting patients who are (*1*) likely to comply with treatment, (*2*) unlikely to drop out of the study or experience toxicity, (*3*) not already taking a medication that is similar to the treatment under study, and (*4*) likely to have the disease being studied and unlikely to die from other factors (33).

Prognostic enrichment strategies involve enrolling patients with a greater likelihood of having an outcome of interest (study endpoint), which increases the statistical power to detect a given level of RRR (Figure 1, Table 2). For example, if an adjuvant chemotherapy that confers a fixed 50% RRR for cancer relapse is studied in a population with a 50% (enriched) or a 10% (general population) placebo rate, then a smaller sample size will be needed to detect the corresponding 25 and 5% change in absolute risk, respectively.

Prognostic enrichment is less straightforward in trials of sepsis and ARDS because, in contrast to studies of cancer and other diseases, the outcome of interest (all-cause mortality) may be due to the disease, or it may be due to factors unrelated to the disease (e.g., age, comorbid conditions). Thus, in sepsis and ARDS trials, enriching for the study outcome does not necessarily increase our ability to detect a beneficial treatment if the deaths are not disease related. For this reason, it is better to enroll patients who are likely to die from the disease (e.g., patients with ARDS with a low Pa_{O_2}/FI_{O_2} ratio, or high Murray score [34]), rather than simply enrolling patients with higher risk of death in general (e.g., patients

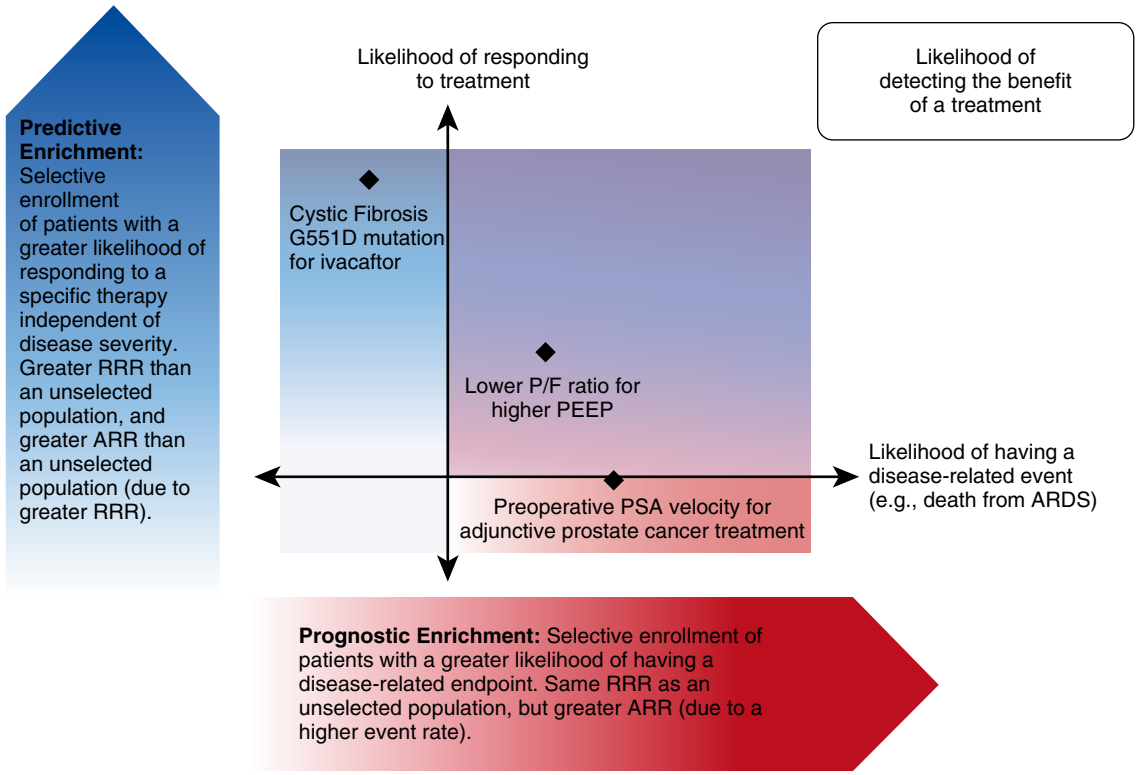

Figure 1. The relationship between predictive and prognostic enrichment strategies. The likelihood that a patient will have an outcome of interest (study endpoint) and the likelihood that a patient will respond to treatment operate on different axes, and both affect our ability to detect treatment benefit. Some biomarkers increase both the likelihood of having the study endpoint and the likelihood of responding to treatment. For example, lower Pa_{O_2}/FI_{O_2} (P/F) ratio identifies patients with a higher risk of dying from hypoxemic respiratory failure, and it also identifies patients with greater lung weight who are more likely to benefit from lung recruitment. Some biomarkers increase the likelihood of having a disease-related event but not the likelihood of responding to treatment. For example, preoperative prostate-specific antigen (PSA) velocity is a prognostic marker only; it is associated with a significantly elevated risk of death from prostate cancer but does not predict the likelihood of responding to a particular treatment. Some markers operate on both axes. Some markers may operate in different directions across the two axes. For example, a G551D mutation is associated with a milder clinical phenotype than F508del homozygotes, but it strongly predicts whether a patient will benefit from ivacaftor. ARDS = acute respiratory distress syndrome; ARR = absolute risk reduction; PEEP = positive end-expiratory pressure; RRR = relative risk reduction.

with ARDS with a high Acute Physiology and Chronic Health Evaluation score). An autopsy study of patients with ARDS supports the merit of this approach: 47% of the deaths in patients with a Pa_{O_2}/FI_{O_2} ratio less than 100 were due to hypoxic respiratory failure, compared with just 11% of the deaths in the cohort overall (35).

Predictive enrichment involves enrolling patients who are more likely to respond to treatment on the basis of pathobiological differences that favor a treatment response in the subset. This has the effect of increasing not only the absolute risk reduction but also the RRR associated with treatment. Trastuzumab for human epidermal growth factor receptor 2–positive breast cancer, vemurafenib for BRAF V600E mutant melanoma, immunomodulation for atopic asthma endotype, and ivacaftor for patients with cystic fibrosis with a G551D mutation are all examples of predictive enrichment. In particular, the beneficial effects of ivacaftor on FEV_1 would not have been detected in an unselected cystic fibrosis population, as only 4 to 5% of patients with cystic fibrosis have a G551D mutation.

There can be overlap between enrichment strategies, because particular characteristics may identify patients with both a higher rate of the study outcome (prognostic enrichment) and a higher likelihood of responding to therapy (predictive enrichment) (Figure 1). For example, a Pa_{O_2}/FI_{O_2} ratio less than 150 in studies of prone positioning and neuromuscular blockage resulted in higher placebo mortality rate (prognostic enrichment), but this criterion also identifies patients with higher lung weight who may be more likely to benefit from lung recruitment (36) and neuromuscular blockade (37) (predictive enrichment). Although there can be overlap between prognostic and predictive enrichment, the distinction is important because not all characteristics achieve both types of enrichment. For example, the G551D mutation in cystic fibrosis results in predictive enrichment for ivacaftor (greater RRR) but not prognostic enrichment, because the G551D mutation is associated with milder disease severity than other common mutations (38).

Identifying Biomarkers to Use for Predictive Enrichment

A major limitation to using predictive enrichment is that different treatments require different target populations, and often we do not know *a priori* which subgroups of patients are most likely to

Table 2. Selected Strategies to Enhance Clinical Trial Efficiency

Strategy	Definition	Why This Strategy Improves Trial Efficiency	Examples
Prognostic enrichment	Identifying and focusing on high-risk patients	Studying patients with a high event rate increases the statistical power to detect a given level of relative risk reduction.	Norepinephrine dosage in septic shock (57) $Pa_{O_2}/F_{I_{O_2}}$ ratio in ARDS (8, 58) APACHE II score in septic shock (42)
Predictive enrichment	Identifying and focusing on patients who are more likely to respond to the therapy being studied	Biologic markers related to a therapy's mechanism of action can be used to identify likely responders.	Response to corticotropin test for corticosteroids in septic shock (59) IL-6 level for monoclonal anti–tumor necrosis factor in sepsis (50) $Pa_{O_2}/F_{I_{O_2}}$ ratio for neuromuscular blockade in ARDS (8) Direct lung injury for surfactant in ARDS (60) $Pa_{O_2}/F_{I_{O_2}}$ ratio for prone positioning in ARDS (58) Vitamin D level for vitamin D replacement in critically ill patients (61) Plasma cell–free hemoglobin for acetaminophen in severe sepsis (62) C-reactive protein level for corticosteroids in community-acquired pneumonia (51)
Adaptive randomization	Adjust trial enrollment on the basis of prespecified decision rules and early results of the trial	Randomization is adapted in order to answer trial question with the fewest people, minimizing the risk of harm and ensuring adequate power.	Anti-PDL1 in septic shock (53)
Risk-based subgroup analysis	Determine average treatment effect by quantile of baseline risk	This strategy helps clarify the expected benefit of treatment for patients on the basis of baseline risk, improving the application of clinical trial results to bedside practice.	Activated protein C in severe sepsis (63) Pulmonary artery catheters in critically ill patients (64) Route of enteral nutrition in critically ill patients (65) Protocol-based early goal-directed therapy in sepsis shock (66)

Definition of abbreviations: anti-PDL1 = antibody against programmed death-ligand 1; APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome.

benefit from a given therapy. One trial of therapy in sepsis may require the presence of a bacterial infection, whereas another may require a particular immune response. Although sepsis trials have traditionally used clinical criteria to identify infection and dysregulated host response, we soon will have the opportunity to leverage molecular diagnostics to rule in particular bacterial infections (39) and increasingly sophisticated lab testing to identify an exaggerated, or impaired, inflammatory response.

When we have a clear idea of how a treatment works, we may select the study population through a hypothesis-driven approach, drawing on existing conceptual models, animal experiments, and prior studies. However, in instances where we do not know *a priori* which patients may benefit from a treatment, we must embark on a multistep discovery-driven approach to identify and vet biomarkers for therapy responsiveness, starting with (*1*) interrogation of observational cohort data to identify putative therapy-responsive biomarkers, or (*2*) *post facto* analyses of clinical trials where treatment is randomized, and ultimately (*3*) prospective trials incorporating therapy-responsiveness biomarkers with the option of adaptive randomization (40) if a handful of biomarkers are still in question.

We now present some examples of promising work to identify endotypes of sepsis and ARDS that may predict therapy responsiveness. In a *post hoc* study of the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis Study) cohort, Man and colleagues sought to identify clinically relevant patient subgroups with differential response to recombinant activated protein C, defined objectively as a genomic marker present in greater than 20% of the study population, with an absolute risk reduction of greater than 12.5% (41). The most significant marker was present in 26% of the cohort and associated with greater than 40% absolute risk reduction. Although this study is hypothesis generating and not confirmatory, it suggests the feasibility of using high-throughput searches for biomarkers of therapy responsiveness (so-called theranostics) to inform subsequent prospective studies. This study also suggests that the failure of activated protein C in the PROWESS-Shock trial may have been related to not identifying the proper patient population (42). Another *post hoc* analysis of the PROWESS study found that disseminated intravascular coagulation was not only predictive of greater risk of

mortality but also showed a trend toward greater RRR with activated protein C treatment (29 vs. 18%, $P = 0.26$) (43). An ongoing phase III study of a related therapy—recombinant human thrombomodulin—now requires evidence of disseminated intravascular coagulation for study enrollment (44).

Rather than examining an extensive number of individual biomarkers for therapy responsiveness, it is also possible to identify endotypes on the basis of a collection of biomarkers, then determine the most influential panel of biomarkers for determining endotypes and assess therapy responsiveness in these parsimoniously defined endotypes.

In one example of this approach, Wong and colleagues identified subclasses of pediatric septic shock based on genome-wide expression profiles in an observational cohort of children (45, 46). The study used an unsupervised learning approach, meaning that patients with similar gene-expression profiles were aggregated without foreknowledge of patients' outcomes. The gene-expression profiles were then condensed to the 100 best subclass predictors, where the key distinguishing genes corresponded with glucocorticoid receptor signaling (47). In the subclass with suppressed glucocorticoid receptor signaling, corticosteroids were independently associated with greater mortality (46). This preliminary work provides a testable hypothesis of which patients with septic shock may benefit from corticosteroids, a therapy that remains controversial because of our current difficulty in identifying which patients will benefit (48).

In another example of this approach, Calfee and colleagues identified endotypes of ARDS using latent class analysis on the basis of clinical and biological variables collected during enrollment in two separate ARDSNetwork trials (49). The two endotypes were associated with widely divergent clinical outcomes. They also had a qualitatively different response to ventilation with higher PEEP. In both trials, one endotype had more severe inflammation, shock, metabolic acidosis, and worse clinical outcomes. This endotype benefitted from a higher PEEP strategy, which was assigned randomly in the original study, whereas the other endotype appeared to be harmed by higher PEEP. Using just three endotype-defining variables, the area under the receiver operating characteristic curve for endotype prediction was greater than 0.9, suggesting that a modest number of variables could potentially be used to determine a patient's endotype in clinical practice.

Incorporating of Biomarkers for Therapy Responsiveness into Clinical Trials

Once putative therapy-responsive biomarkers are identified, they must be incorporated into prospective clinical trials to confirm that they identify patients likely to benefit from treatment. To date, only a limited number of critical care trials have used predictive enrichment (*see* Table 2 for additional examples). A 2004 trial examining anti–tumor necrosis factor therapy in patients with severe sepsis with elevated levels of IL-6 is a classic failed example. Although IL-6 was a strong prognostic marker (higher mortality in patients in the placebo arm with elevated IL-6), it did not predict treatment response (similar RRR between IL-6–positive and IL-6–negative patients) in the primary unadjusted analysis (50).

Recent trials using predictive enrichment have met greater success. A 2015 study by Torres and colleagues found that corticosteroid treatment in patients with severe community-acquired pneumonia and high inflammatory response (C-reactive protein > 15 mg/dl) reduced the composite outcome of treatment failure (51). Because of the narrow inclusion criteria, the study took 8 years to complete enrollment, and a larger study will still be needed to confirm mortality benefit. The accompanying editorial notes that we tend to relax tightly defined inclusion criteria to increase feasibility and clinical relevance, but this inclination is counterproductive in this case, because it is unreasonable to expect that all patients with community-acquired pneumonia will benefit from corticosteroids (52). We agree that tightly defined inclusion criteria enriching for treatment benefit will be key to advancing treatment for sepsis and ARDS, even if these trials take longer to complete and generalize to fewer patients.

More studies using predictive enrichment strategies are currently being designed, such as a phase II study of a monoclonal antibody directed against a programmed cell death-1 protein ligand (anti–PD-L1) for the treatment of severe sepsis (53). The study population will be enrolled and stratified based on biomarkers of immune suppression to both enrich for patients likely to benefit and determine which biomarker is better at predicting treatment response (53). Because the optimal biomarker(s) to predict responsiveness to anti–PD-L1 are unknown, this study uses an adaptive randomization scheme. The randomization will evolve over the course of the trial for each of the biomarker-defined subgroups, as informed by early trial results and as directed by prespecified decision rules. So, if a particular biomarker-defined subgroup appears to be harmed by the treatment, then the randomization will no longer be 50:50 but instead will preferentially randomize patients to the control treatment until enough information is accrued and the trial can be closed for the particular biomarker-defined subgroup. This approach minimizes the number of patients exposed to potentially harmful treatment, while still maintaining randomization and acquiring enough data to determine whether anti–PD-L1 is beneficial or not for each biomarker-defined subgroup.

Challenges and Limitations

Although we believe that treatment advances for sepsis and ARDS will require greater personalization of care, there are limitations to this approach. If the indication for a treatment depends on a biomarker, then the biomarker must be inexpensive, rapidly obtainable, and have low measurement error to advance routine practice. There will likely be trade-offs when selecting biomarkers. For example, although routinely collected clinical data may be easier to implement, biological data may better predict treatment response.

Second, although we believe that many sepsis and ARDS pharmacotherapies should be tailored toward distinct endotypes, we cannot neglect the importance of evidence-based treatments that are broadly applicable (e.g., sedation minimization and early mobility). Although targeted treatments such as ivacaftor are highly beneficial for select patients, they are costly and often have only minimal impact on population health given the small numbers of patients they treat (54). However, sepsis and ARDS are

common and deadly enough that expensive targeted therapies may still be cost effective.

Third, although precision medicine has advanced the treatment of some diseases, substantial investments into disease subtyping have not always translated into effective targeted treatments, as in the case of dementia (55). Nevertheless, the attributes of personalized medicine can still inform our approach to treating and studying critical illness syndromes, where a pragmatic, public health approach has guided practice over the past 2 decades. Certainly, early identification and treatment remain key goals, but we must move beyond "one-size-fits-all" treatment for sepsis and ARDS.

Fourth, although adaptive randomization can improve trial safety and efficiency, it will be important to have rigorous prespecified criteria to avoid the well-known pitfalls of stopping trials early (56).

Conclusions

Patients with sepsis and ARDS present with heterogeneous biology, severity of illness, and duration of disease, yet our approach to treatment is largely the same for all patients. In some instances, such as new trials of supportive care strategies likely to have broadly applicable benefit, this approach may be appropriate. However, to advance the study and treatment of sepsis, ARDS, and other critical illness, we should not reflexively study new therapies in all-comers with sepsis or ARDS but should instead use prognostic and predictive enrichment strategies to efficiently test treatments in the patients most likely to benefit. When there is uncertainty about the optimal markers for predictive enrichment, we recommend interrogation of cohort and/or RCT data first, followed by prospective assessment of a handful of markers using adaptive randomization. ■

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

References

1. Torio CM, Andrews RM. National inpatient hospital costs: the most expensive conditions by payer, 2011. HCUP Statistical Brief #160. Rockville, MD: Agency for Healthcare Research and Quality. August 2013 [accessed 2015 Dec 30]. Available from: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb160.jsp
2. Bice T, Cox CE, Carson SS. Cost and health care utilization in ARDS: different from other critical illness? *Semin Respir Crit Care Med* 2013; 34:529–536.
3. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, Iwashyna TJ. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA* 2014;312:90–92.
4. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, *et al*.; LUNG SAFE Investigators; ESICM Trials Group. 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.
5. Opal SM, Dellinger RP, Vincent J-L, Masur H, Angus DC. The next generation of sepsis clinical trial designs: what is next after the demise of recombinant human activated protein C? *Crit Care Med* 2014;42:1714–1721.
6. Frank AJ, Thompson BT. Pharmacological treatments for acute respiratory distress syndrome. *Curr Opin Crit Care* 2010;16:62–68.
7. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
8. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, *et al*.; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363:1107–1116.
9. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, *et al*. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303:865–873.
10. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006;354:1671–1684.
11. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, Jaton K, Giulieri S, Delaloye J, Opal S, *et al*. Sepsis: a roadmap for future research. *Lancet Infect Dis* 2015;15:581–614.
12. Parliamentary and Health Service Ombudsman. Time to act. Severe sepsis: rapid diagnosis and treatment saves lives. 2013 [accessed 2015 Nov 11]. Available from: http://www.ombudsman.org.uk/__data/assets/pdf_file/0004/22666/FINAL_Sepsis_Report_web.pdf
13. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med* 2003;29: 530–538.
14. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, *et al*. The Third International Consensus Definitions for Sepsis and Septic Shock (sepsis-3). *JAMA* 2016;315:801–810.
15. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–824.
16. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307: 2526–2533.
17. Balk RA. Systemic inflammatory response syndrome (SIRS): where did it come from and is it still relevant today? *Virulence* 2014;5:20–26.
18. Blank R, Napolitano LM. Epidemiology of ARDS and ALI. *Crit Care Clin* 2011;27:439–458.
19. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 2014;311: 1308–1316.
20. Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. *Crit Care Med* 2014;42:625–631.
21. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, *et al*. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–134.
22. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, *et al*. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373: 1874–1882.
23. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci MdeO, Damasceno MC, Schultz MJ. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA* 2012;308:1651–1659.
24. Sykiotis GP, Kalliolias GD, Papavassiliou AG. Pharmacogenetic principles in the Hippocratic writings. *J Clin Pharmacol* 2005;45: 1218–1220.

25. Leligdowicz A, Dodek PM, Norena M, Wong H, Kumar A, Kumar A; Co-operative Antimicrobial Therapy of Septic Shock Database Research Group. Association between source of infection and hospital mortality in patients who have septic shock. *Am J Respir Crit Care Med* 2014;189:1204–1213.
26. Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. *J Infect Dis* 2000;181: 176–180.
27. Spagnolo F, Ghiorzo P, Orgiano L, Pastorino L, Picasso V, Tornari E, Ottaviano V, Queirolo P. BRAF-mutant melanoma: treatment approaches, resistance mechanisms, and diagnostic strategies. *Onco Targets Ther* 2015;8:157–168.
28. Rothwell PM. Can overall results of clinical trials be applied to all patients? *Lancet* 1995;345:1616–1619.
29. Iwashyna TJ, Burke JF, Sussman JB, Prescott HC, Hayward RA, Angus DC. Implications of heterogeneity of treatment effect for reporting and analysis of randomized trials in critical care. *Am J Respir Crit Care Med* 2015;192:1045–1051.
30. Angus DC, Seymour CW, Coopersmith CM, Deutschman CS, Klompas M, Levy MM, Martin GS, Osborn TM, Rhee C, Watson RS. A framework for the development and interpretation of different sepsis definitions and clinical criteria. *Crit Care Med* 2016;44: e113–e121.
31. Seymour CW, Coopersmith CM, Deutschman CS, Gesten F, Klompas M, Levy M, Martin GS, Osborn TM, Rhee C, Warren DK, *et al*. Application of a framework to assess the usefulness of alternative sepsis criteria. *Crit Care Med* 2016;44:e122–e130.
32. Matthay MA, Liu KD. New strategies for effective therapeutics in critically ill patients. *JAMA* 2016;315:747–748.
33. US Food and Drug Administration. Guidance for industry: enrichment strategies for clinical trials to support approval of human drugs and biological products. 2012 [accessed 2015 Sept 24]. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf
34. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138:720–723.
35. Thille AW, Esteban A, Fernández-Segoviano P, Rodriguez JM, Aramburu JA, Peñuelas O, Cortés-Puch I, Cardinal-Fernández P, Lorente JA, Frutos-Vivar F. Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. *Am J Respir Crit Care Med* 2013;187:761–767.
36. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, Malacrida R, Di Giulio P, Fumagalli R, Pelosi P, *et al*.; Prone-Supine Study Group. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001;345: 568–573.
37. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. The comparison of spontaneous breathing and muscle paralysis in two different severities of experimental lung injury. *Crit Care Med* 2013; 41:536–545.
38. Comer DM, Ennis M, McDowell C, Beattie D, Rendall J, Hall V, Elborn JS. Clinical phenotype of cystic fibrosis patients with the G551D mutation. *QJM* 2009;102:793–798.
39. Chang S-S, Hsieh W-H, Liu T-S, Lee SH, Wang CH, Chou HC, Yeo YH, Tseng CP, Lee CC. Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis: a systemic review and meta-analysis. *Plos One* 2013;8:e62323.
40. Adamina M, Tomlinson G, Guller U. Bayesian statistics in oncology: a guide for the clinical investigator. *Cancer* 2009; 115:5371–5381.
41. Man M, Close SL, Shaw AD, Bernard GR, Douglas IS, Kaner RJ, Payen D, Vincent JL, Fossceco S, Janes JM, *et al*. Beyond single-marker analyses: mining whole genome scans for insights into treatment responses in severe sepsis. *Pharmacogenomics J* 2013; 13:218–226.
42. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gårdlund B, Marshall JC, Rhodes A, Artigas A, *et al*.; PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012;366:2055–2064.
43. Dhainaut J-F, Yan SB, Joyce DE, Pettilä V, Basson B, Brandt JT, Sundin DP, Levi M. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. *J Thromb Haemost* 2004; 2:1924–1933.
44. Phase 3 safety and efficacy study of ART-123 in subjects with severe sepsis and coagulopathy: full text view. ClinicalTrials.gov [accessed 2016 Mar 15]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01598831
45. Wong HR, Cvijanovich N, Lin R, Allen GL, Thomas NJ, Willson DF, Freishtat RJ, Anas N, Meyer K, Checchia PA, *et al*. Identification of pediatric septic shock subclasses based on genome-wide expression profiling. *BMC Med* 2009;7:34.
46. Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald J, Checchia PA, Meyer K, *et al*. Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med* 2015;191:309–315.
47. Wong HR, Wheeler DS, Tegtmeyer K, Poynter SE, Kaplan JM, Chima RS, Stalets E, Basu RK, Doughty LA. Toward a clinically feasible gene expression-based subclassification strategy for septic shock: proof of concept. *Crit Care Med* 2010;38:1955–1961.
48. Patel GP, Balk RA. Systemic steroids in severe sepsis and septic shock. *Am J Respir Crit Care Med* 2012;185:133–139.
49. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014;2: 611–620.
50. Panacek EA, Marshall JC, Albertson TE, Johnson DH, Johnson S, MacArthur RD, Miller M, Barchuk WT, Fischkoff S, Kaul M, *et al*.; Monoclonal Anti-TNF: a Randomized Controlled Sepsis Study Investigators. Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. *Crit Care Med* 2004;32:2173–2182.
51. Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, Gabarrús A, Sellarés J, Restrepo MI, Anzueto A, *et al*. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015; 313:677–686.
52. Wunderink RG. Corticosteroids for severe community-acquired pneumonia: not for everyone. *JAMA* 2015;313:673–674.
53. National Institutes of Health Research Portfolio Online Reporting Tools (RePORT) [accessed 2015 Nov 12]. Available from: https://projectreporter.nih.gov/project_info_description.cfm?aid=8988802&icde=27081261&ddparam=&ddvalue=&ddsub=&cr=2&csb=default&cs=ASC
54. Joyner MJ, Paneth N. Seven questions for personalized medicine. *JAMA* 2015;314:999–1000.
55. Karlawish J. Is the brain ready for personalized medicine? Studies suggest not quite yet. Robert Wood Johnson Foundation. 2013 Sept 6 [accessed 2016 Apr 9]. Available from: http://www.rwjf.org/en/culture-of-health/2013/09/is_the_brain_readyf.html
56. Guyatt GH, Briel M, Glasziou P, Bassler D, Montori VM. Problems of stopping trials early. *BMJ* 2012;344:e3863.
57. Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, *et al*.; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877–887.
58. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, *et al*.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–2168.
59. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, *et al*. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862–871.
60. Spragg RG, Taut FJH, Lewis JF, Schenk P, Ruppert C, Dean N, Krell K, Karabinis A, Günther A. Recombinant surfactant protein C-based surfactant for patients with severe direct lung injury. *Am J Respir Crit Care Med* 2011;183:1055–1061.

61. Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, Urbanic Purkart T, Waltensdorfer A, Münch A, Warnkross H, *et al*. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. *JAMA* 2014;312:1520–1530.
62. Janz DR, Bastarache JA, Rice TW, Bernard GR, Warren MA, Wickersham N, Sills G, Oates JA, Roberts LJ II, Ware LB; Acetaminophen for the Reduction of Oxidative Injury in Severe Sepsis Study Group. Randomized, placebo-controlled trial of acetaminophen for the reduction of oxidative injury in severe sepsis: the Acetaminophen for the Reduction of Oxidative Injury in Severe Sepsis trial. *Crit Care Med* 2015;43:534–541.
63. Ely EW, Laterre P-F, Angus DC, Helterbrand JD, Levy H, Dhainaut JF, Vincent JL, Macias WL, Bernard GR; PROWESS Investigators. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003;31:12–19.
64. Harvey S, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, Bellingan G, Leonard R, Mythen MG, Rowan KM; CALORIES Trial Investigators. *N Engl J Med* 2014;371:1673–1684.
65. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, Bellingan G, Leonard R, Mythen MG, Rowan KM; CALORIES Trial Investigators. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014;371:1673–1684.
66. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, *et al*.; ProMISe Trial Investigators. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015;372:1301–1311.