Open Forum Infectious Diseases

REVIEW ARTICLE

Applying Lessons Learned From COVID-19 Therapeutic Trials to Improve Future ALI/ARDS Trials

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Host-directed therapeutics targeting immune dysregulation are considered the most promising approach to address the unmet clinical need for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) related to coronavirus disease 2019 (COVID-19). To better understand the current clinical study landscape and gaps in treating hospitalized patients with severe or critical COVID-19, we identified COVID-19 trials developing host-directed therapies registered at ClinicalTrials.gov and discussed the factors contributing to the success vs failure of these studies. We have learned, instead of the one-size-fits-all approach, future clinical trials evaluating a targeted immunomodulatory agent in heterogeneous patients with ALI/ARDS due to COVID-19 or other infectious diseases can use immune-based biomarkers in addition to clinical and demographic characteristics to improve patient stratification and inform clinical decision-making. Identifying distinct patient subgroups based on immune profiles across the disease trajectory, regardless of the causative pathogen, may accelerate evaluating host-directed therapeutics in trials of ALI/ARDS and related conditions (eg, sepsis).

Keywords. acute respiratory distress syndrome; COVID-19; clinical trial; host-directed therapy; sepsis.

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is the main cause of intensive care unit (ICU) admission for patients with coronavirus disease 2019 (COVID-19), leading to a high mortality rate of 40.5% in ICU patients [1]. As such, >1 million people have died from COVID-19 in the United States since the pandemic began, making COVID-19 the deadliest disease outbreak in recent American history. While COVID-19 vaccination remains the best strategy to prevent severe illness and death from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, more effective treatments are still urgently needed, particularly for patients with COVID-19 whose disease progresses to severe and critical illness (ie, ARDS). COVID-19 therapeutic development becomes increasingly important as breakthrough COVID-19 cases in vaccinated individuals are rising due to waning immunity and emerging variants of SARS-CoV-2.

While COVID-19 has recently emerged, a dysregulated host response to infection leading to organ dysfunction (ie, ARDS and sepsis) was well established before the emergence of SARS-CoV-2. Approximately 15% of COVID-19 cases progress to severe pneumonia, and about 5% of them eventually develop ALI/ARDS, sepsis, septic shock, or multiple-organ failure [2, 3]. Increased incidence and mortality risk for severe COVID-19, ARDS, and sepsis are associated with older age and preexisting comorbidities (eg, obesity, diabetes, cardiovascular diseases, and chronic lung diseases) [4]. Nearly 75% of patients with COVID-19 admitted to the ICU have ARDS and meet the Third International Consensus Definitions for Sepsis (Sepsis-3) [5]. Therefore, the most severe outcomes of COVID-19 directly overlap with ARDS and viral sepsis. To fully address the continuing threat of COVID-19 and prepare for emerging infectious diseases, therapeutic solutions that mitigate the most severe clinical sequelae of these infections, including systemic inflammation, lung injury, viral or bacterial sepsis, and ARDS, are critical. In this review, we identified and analyzed the current clinical trial landscape and gaps in developing pharmacological treatments for hospitalized patients with COVID-19. Lessons learned from the success and failure of these COVID-19 therapeutic trials offer valuable insights for improving the future design of clinical trials of ALI/ARDS and related conditions (eg, sepsis).

CURRENT THERAPEUTIC CLINICAL TRIAL LANDSCAPE FOR HOSPITALIZED PATIENTS WITH COVID-19

Early success in the medical countermeasure response to COVID-19 came from the rapid development, manufacturing, and deployment of COVID-19 vaccines, anti-SARS-CoV-2

Received 19 May 2022; editorial decision 26 July 2022; accepted 28 July 2022; published online 30 July 2022

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https://doi.org/10.1093/ofid/ofac381

monoclonal antibodies, convalescent plasma, and a direct-acting small-molecule antiviral drug (Veklury, remdesivir). In contrast, for hospitalized patients with COVID-19, data on the efficacy of antiviral therapies are mixed. The results suggest that direct-acting antivirals are effective in patients with COVID-19 with early and mild symptoms but less effective on their own to treat severe or critical COVID-19 when immune dysregulation (not direct viral cytopathic effects) drives disease pathogenesis [6–10]. For these reasons, host-directed therapeutics targeting immune dysregulation or promoting tissue repair may be the most promising approaches to address the unmet clinical need for preventing and treating ALI/ARDS caused by COVID-19.

There has been an extraordinary effort to find effective treatments for hospitalized patients with COVID-19, with an unprecedented number of clinical trials rapidly executed to address the current pandemic. To better understand the current clinical trial landscape of host-directed therapeutics for hospitalized patients with COVID-19 and learn lessons from these studies, we identified COVID-19 clinical trials registered at ClinicalTrials.gov (the largest database of clinical studies) between December 1, 2019, and October 5, 2021, and classified them according to study design, intervention type, patient population (outpatient vs inpatient), target enrollment, and drug mechanism of action. As of October 5, 2021, a total of 6692 clinical research studies were related to COVID-19 based on the search term "COVID-19," including 1575 (24%) interventional treatment trials involving small-molecule drugs or biological products, with almost half of them using an open-label design (Figure 1). Next, to emphasize specific host-directed therapies, we excluded clinical trials in an outpatient setting and inpatient studies examining drugs or products targeting SARS-CoV-2 (i.e., convalescent plasma, anti-SARS-CoV-2 monoclonal antibodies, intravenous immune globulin, and small-molecule drugs against SARS-CoV-2). As misleading data have often emerged from small, nonrandomized, or poorly controlled studies, in order to obtain meaningful insights, we further narrowed down clinical trials with robust designs, defined as randomized controlled trials (RCTs) with at least 100 participants per arm in a double-blind study or 250 participants per arm for an open-label study [11–13]. Finally, 100 clinical trials evaluating immunomodulators or host-directed therapies in hospitalized patients with COVID-19 were identified. We reviewed and analyzed these trials by categorizing and summarizing the information to present a detailed view of the current landscape for host-directed therapies in hospitalized patients with COVID-19.

Overall, therapeutic products aiming to reduce overactive inflammatory responses or tissue damage caused by SARS-CoV-2 infection are studied frequently in hospitalized patients across the spectrum of COVID-19 ranging from pneumonia to associated ARDS. These include repurposed or investigational immunomodulatory agents:

1. Targeting a specific pro-inflammatory cytokine, such as inhibitors of interleukin (IL)-1 (anakinra, canakinumab, and RPH-104), IL-6 (tocilizumab, sarilumab, levilimab, olokizumab, and siltuximab), tumor necrosis factor–alpha (infliximab and INB03), and granulocyte-macrophage colony-stimulating factors (gimsilumab, lenzilumab, mavrilimumab, otilimab, and TJ003234);
2. Targeting a critical kinase signaling pathway, such as Janus kinase (JAK) inhibitors (baricitinib, tofacitinib, ruxolitinib, and TD-0903), spleen tyrosine kinase inhibitor (fostamatinib), sphingosine kinase-2 inhibitor (opaganib), and tyrosine kinase inhibitors (abivertinib, masitinib);
3. Inhibiting complement pathways (avdoralimab and vilobelimab);
4. Targeting broader inflammatory responses, such as glucocorticoids (dexamethasone and methylprednisolone), dihydroorotate dehydrogenase inhibitors (IMU-838 and PTC299), androgen receptor inhibitors (proxalutamide and HC-1119), and sodium-glucose cotransporter-2 inhibitor (dapagliflozin);
5. Targeting coagulation pathways (heparin, aspirin, and nafamostat mesylate);
6. Targeting histamine receptors (famotidine); and
7. Cell therapies, such as mesenchymal stromal cells (MultiStem®).

Many COVID-19 inpatient trials testing novel immunomodulatory agents targeting inflammation or endothelial dysfunction are still underway. The available results to date are limited to interleukin-1 receptor (IL-1R) antagonists, interleukin-6 receptor (IL-6R) antagonists, JAK inhibitors, and glucocorticoids. The major findings of peer-reviewed publications related to these trials are summarized in Table 1. Although our focus is not on the potential therapeutic benefits from the mechanisms of action of these immunomodulatory candidates in the evaluation, this should not be a reflection of the opportunity and need to expound on the varying potential benefits of these immune-modulating therapies as possible treatment options for similar disease pathophysiology (ie, ARDS and sepsis) and potential therapeutic strategies for addressing emerging infectious diseases.

SUCCESSFUL HOST-DIRECTED THERAPEUTIC CLINICAL STUDIES IN HOSPITALIZED PATIENTS WITH COVID-19: SUBPOPULATION ANALYSIS BENEFIT AND INSIGHT FOR FUTURE ALI/ARDS TRIALS

Despite the number of clinical trials, there are only 3 host-targeted products currently available for treating hospitalized COVID-19: (1) corticosteroids (eg, dexamethasone) without

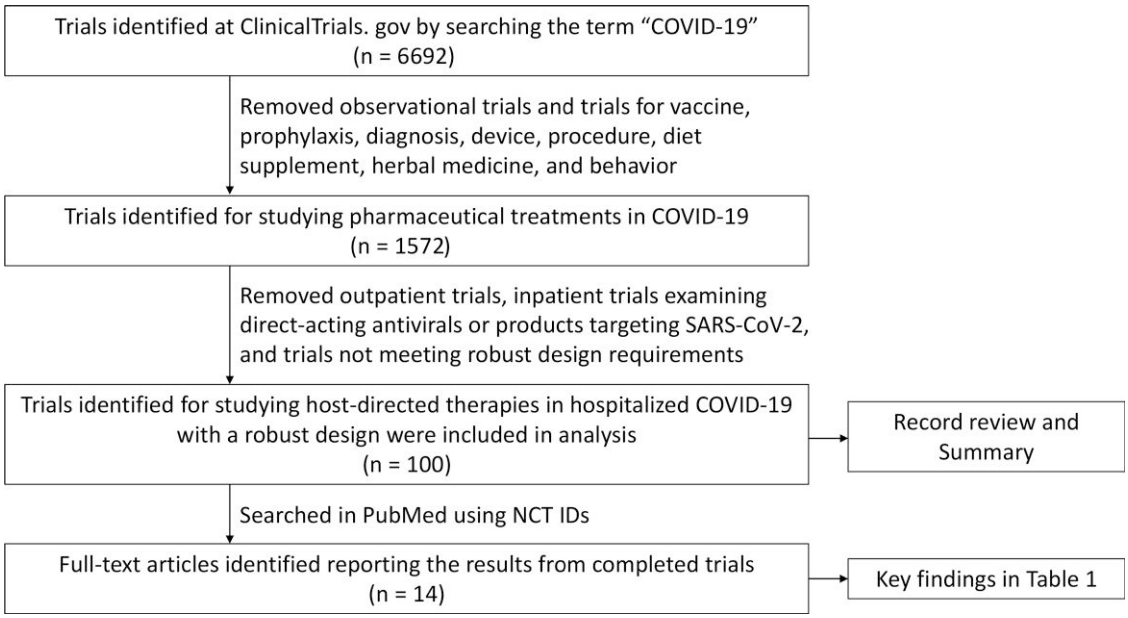

Figure 1. Clinical trial identification and analysis process. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

a specific Emergency Use Authorization (EUA) but being adopted as the standard of care for critically ill patients with COVID-19; (2) Actemra®/tocilizumab with an EUA since June 2021 for certain hospitalized patients with COVID-19; and (3) Olumiant®/baricitinib with an EUA since November 2020 and then full approval from the Food and Drug Administration (FDA) for certain hospitalized patients with COVID-19 in May 2022. Of note, these host-targeted therapeutics are each recommended or authorized for use only in specific subpopulations but not the general population of hospitalized patients with COVID-19. Interestingly, there are examples of drugs with the same target, even the same drug tested in multiple well-designed trials, demonstrating conflicting results (such as anti-IL-1R and anti-IL-6R in Table 1). Hence, identifying the factors contributing to trials yielding different conclusions regarding efficacy in hospitalized patients with COVID-19 can provide valuable insights to improve the future clinical trial design in patients with ALI/ARDS and related conditions (eg, sepsis).

Dexamethasone or similar corticosteroids are recommended for treating hospitalized patients with severe or critical COVID-19 requiring respiratory support based on 28-day mortality benefit data from the RECOVERY trial [24, 28]. Of note, due to large enrollment numbers, a single study was able to identify a subset of hospitalized patients with COVID-19 who benefitted from corticosteroids vs another subset that did not. Early in the pandemic, there was hesitancy to administer corticosteroids in hospitalized patients with COVID-19 based on a long history of contrary recommendations for corticosteroid therapy in patients with viral pneumonia, ARDS, and sepsis. Decades of clinical studies have demonstrated both benefits and potential harms of corticosteroids in treating those conditions. For example, corticosteroids increased mortality and nosocomial infection in patients with severe influenza pneumonia and associated ARDS [29, 30]. Corticosteroid treatment delayed viral clearance in patients with severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus [31]. For sepsis, clinical protocols have historically waffled between recommending for or against the routine use of steroids based on various clinical trials that demonstrated efficacy, no efficacy, or worse outcomes [32–34]. The current surviving sepsis guidelines only recommend glucocorticoid therapy in patients with septic shock (conditional recommendation for sepsis patients without shock). These findings align with the current recommendations of corticosteroid use in patients with more severe COVID-19 requiring high-flow oxygen, mechanical ventilation, or ICU admission, but not those who do not require supplemental oxygen. Recent data suggest a possible mechanism underlying the beneficial effects of dexamethasone in severe/critical COVID-19 by restoring the glucocorticoid receptor expression that is downregulated in patients with severe/critical COVID-19 but not mild COVID-19 [35]. Further efforts are required to identify distinct patient profiles/biomarkers for classifying patients with COVID-19 at a specific disease stage that will benefit from corticosteroids. The findings may likewise inform the identification of appropriate patient subpopulations for corticosteroid treatment in non-COVID-19 ALI/ARDS and sepsis.

Blocking the IL-6 pathway to reduce systemic inflammation is appealing because increased IL-6 levels are highly associated

Table 1. Major Findings From Well-Designed Clinical Trials of Host-Directed Therapies in Hospitalized Patients With COVID-19

Category	Target Pathway	Drug (MOA)	Disease Stage	Key Findings
Pro-inflammatory cytokines	IL-1 pathway	Anakinra (rhIL-1R antagonist blocking IL-1α and IL-1β)	COVID-19 pneumonia	Early suPAR (plasma suPAR ≥6 ng/mL)-guided anakinra treatment prevented COVID-19 respiratory failure [14].
		Canakinumab (anti-IL-1β)	Severe COVID-19	Canakinumab did not improve survival in patients with COVID-19 who did not require invasive mechanical ventilation [15].
	IL-6 pathway	Tocilizumab (anti-IL-6R)	Severe or critical COVID-19	Tocilizumab reduced mechanical ventilation and was associated with a short-term mortality benefit [16–18].
		Sarilumab (anti-IL-6R)	Severe or critical COVID-19	Sarilumab showed no efficacy in patients with COVID-19 receiving oxygen therapy [19].
		Levilimab (anti-IL-6R)	Severe COVID-19	Levilimab treatment resulted in clinical improvement in patients with COVID-19 without or with oxygen therapy (not on ventilation) [20].
Kinase cascades	Janus kinase pathway	Baricitinib (JAK1/JAK2 inhibitor)	Moderate to severe COVID-19	Baricitinib plus remdesivir reduced recovery time and accelerated clinical improvement in COVID-19, mainly on high-flow oxygen or noninvasive ventilation [21].
				Baricitinib, on top of standard of care (eg, dexamethasone), was associated with reduced mortality in COVID-19, most evident in patients on high-flow oxygen or noninvasive ventilation [22].
		Tofacitinib (JAK1/JAK3 inhibitor with partial selectivity to JAK2)	COVID-19 pneumonia	Tofacitinib reduced the risk of death or respiratory failure in patients with COVID-19 who were not on ventilation and received glucocorticoids [23].
Other	Immunosuppression	Dexamethasone	Severe COVID-19	Dexamethasone reduced 28-day mortality in patients with COVID-19 who received invasive mechanical ventilation or supplemental oxygen, but not those who did not require respiratory support [24].
		Methylprednisolone	COVID-19 pneumonia	Methylprednisolone did not reduce mortality in the overall hospitalized COVID-19 population. But subgroup analysis found that it lowered 28-day mortality rate in patients aged ≥60 years [25].
	Multiple pathways (glycolysis/lipolysis/ oxidative stress)	Dapagliflozin (sodium-glucose cotransporter-2 inhibitor)	COVID-19 pneumonia	Dapagliflozin did not reduce organ dysfunction or death or improve recovery in patients with COVID-19 on low-flow oxygen with cardiometabolic risk [26].
	Coagulation pathway	Heparin	Severe COVID-19	In patients with severe COVID-19, therapeutic-dose heparin was not associated with a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than was usual-care pharmacologic thromboprophylaxis [27].

Abbreviations: COVID-19, coronavirus disease 2019; IL-1R, interleukin-1 receptor; IL-6R, interleukin-6 receptor; JAK, Janus kinase; MOA, mechanism of action; rh, recombinant human; suPAR, soluble urokinase plasminogen activator receptor.

with disease severity and death in COVID-19 [36]. Anti-IL-6R antibodies (eg, tocilizumab) were employed very early in the COVID-19 response based on their anti-inflammatory mechanism of action, particularly their approval to treat the overactive immune response (known as cytokine release syndrome) after chimeric antigen receptor T-cell therapy [37]. Several studies have demonstrated the efficacy of anti-IL-6R antibodies in hospitalized patients with COVID-19; however, most failed to meet their clinical end points [38, 39]. Despite showing no significant clinical benefit in initial trials [16, 17, 40], tocilizumab demonstrated a mortality benefit in patients hospitalized for COVID-19 with hypoxia and systemic inflammation in early 2021 [18]. It is worth mentioning that elevated C-reactive protein was used as a trial enrollment criterion, and most patients were treated with corticosteroids in this study, potentially contributing further to the patient stratification and therapeutic benefit effect. In June 2021, tocilizumab was authorized for emergency use in hospitalized patients with COVID-19 receiving systemic corticosteroids and requiring supplemental oxygen, noninvasive ventilation, or invasive mechanical ventilation. Sarilumab, another FDA-approved anti-IL-6R antibody, demonstrated similar efficacy to tocilizumab in 1 study but failed to meet its primary end point in another study for hospitalized patients with COVID-19. The successful trial focused on hospitalized patients with more severe cases of COVID-19 (critically ill COVID-19) who required high-flow supplemental oxygen, nonmechanical or mechanical ventilation, or cardiovascular support, and most patients (>80%) received systemic corticosteroids [41]. The failed trial enrolled a broader population of hospitalized patients with

COVID-19, ranging from severe COVID-19 (requiring moderate levels of supplemental oxygen) to critical COVID-19 (requiring high-flow supplemental oxygen and nonmechanical or mechanical ventilation). In this trial, sarilumab was ineffective for treating patients hospitalized for COVID-19; however, a trend toward mortality benefit was seen among critically ill patients with COVID-19 who required intensive respiratory support [19]. Together, these results strongly suggest that targeting a defined patient subpopulation for host-directed therapy can improve clinical trial outcomes, in this case, targeting critically ill patients with COVID-19 who have elevated C-reactive protein for IL-6-blocking treatment.

Neither anti-IL-6 nor anti-IL-6R antibodies have been extensively studied in robust clinical trials for non-COVID-19 ALI/ARDS or sepsis. While it is interesting to speculate on their potential efficacy for treating non-COVID-19 ALI/ARDS or sepsis, serum IL-6 levels are significantly lower in critically ill patients with COVID-19 compared with non-COVID-19 ALI/ARDS or sepsis [42, 43]. Therefore, future clinical trials evaluating IL-6-targeting therapeutics in patients with non-COVID-19 ALI/ARDS or sepsis should consider enrollment restricted to a target subgroup based on biomarker thresholds on top of other stratification factors or in combination with other immunomodulators (eg, corticosteroids).

Baricitinib (a JAK1/2 inhibitor) received an EUA and then full approval for use with or without remdesivir in certain hospitalized patients with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation. Baricitinib plus remdesivir has been shown to reduce recovery time and accelerate clinical improvement in hospitalized patients with COVID-19, particularly those receiving high-flow oxygen or noninvasive ventilation [21]. Recently, baricitinib, on top of the standard of care including dexamethasone, demonstrated a mortality benefit in hospitalized patients with COVID-19, which was most pronounced in those on high-flow oxygen or noninvasive ventilation [22]. These data suggest that baricitinib is most effective in patients with less severe COVID-19 compared with the use of tocilizumab and corticosteroids. Interestingly, signal transduction of the IL-6 pathway involves JAK1/2 activation [44], and both baricitinib and dexamethasone are known to inhibit IL-6 production [45, 46]. To date, the efficacy of JAK inhibitors in patients with non-COVID-19 ALI/ARDS or sepsis and in specific subpopulations who are most likely to benefit from treatment has not yet been explored.

FAILED CLINICAL TRIALS OF HOST-DIRECTED THERAPIES IN HOSPITALIZED PATIENTS WITH COVID-19: LESSONS LEARNED FOR FUTURE ALI/ARDS TRIALS

Despite the success of the anti-inflammatory drugs mentioned above, many immunomodulatory drugs failed to show clinical efficacy in hospitalized patients with COVID-19. The failures may arise from suboptimal drug choice, unsuitable patient inclusion/exclusion criteria, lack of appropriate randomization for covariates, end point selection, or safety issues. Choosing appropriate end points is a critical aspect of designing clinical trials for assessing treatment effects in hospitalized patients with COVID-19 across a broad spectrum of disease severity and remains challenging [47, 48]. However, it should be noted that inconsistent effectiveness of the same drug in hospitalized patients with COVID-19 has been observed across multiple studies, suggesting that some discrepancies may be due to study design rather than the drug's mechanism of action. The same challenges in recognizing disease complications and effective treatments also occur in sepsis, a serious complication in patients with severe/critical COVID-19 [5]. Therefore, we underscored important lessons shared by recent COVID-19 and past sepsis clinical trials to inform the study design for future ALI/ARDS trials.

First, many COVID-19 inpatient trials failed because of insufficient attention to the pathophysiological heterogeneity of hospitalized patients with COVID-19. The ongoing impact of the pandemic may allow for continued large-scale studies; however, more efficient approaches for identifying a suitable subgroup, with reduced heterogeneity, of hospitalized patients with COVID-19 who may benefit from a specific drug are required. Recent studies have revealed that hospitalized patients with COVID-19 present diverse clinical phenotypes associated with disease severity, thereby responding differently to clinical interventions [49, 50]. These hospitalized patients with COVID-19 exhibit a broad spectrum of inflammatory responses from hyperinflammation to hypo-inflammation (immunosuppression) [43, 51]. Critically ill patients with COVID-19 have diverse immunological profiles (immunophenotypes) associated with different clinical outcomes [52]. Therefore, this dynamic nature of immune response during disease progression in hospitalized patients with COVID-19 affects health care providers' ability to manage these patients uniformly.

Mixed hyperinflammatory and hypo-inflammatory phenotypes are also common in response to other infections and have been recognized in non-COVID-19 ALI/ARDS and sepsis [53, 54]. Although we can argue that narrowing trial populations to specific etiologies could reduce patient heterogeneity, the underlying pathogen may not be the only common theme to focus on in trial enrollment. There may be pathogenetic similarities unrelated to the pathogen among patients with COVID-19 ARDS, non-COVID-19 ALI/ARDS, or sepsis resulting from common pathophysiologic mechanisms. Therefore, we posit that targeted immunomodulatory therapy should be evaluated in an optimal subgroup of ALI/ARDS patients and patient enrollment should not be restricted solely to a specific etiology of ALI/ARDS. Of note, patient demographic characteristics (eg, age, sex/gender, race/ethnicity, and

underlying comorbidities) significantly influence the development and outcome of ALI/ARDS, as well as a patient's response to a therapeutic candidate [55, 56]. Therefore, we need to include diverse phenotypes to help ensure that clinical trials better reflect this patient population. The baseline demographic factors should be balanced during patient stratification at enrollment and considered again during the statistical data analysis when interpreting clinical trial results. In addition to these stratification factors, distinct immunophenotypes could serve as a basis for further stratifying patients of ALI/ARDS into the subgroups that are most likely to respond to a given treatment in the clinical trial. Dose adjustment, combination therapy, and tailored approaches for monitoring therapeutic response are required with similar products in different ALI/ARDS subgroups. In addition, some people who survive ARDS and recover from COVID-19 develop long COVID and experience persistent symptoms, likely due to prolonged or altered immune responses [57, 58]. The same heterogeneity may continue through progression of disease sequelae for hindering clinical trial success and management of long COVID. Therefore, immunophenotypic profiling of these patients is also urgently needed to better understand the heterogeneity of this patient population, identify subtype classification, and provide effective personalized treatment for long COVID. Ultimately, the diversity that makes patient care challenging can be leveraged to stratify individuals for improved care.

Second, reliable immune-related biomarkers or immunological signatures with potentially other clinical features should be used as trial eligibility criteria for specific host-targeted therapy. Lee et al. suggest using a combination of CD8–CD4 disequilibrium and transcriptomic markers to differentiate patient populations based on immune resilience for COVID-19 patients [59]. Similarly, in 2014, phenotypes for ARDS were suggested based on a patient's biomarkers, radiological findings, and physiologic data [60]. In fact, early on in the SARS-CoV-2 pandemic, Horie et al. discussed the challenges presented by ARDS trials in the past and suggested an investigation of immune phenotypes to better inform clinical trial enrollment [61]. Unfortunately, as of the time we completed our survey at ClinicalTrials.gov, only 14 of 100 (14%) COVID-19 inpatient RCTs with robust designs evaluating host-directed therapeutics have reported results on this website or in peer-reviewed journals. Only a few sponsors have published the results of their clinical trials for failed drugs. Besides, Seymour et al. have initiated a retrospective analysis to ascertain the potential benefit of clinical phenotyping for sepsis trials [62]. However, there has been little effort to examine immune-related biomarker profiles in those COVID-19 patient samples with failed drugs for differentiating treatment effects in subgroups. This gap hinders our understanding of COVID-19 pathophysiology and our chance to improve the study design to identify effective immunomodulatory therapies in a specific subgroup of hospitalized patients with COVID-19. Researchers should be encouraged to share negative results more openly by creating space in journals and in scientific meetings for such results to be presented as well as to conduct retrospective analyses if clinical samples allow to determine if patient subtyping could have informed a better clinical study design.

Fortunately, clinical study investigators have come to realize that the traditional one-size-fits-all recruitment strategy is unsuitable for studying the highly heterogeneous hospitalized COVID-19 patient population. Several COVID-19 inpatient RCTs evaluating host-directed therapies have started implementing biomarker-based patient stratification as a critical step of the study design to increase the likelihood of achieving clinical efficacy of investigational drugs. For example, the IL-1R antagonists anakinra and canakinumab have been previously evaluated in hospitalized patients with COVID-19 but failed to show clinical efficacy [15, 63]. Shown in Table 1, a recent trial stratified hospitalized patients with COVID-19 based on the level of soluble urokinase plasminogen activator receptor (suPAR), an independent predictor of COVID-19 disease severity [64, 65]. Using elevated suPAR serum level (≥6 ng/mL) as an enrollment criterion, treatment with anakinra prevented severe respiratory failure, improved recovery, and reduced 28-day mortality in hospitalized patients with moderate to severe COVID-19 [14]. Although IL-1-targeted drugs have not yet demonstrated clear efficacy for sepsis, a retrospective analysis of previous sepsis trials suggests that anakinra may benefit sepsis patients with macrophage activation syndrome, as indicated by elevated serum ferritin levels, showing the value of ferritin as a biomarker for sepsis trial enrollment eligibility [66].

Lastly, multiple immunologic processes are involved in the pathogenesis of ALI/ARDS (eg, COVID-19 ARDS) and sepsis, including the release of pro-inflammatory and anti-inflammatory cytokines, activation of complement and coagulation cascades, and endothelial dysfunction [67, 68]. Hence, using biomarker clusters to reflect multiple pathways associated with disease progression and therapeutic response is likely to provide greater specificity in identifying a responding subgroup of patients. Better identification of distinct subgroups of patients based on immune phenotypes and potentially other clinical features across the disease trajectory, regardless of the causative pathogen, may accelerate evaluating potential immunomodulators or host-directed therapeutics in future trials of ALI/ARDS and related conditions (eg, sepsis). However, although great efforts have been put into discovering novel biomarkers for the identification of specific patient subgroups associated with ARDS subphenotypes, the current data are still experimental and need to be validated for clinical implementation. The pulmonary field could learn from oncology where clinicians include whole-genome sequencing of tumors to find therapeutics to treat a patient's tumor specifically.

Oncologists have a wide variety of diagnostic tools to aid in targeting treatment for their patients [69, 70]. For ARDS, these tools are lacking; however, there are published studies for sepsis where diagnostic companies are thinking about biomarkers and diagnostic development [71]. New technologies for developing point-of-care devices and diagnostic tests for validated biomarkers are therefore required to pave the way for the implementation of ARDS subtyping in future clinical trials.

Besides, other efforts early in the pandemic adapted preexisting clinical trial platforms, such as REMAP-CAP trials, to evaluate multiple products leveraging prognostic or predictive enrichment of patients based on biomarker-driven subtypes. Such studies are designed to rapidly identify therapies that may graduate to a larger phase 3 design and are valuable tools for evaluating immunotherapies in a stratified patient population. In addition, international platform trials like the Adaptive COVID-19 Treatment Trial (ACTT), Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), and Solidarity developed during the current pandemic may offer opportunities to accelerate the evaluation of therapeutic candidates by using established collaborative infrastructures for future pandemics.

CONCLUSIONS

COVID-19 clinical trial successes and failures offer valuable insights into future studies in respiratory viral diseases. Several immunomodulators have demonstrated efficacy in treating severe/critical COVID-19, but other pathogen-agnostic therapies are still needed to prevent or treat ALI/ARDS due to different causes. The one-size-fits-all approach is unsuitable for studying highly heterogeneous patients with ALI/ARDS. Instead, the evidence presented in this paper suggests that it is essential to stratify patients with ALI/ARDS by using immunological signatures or other clinical feature-based phenotyping at enrollment for therapeutic clinical evaluation and to ultimately utilize these approaches to inform clinical decision-making over the disease course. Demographics, including age, sex/gender, race/ethnicity, and comorbidities, are also crucial contributors to potential patient heterogeneity. Any studies designed to identify biomarkers to inform on treatment need to enroll demographically diverse participants to ensure that findings are broadly applicable. Similarly, any analyses of results from such studies need to account for covariates, including patient demographics, as variables to account for differing phenotypes. Finally, negative clinical trial findings of failed drugs should be published promptly in peer-reviewed journals so that we can have the lessons learned for subsequent studies and potential opportunities for retrospective analysis to identify subpopulations that may have benefited from the drug.

The incredibly fast-paced COVID-19 therapeutics trials provided vital lessons for the Biomedical Advanced Research and Development Authority (BARDA) in public health emergency preparedness. BARDA is committed to developing new pharmaceutical interventions to treat patients with ALI/ARDS caused by various insults, including influenza, COVID-19, sepsis, and other severe outcomes due to infectious disease, radiation, and chemical threats, and to simultaneously preparing for the next pandemic. Considering the lessons learned from COVID-19, the development of ALI/ARDS treatments should no longer be restricted to direct-acting antiviral, antibacterial, or chelating agents. Instead, threat-agnostic therapeutics will be prioritized to treat specific ALI/ARDS patient subpopulations with common immunophenotypes. BARDA is interested in partnering in phase 2 trials that collect biomarker data of disease severity and immune status to identify the subgroups of patients with ALI/ARDS most likely to benefit from specific host-targeted therapeutics for phase 3 trials. By concentrating on ALI/ARDS indications, these BARDA partnerships may find treatments that not only apply to COVID-19 but also to radiation or chemical-induced lung injury or other emerging pandemic threats that lead to severe outcomes, like sepsis.

Acknowledgments

We would like to thank Dr. Ruben Donis, the acting Director of the Influenza and Emerging Infectious Diseases Division of BARDA, for constructive feedback.

Financial support. No funding to declare.

Potential conflicts of interest. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Department of Health and Human Services or its components. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. All the authors contributed to the manuscript conception and design, Q.W. and M.E.P. conducted the literature review and drafted the manuscript, J.N.B., M.L.K., K.H., K.L.S., and K.L.A. interpreted the literature and made revisions. All authors have reviewed and approved the manuscript.

Patient consent. This study does not include factors necessitating patient consent.

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