Update in COVID-19 2020

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As 2020 evolved, coronavirus disease (COVID-19) presented the greatest global health crisis in a century, affecting medical, social, and economic systems (Figure 1). Despite challenging society with new ways of living, working, and communicating, its significant clinical, research, and public health impact was admirably managed by clinicians and scientists worldwide against a backdrop of continually evolving evidence (1). In this update, we review important publications from the American Thoracic Society journals and others that provide insight into pathophysiology, clinical manifestations, and treatment advances of COVID-19 disease while also considering broader societal effects (2, 3). Throughout the update, we use "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" when referencing the virus and use "COVID-19" in relation to the associated illness.

Pathophysiology of COVID-19

Viral transmission, infection, and subsequent cell entry primarily occurs through direct or indirect close contact with an infected individual. Although primarily facilitated by respiratory secretions, droplets, and salivary exchange, airborne and environmental fomite spread have also been described (4). Similar to coughing, activities like speaking, laughing, and singing facilitate impulse aerosol dispersal, which is greatest in the frontal direction (5). Airborne transmission is further facilitated during aerosol-generating procedures such as forced exhalation during spirometry, nebulization, oxygen therapy via a high-flow nasal cannula (HFNC), and nasopharyngeal swabbing. In a small study of healthy volunteers without lung disease, droplet generation was greatest during FVC and maximum voluntary ventilation as opposed to breathing at V_T (6).

SARS-CoV-2 is a single-stranded RNA virus sharing significant homology with SARS-CoV, and, despite only a ~75% similarity in their S (spike) protein sequence, both use ACE2 (angiotensin-converting enzyme 2) to gain cellular entry and establish infection (7). Critically, however, SARS-CoV-2 harbors a furin-like cleavage site within its receptor binding domain, a feature conferring a gain-of-function advantage to cellular entry absent from SARS-CoV (7, 8). RNA sequencing reveals the differential cellular patterns of ACE2 expression within various lung compartments, including factors influencing its expression. ACE2 gene expression is present throughout the tracheobronchial tree, as observed by using microarrays and bulk and single-cell RNA

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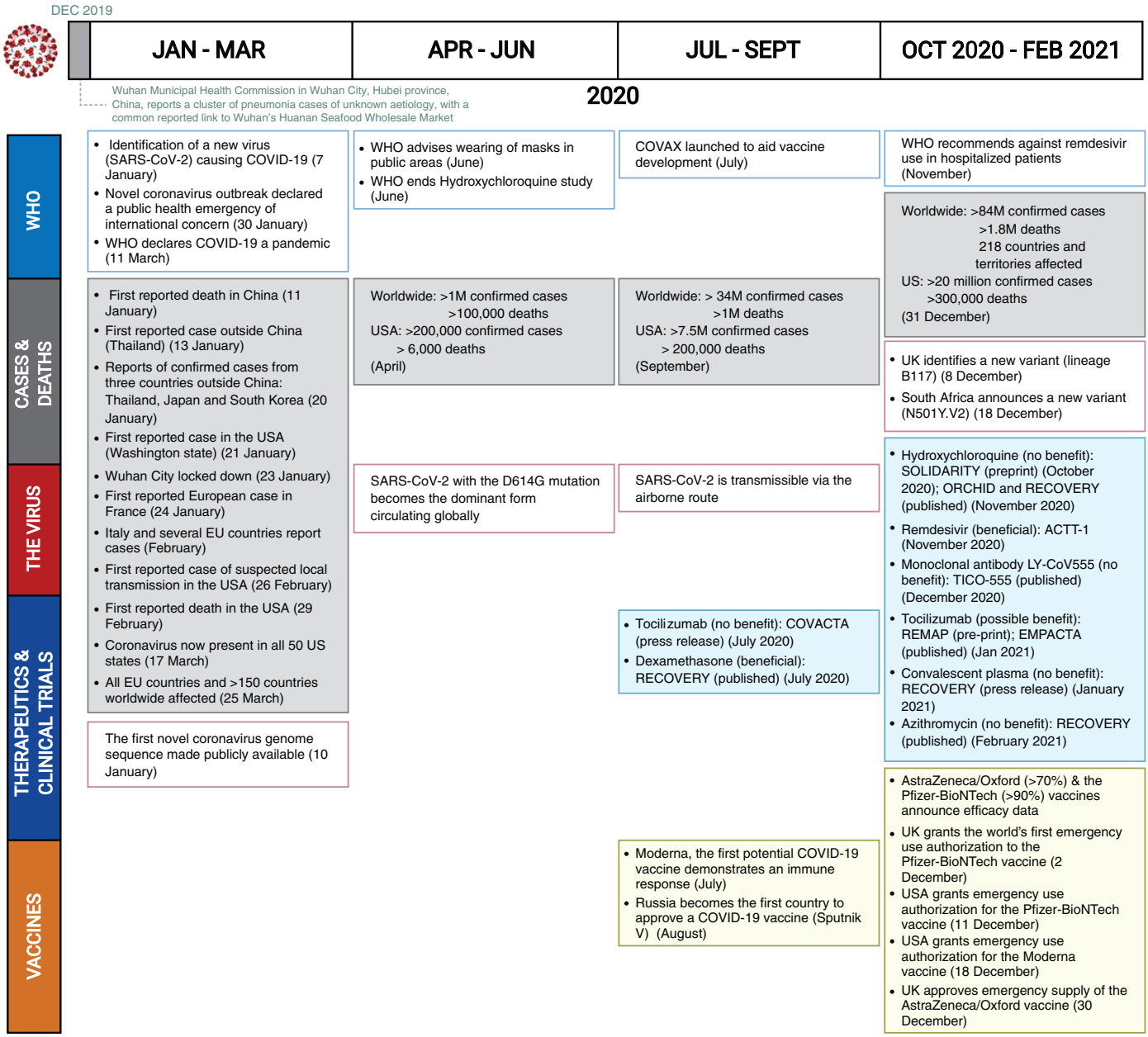

Figure 1. A summary of key milestones related to the COVID-19 pandemic in 2020. COVID-19 = coronavirus disease; EU = European Union; M = million; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UK = United Kingdom; WHO = World Health Organization.

sequencing. Expression was highest proximally, and all major lung epithelial cell types, including basal, intermediate, club, mucous, and ciliated cells, demonstrate ACE2 expression (9). In parallel work, at single-cell resolution using healthy donor tissue, ACE2 expression appeared to be concentrated in a small population of alveolar type 2 cells that concurrently express other genes facilitating viral infection (10). Analyses of ACE2-expressing cell populations demonstrate overrepresentation of viral life cycle–related functions including the gene components of caveolae (CAV2 and ITGB86) and several endosomal sorting complexes required for transport machine gene members, including CHMP3, CHMP5, CHMP1A, and VPS37B. Collectively, these findings suggest enhanced susceptibility to and severity of COVID-19 (10). Smoking is associated with higher pulmonary ACE2 expression, particularly in males and in small airways, potentially explaining COVID-19 sex disparities and worse outcomes observed in chronic obstructive pulmonary disease (9, 11). The cellular protease furin is similarly upregulated by smoking, but to a lesser extent than ACE2 (11). Other key COVID-19 outcome determinants linked to increased ACE2 (and cellular protease TMPRSS2) include age, Black race, and diabetes (12). Sputum analysis from healthy control subjects and people with asthma enrolled in SARP-3 (Severe Asthma Research Program 3) revealed no differences in ACE2 expression but interestingly showed that inhaled corticosteroid use diminished sputum ACE2 and TMPRSS2, a relationship most pronounced at higher steroid dosages

(12, 13). However, epithelial brushings from patients with asthma and exercise-induced bronchoconstriction exhibit elevated ACE2 that correlates with disease severity, pulmonary function, and sputum TMPRSS2 (12, 14). Furthermore, human rhinovirus infection (human rhinovirus A16) or IFNβ1 stimulation of *ex vivo* lower airway cultures from children with asthma demonstrate upregulation of ACE2 and TMPRSS2 within 48 hours, which is suggestive of increased COVID-19 susceptibility after the initial insult (14). These findings, confirmed in parallel work, demonstrate the strong association of viral infection, asthma exacerbation, and synergistic biomolecular interaction with SARS-CoV-2 (15).

The small airway epithelium expresses additional cofactors important for viral cell entry and in COVID-19 pathogenesis; ADAM10 and ADAM17 are cell surface disintegrins mediating ACE2 shedding, whereas inhibition of TMPRSS11A, TMPRSS1D, or PI4KB blocks SARS-CoV-2 infection (9). The membrane-bound coreceptor NRP1 (neuropilin 1) is highly expressed on the olfactory epithelium and possesses binding capabilities toward furin-cleaved substrates, potentially serving as a novel host factor facilitating COVID-19 infection by potentiating viral infectivity (16). Studies using primary nasal epithelial cells treated with azithromycin detected a downregulation of IL-1β gene expression in addition to downregulation of pathways involving TMPRSS2 and TMPRSS11D (17). Although this suggested a potential therapeutic pathway for treating COVID-19, this failed to bear out in randomized clinical trials of azithromycin, including the RECOVERY trial (18, 19). Work with other β-coronavirus, SARS-CoV and Middle East respiratory syndrome coronavirus, suggested that Toll-like receptor ligands may be used to induce epithelial resistance to CoV pneumonia (20). Ultimately, animal models that recapitulate the full spectrum of COVID-19 will be needed to causally test the biological significance of these and other putative pathophysiological and therapeutic mechanisms (21).

Clinical Manifestations of COVID-19

On the basis of early pragmatic definitions, mild or moderate COVID-19 does not require hospitalization, whereas severe illness necessitates supplemental oxygen and hospital admission. Patients with critical disease have respiratory failure, shock, and/or multiorgan dysfunction (22). How best to grade COVID-19 severity remains unclear, although the degree of respiratory support correlates well with disease outcomes. Alternate approaches for grading severity include the site of care, degree of hypoxemia, organ dysfunction, or severity of inflammation. Current conceptualization describes a biphasic disease: an initial "viral phase" followed by either resolution or a "hyperinflammatory phase" driven by host-mediated organ damage (23). Although such a division is more heuristic than biological, a dynamic balance exists between antiviral defenses and excess inflammation. Immunological profiling supports a mortality signal driven primarily by an excessive host response rather than by the virus, which is supported by histological evidence of end-organ damage without viral invasion (24, 25). Nevertheless, the disease likely exists across a continuum, and virus-associated effects may also have important roles in late disease.

Common COVID-19 symptoms include fever, dyspnea, cough, and fatigue (26, 27). Dyspnea is often reported by those who develop critical illness and correlates with a worse prognosis. The median time from symptom onset to diagnosis ranges between 4 and 8 days, with hospital admission around Day 6 (28, 29). The average age of hospitalized patients is 54 years, with increased risks of severe disease and mortality in older patients (27, 28). The median age for patients requiring ICU care is 61–64 years, with higher percentages of patients older than 75 developing critical illness (28, 29). Every 10-year age increase is associated with an additional 58% relative risk of death (27, 29).

Most patients have normal or low white blood cell counts; lymphopenia or relative lymphopenia is a feature of COVID-19 (26, 27, 29). In contrast to classic acute respiratory distress syndrome (ARDS), COVID-19 ARDS is characterized by severe lymphopenia and delayed lymphocyte activation (30, 31). In addition, anemia and thrombocytopenia are common (27). Neutrophilia with evidence of emergency myelopoiesis is also frequently observed (26–29, 32). Evidence of coagulopathy is common, and many patients demonstrate elevated aminotransferases. Patients with severe illness have higher C-reactive protein, ALT, AST, total bilirubin, LDH, myoglobin, and D-dimer than those with moderate illness (28). In addition, patients with critical illness may have evidence of myocardial dysfunction illustrated by higher troponin, serum creatine kinase–myocardial band, and brain natriuretic peptide compared with those with less severe disease (28, 32). Largely analogous to ARDS, levels of IL-1β, IL-6, IL-8, and soluble TNF receptor 1 are elevated in COVID-19 and are even higher in those requiring ICU care (33). In this latter group, elevated ratios of IL-6 and IL-1β to the antiinflammatory cytokine IL-10 are observed, patients with severe COVID-19 demonstrate increased AAT (alpha-antitrypsin) levels, and patients with lower IL-6 to AAT ratios exhibit improved outcomes (24, 26). Neutrophils have a key role in producing IL-1β, IL-6, and IL-10, and metabolic reprogramming in severe COVID-19 is likely due to the combined effects of proinflammatory mediators and severe hypoxemia (24, 34). For adequate recovery, T-cell immunity remains essential but requires sufficient neutralizing antibody production to achieve disease resolution (35). Recent clinical phenotyping and peripheral blood analysis results suggest a COVID-19–specific state of immune system dysregulation. To determine the cellular composition and immune signatures within the alveolar space, BAL fluid from over 300 patients with severe pneumonia, 88 of whom had severe COVID-19, were examined (36). This revealed an enrichment in alveolar T cells and monocytes in COVID-19 and uncovered that IFN-γ–producing T cells formed positive feedback loops with infected macrophages in the alveolar space, driving the spatially restricted alveolitis characteristic of COVID-19 pneumonia.

Chest computed tomography abnormalities consistent with parenchymal change are characteristic of COVID-19 (28, 29, 32, 37, 38). Ground-glass opacities, consolidation, and pleural thickening are common, and disease severity correlates with the extent of lobar involvement; most discharged patients achieve radiological resolution by 4 weeks (28, 32, 37). Comorbidities are commonly present in patients with COVID-19 pneumonia, particularly hypertension, diabetes, and cardiovascular disease (28, 32). Comorbidity is more common in those developing critical illness, with 68% of nonsurvivors having at least one comorbidity (32). Interstitial lung

disease, long known as a risk factor for poor outcomes from viral pneumonia, appears to contribute an independent mortality risk to COVID-19 (39–41). This contrasts with asthma, for which prevalence among patients with COVID-19 is comparable to that of the general population, suggesting no additional risk (42). Furthermore, surveys estimate that the cumulative incidence of COVID-19 in patients with pulmonary arterial hypertension remains similar to that of the general U.S. population, although outcomes, including mortality, are significantly worse (43, 44).

In its most severe form, COVID-19 pneumonia causes air hunger and acute hypoxemic respiratory failure meeting the Berlin criteria for ARDS, necessitating mechanical ventilation for an average of 10–16 days (45). The heterogeneity of severe COVID-19 and ARDS in general prompted questions about distinct endophenotypes of COVID-19–induced respiratory failure. Early in the pandemic, Ziehr and colleagues reported physiological parameters and lung mechanics in severe COVID-19 (46). They found continuous distributions of $Pa_{O_2}/F_{I_{O_2}}$, plateau pressure, positive end-expiratory pressure (PEEP), and respiratory system compliance without ascertaining distinct phenotypes. These results were contextualized in a larger series of greater than 1,000 patients with non–COVID-19–induced ARDS (47, 48) and were confirmed in an observational study that included patients with COVID-19 ARDS (49).

Clinical observations support vascularly predominant pathophysiological derangements in some patients with severe COVID-19 (50). Pulmonary vascular change is observed on computed tomography images. A retrospective case series of mechanically ventilated patients with severe COVID-19 found increased physiological dead space and substantial vascular involvement, indicated by dilated peripheral vessels, tree-in-bud patterns, and perfusion deficits (51). Available data support a propensity for patients with COVID-19 to develop platelet-rich microthrombi, although a mechanistic basis for this phenomenon remains to be defined. Moreover, vascular disorders, including cardiovascular disease and diabetes, are overrepresented in severe COVID-19, and highly vascular organs such as the kidneys are injured at substantial rates (52). In further support of this vascularly predominant COVID-19 phenotype are the observation of reported angioedema in some patients and the evidence of endothelial infection with accompanying endotheliitis (53, 54). Disruption of the protective endothelial glycocalyx in early-phase critical COVID-19 represents a hallmark of later and more severe endothelial injury during severe disease, which is largely ascribable to the loss of vascular homeostasis (55).

The duration of viral PCR positivity varies between individuals, and detection of viral RNA weeks after infection does not necessarily imply infectiousness (56). A small case series published early in the pandemic suggested a median time from symptom onset to PCR test negativity of 10.5 days (interquartile range, 6–12 d) and a median time to symptom resolution of 8 days (interquartile range, 6.25–11.5 d), respectively (57). The duration of symptoms may be substantially longer in severe disease, and SARS-CoV-2 RNA may be isolated from extrapulmonary compartments as disease progresses (58). Obtaining high-precision, high-accuracy validation of time frames in relation to symptoms and viral shedding remains a key element for improving predictive modeling (59). Bronchoscopic sampling of the lower respiratory tract is feasible, can confirm COVID-19 pneumonia, and aids the diagnosis of bacterial superinfection, although the risk–benefit ratio of invasive procedures needs to be considered at the individual level (60, 61). In addition, whether due to inherent features of COVID-1, viral infection in general, or immunomodulatory therapies, an association between COVID-19 pneumonia and fungal superinfection is described, underscoring the importance of microbial diagnostics in determining appropriate antiinfective therapy in COVID-19 (62–64).

Treatment Approaches in COVID-19

Consistent with the "two-phase" framing of COVID-19 illness, it is anticipated that antiviral therapies will have their greatest benefit in early disease and that therapies targeting the host immune response will be beneficial later. That division is best expressed in terms of care setting (outpatient, inpatient, intensive care) and we follow this categorization in this update. We emphasize that among severely and critically ill patients, the most important therapy is high-quality, multidisciplinary supportive care (65).

The *outpatient* setting has proved difficult for generating evidence from clinical trials, largely because the large majority of those infected by SARS-CoV-2 have self-limited infection. Prior work suggests possible efficacy for neutralizing monoclonal antibodies in preventing more severe illness among outpatients, although definitive trials have not been published to date (66, 67). The combination of bamlanivimab and etesevimab, monoclonal antibodies that bind to overlapping epitopes of the SARS-CoV-2 S protein, reduced viral load in nonhospitalized patients with mild-to-moderate COVID-19 compared with placebo (68). These antibodies target the receptor binding domain of the viral S protein, potentially blocking viral cell entry. Early hopes that such antibodies would limit hospitalizations and protect health systems have yet to be realized, although a recent study demonstrating a significant reduction in symptomatic infections after postexposure prophylaxis with bamlanivimab is encouraging (69). The large multinational COLCORONA trial suggested a modest decrease in hospitalization (number needed to treat, 71) with a prolonged course of colchicine, although the primary efficacy endpoint of death or hospitalization for COVID-19 was not met (70). To date, no other outpatient therapies have achieved even the modest evidential thresholds required for U.S. Food and Drug Administration Emergency Use Authorization.

Data on *hospitalized patients who are not critically ill* suggest benefit from treatment directed at both the virus and systemic inflammation caused by infection. Remdesivir, an inhibitor of the viral RNA polymerase, is the only U.S. Food and Drug Administration–approved treatment for hospitalized patients with COVID-19. In a multicenter randomized trial (ACTT-1 [Adaptive COVID-19 Treatment Trial-1]) of 1,062 hospitalized patients with COVID-19 pneumonia, patients treated with remdesivir had a faster time to recovery than patients receiving a placebo (median of 10 vs. 15 d, $P < 0.001$) (71). The overall beneficial effect appeared to be driven by hospitalized non–critically ill patients. However, the multicenter, open-label SOLIDARITY trial that evaluated remdesivir together with three other repurposed antiviral treatments for

COVID-19 found no mortality benefit of remdesivir compared with its control (72). In RECOVERY, a pragmatic, randomized, open-label trial enrolling 6,425 patients at 176 hospitals in the United Kingdom, treatment with dexamethasone (6 mg daily for 10 d) was associated with decreased 28-day mortality among patients hospitalized with COVID-19 (73). Meta-analyses of other smaller trials of glucocorticoids in COVID-19 were consistent with the RECOVERY results. The mortality reduction appeared to be limited to inpatients receiving supplemental oxygen, including through an HFNC or mechanical ventilation. Unfortunately, RECOVERY did not distinguish conventional oxygen from HFNC oxygen, so questions remain about the treatment effect in the non–critically ill. Because of the association of COVID-19 and thrombosis, a coalition of three multicenter, randomized, open-label trials evaluated full-dose anticoagulation and standard prophylactic dosing in hospitalized patients with COVID-19. Study findings suggest a decrease in organ failure for non–critically ill inpatients with full-dose anticoagulation but suggest no benefit in critically ill patients receiving full-dose anticoagulation (74, 75).

In the *critically ill* with COVID-19, the most common reason for ICU admission is ARDS. The relevant therapies for COVID-19 ARDS are supportive ARDS care; antiinflammatory, immune-modulating, and antiviral therapies; and therapies targeting extrapulmonary complications.

Early in the pandemic, two controversies raged about the treatment of patients with COVID-19 ARDS. One question was whether to use an HFNC or noninvasive ventilation (NIV) when indicated or to immediately initiate invasive mechanical ventilation (IMV). The avoidance of HFNC use and NIV was based on a combination of fear of infection in healthcare workers because of aerosol-generation and concern that patients may decompensate quickly and require emergent intubation, creating a situation in which healthcare team members lacked time to don adequate personal protective equipment (PPE) (76, 77). The significant need for intensive care in severe COVID-19 prompted further investigation into the potential risk of viral dissemination associated with extracorporeal organ support modalities, including continuous renal replacement therapy and venovenous extracorporeal membrane oxygenation (ECMO). Reassuringly, viral RNA was not detectable in the dialysis fluid of patients on continuous renal replacement therapy, even if their plasma was positive for viral RNA; in patients receiving ECMO, viral RNA was not even detectable in the gas condensate of the membrane oxygenator (78). As clinical experience and data emerged, HFNC use became standard practice, as at least half of patients needing an HFNC do not progress to intubation (79).

Another debate early in the pandemic centered around whether COVID-19 ARDS caused a high-compliance phenotype that merited higher V_T ventilation and lower PEEP than standard lung-protective IMV for ARDS (46, 80). Respiratory mechanics and lung recruitability in a single-center cohort of patients with COVID-19 ARDS were heterogeneous and similar to a cohort of patients with non–COVID-19 ARDS (81). Other investigators pursued strategies to individualize PEEP titration in patients with COVID-19–associated ARDS, such as recruitment to inflation index to measure lung recruitability and electrical impedance tomography to titrate PEEP (82, 83). Over time, consensus emerged that, as with other causes of ARDS, there is heterogeneity in COVID-19 ARDS, and current evidence suggests that patients with COVID-19 ARDS should routinely receive low V_T and moderate PEEP ventilation, just like others with non–COVID-19 ARDS (84).

Supportive therapies, with at least one important trial suggesting efficacy, are now routinely implemented in the clinical care of COVID-19 ARDS. Prone ventilation for patients receiving IMV has been shown to improve oxygenation and is recommended in IMV guidelines for patients with ARDS and low $Pa_{O_2}/F_{I_{O_2}}$ ratio (85). However, uptake of prone ventilation in patients receiving IMV had been low before COVID-19 (86). In patients with hypoxemia due to COVID-19, many received prone ventilation, including patients not requiring IMV. Case series suggest improved oxygenation and less deterioration with prone ventilation, even in nonintubated patients with COVID-19 pneumonia (87). However, no causal claims can be made with current evidence on whether prone ventilation improves outcomes in nonintubated patients. Although prone positioning is now common, it is important to monitor these patients carefully because resulting pressure ulcers and nerve injuries are common. ECMO has long been used in patients with refractory hypoxemia due to ARDS of any cause, despite a lack of evidence for efficacy. Case series of patients receiving ECMO for COVID-19 ARDS report 60-day mortality of 31–35%, similar to results from a pre–COVID-19 trial of ECMO in non–COVID-19 ARDS (88–90). Overall, there is no clear evidence that a unique approach to supportive COVID-19 ARDS care is necessary, and therefore care provided to the standards of non–COVID-19 ARDS in general is appropriate (91, 92).

Antiinflammatory treatments have long been of interest in ARDS, with mostly disappointing results, but evidence of benefit in specific syndromes, such as ARDS due to *Pneumocystis jirovecii* infection, are well-described (93). A pre–COVID-19 randomized trial suggested possible benefits of dexamethasone in moderate-to-severe ARDS, and in the RECOVERY trial of patients with COVID-19, subgroup analysis found dexamethasone to be most efficacious in patients with ARDS (73, 94). Other smaller trials included in a meta-analysis with RECOVERY estimated an odds ratio of 0.66 (95% confidence interval, 0.53–0.82) for 28-day mortality with low-dose corticosteroids (95). The optimal dose, duration of treatment, choice of glucocorticoid, and management of patients who worsen despite steroids remain open questions.

Baricitinib is a selective inhibitor of Janus kinases 1 and 2. In ACTT-2, baricitinib combined with remdesivir reduced the time to recovery compared with remdesivir alone, with the most robust signal appearing in ARDS (96). However, it remains unclear whether baricitinib confers added benefit for patients already receiving glucocorticoids. Because inhibition of IL-6 is effective in cytokine release syndrome, which may have some similarity to critical COVID-19, studies of tocilizumab and sarilumab have been pursued. Although overall results appear to be mixed, multiple trials suggest potential benefits to tocilizumab in some subgroups of sicker patients, particularly when given within 24 hours of ICU admission in patients requiring HFNC use, NIV, or IMV (97–99).

Although remdesivir reduces the time to recovery in hospitalized patients, whether this effect is present among patients with

COVID-19 ARDS is currently unknown. Although persistent detection of SARS-CoV-2 RNA is often noted in patients with COVID-19 ARDS, other processes, including fibrosis, may predominate in patients who develop ARDS. In the absence of strong current evidence for efficacy in this population, remdesivir has been removed from the NIH treatment guidelines as a recommended treatment in patients with COVID-19 ARDS (23).

Two key areas of uncertainty exist regarding treatments for COVID-19, relating primarily to the generation and interpretation of evidence. First, pragmatic trials have generated substantial interest as mechanisms for evidence generation. Pragmatic trials are superior to observational studies, with a "real-world" approach to targeting a specific population definition and safety monitoring allowing such trials to provide precise (if possibly biased because of a common lack of blinding) estimates of "effectiveness." Traditional randomized, blinded trials tend to provide less precise, but also less biased, estimates of "efficacy." Large pragmatic trials are thus useful for identifying agents with a known safety profile and large effect, but the effective type 2 error rate across the trials' enterprise may be substantial. Second, do the expected effects of a drug change on basis of a changing therapeutic context? What is the efficacy of remdesivir on the background of dexamethasone? Does baricitinib provide any additional benefit for patients already treated with glucocorticoids and remdesivir? These and other important questions remain unanswered and may be suitable for large, pragmatic trials as we continue to grapple with the virus.

Societal Implications of COVID-19

COVID-19 has had a profound impact on society. The public perception of the pandemic and its implications for people's lives were influenced by government messaging, dynamic and geographically disparate policies, and both mainstream and social media. Public debate over the use of face mask usage represents just one factor affecting SARS-CoV-2 spread that became a flashpoint of societal debate (100). Economic dislocation and debate about the role of government likely contributed to pandemic-associated worsening of preexisting societal tensions. The psychological effect of other mitigation measures, including social distancing, lockdowns, and travel bans, may have also affected social cohesion in many areas.

The ethical imperative to provide health care to those who most need it has been challenged by COVID-19. The need for rapid and large-scale deployment of resources exacerbated preexisting inequities (101). Emergency triage plans were implemented globally. Innovative ventilator-sharing strategies to address shortages during surges when hospital systems were overwhelmed were deployed, allowing two patients to receive support from a single device through thoughtful selection of patient pairs, altered circuit configuration, and sedative management (102). This strategy has practical limitations, including uncertain safety and long-term feasibility and the need for additional training (103). In some cases, clinicians refused to provide mechanical ventilation on the basis of underlying medical conditions. Ramos and colleagues argue against such an approach and propose that disease-specific prognostic information be considered in, for instance, younger individuals with cystic fibrosis, in whom potentiator and corrector therapeutics have dramatically improved life expectancy (104).

The pandemic has also amplified longstanding racial and ethnic healthcare disparities (105). A retrospective cohort study from the University of Chicago found that Black race was associated with a higher likelihood of COVID-19 including hospitalization, findings replicated in a study from Louisiana (106, 107). Of note, however, in-hospital outcomes, including mortality, were similar to those of white patients after adjustment for sociodemographic and clinical COVID-19 characteristics.

The collateral damage of emergency care of patients with COVID-19 to those with non–COVID-19 illness is substantial. Valley and colleagues describe the impact on patients, family members, clinicians, and the healthcare system because of institutional visitation policy changes in ICUs across Michigan and evaluated possible solutions (108). The physical, emotional, and mental exhaustion of the healthcare workforce from COVID-19 is demonstrated in a cross-sectional study in French ICUs, with a significant prevalence of anxiety, depression, and peritraumatic dissociation, all linked to fears of infection, inadequate rest, and emotional struggles related to family, visitation policies, and hasty end-of-life decisions, being shown (109). This important work, editorialized by Jun and Costa, exposes the vulnerability of healthcare workers and highlights the need for strategies to support workers at the individual, organizational, and national levels (110). Public health containment policies and the associated economic recession have additional negative consequences for physical and mental well-being. Although early focus was appropriately placed on the critically ill, the increasing surfeit of delayed, deferred, or cancelled healthcare appointments and procedures for episodic, continued, and/or chronic non–COVID-19 care should not be ignored. Jain and Santhosh highlight the beneficial use of telemedicine, although it cannot replace physical examinations, pulmonary function testing, and bronchoscopy (111). Addressing collateral damage amid an ongoing pandemic will necessitate structural changes to the allocation of resources, including staff, PPE, and testing (111). This is further supported by an American Thoracic Society–led taskforce document that provides practical advice for restarting pulmonary and sleep services. This includes the need for an operational strategy addressing patient prioritization, testing, physical distancing, and infection control to protect staff and patients from COVID-19 while considering resource constraints in staffing, space, and equipment (112).

A long-term view embracing a new reality and considering the sustainability of healthcare delivery is needed to protect society. The healthcare workforce will need to adjust to novel ways to learn and work with specific protection mechanisms for those who have suffered most because of COVID-19. This includes early-career clinicians, scientists, and clinician–scientists who experienced pandemic-related disruption to their family lives, education, work practices, and career progression, with inequity being demonstrated for women (113, 114). Many are also caregivers, and there are disproportionate effects on pulmonary and critical care medicine faculty because of the inherent need for their clinical expertise in managing patients with COVID-19 (113, 114). Work practices, policies, and workplaces of the future will change to incorporate technology. Novel applications

of telemedicine to communicate with patients in biocontainment should be embraced, as they reduce exposure risk, conserve PPE, and efficiently manage higher patient loads despite the limitation of lacking true face-to-face interaction (115).

The COVID-19 pandemic has had myriad impacts on medical education. Early in the pandemic, the American Association of Medical Colleges issued a recommendation to pause medical student clinical rotations (116). Resident and fellow involvement in the care of patients with COVID-19 was variable. A survey of 316 medical students, residents, and fellows who experienced COVID-19 early in the course of the pandemic revealed moral distress from caring for critically ill patients who were dying alone because of visitation policy changes and concerns for personal health and the health of family, friends, and colleagues (117). In New York City, medical students were given the option of graduating early to work on the front lines (118). Pulmonary and critical care medicine fellows at the end of their fellowship training contributed clinically and helped train workforce members on core critical care topics such as IMV, ARDS, and septic shock (119). One intensivist who had recently completed training shared the challenges of beginning work as an attending physician in a COVID-19 ICU in Chile while facing medical uncertainty, long hours, PPE shortages, and fear of contagion (120). The first U.S. case of COVID-19 was identified in Washington, and the University of Washington pulmonary and critical care medicine fellowship program shared their early program experience with COVID-19 (121, 122). They outlined their response to clinical care, communication, well-being, and formal education (122). Another perspective from Ireland highlighted the impact on pulmonary fellowship training (123). With pulmonary fellows redeployed to ward-based internal medicine service, the program reported decreased specialty pulmonary exposure and procedural experience for trainees. The longer-term effects of these pandemic-related disruptions to training remain unknown. Educators adapted to pandemic-related disruptions by moving most formal teaching sessions online. PPE shortages and physical distancing among care team members impacted bedside educational opportunities. One center created a tele-ICU learning experience for residents as part of an underserved medicine rotation. Residents and intensivists provided remote consultation to rural ICU providers, with residents reporting an improved ability to deliver critical care in resource-limited settings (124). Born of necessity, such telemedicine programs should be used long after the pandemic is over. Most formal educational conferences and society meetings also moved to a telepresence format. The leadership of the Association of Pulmonary and Critical Care Medicine Program Directors described their experience transitioning to a virtual annual conference in only 5 days and provided helpful tips for success (125). They highlighted the need for clear communication, the establishment of roles within the team, speaker preparation, and session facilitation and shared strategies to promote interaction. Educators shared tips for synchronous videoconferencing and asynchronous learning, recognizing that these skills may well be needed even after the pandemic (126, 127). Although distance learning is new for many, they noted the importance of applying best practices for adult learning in virtual formats and focused on active learning techniques and interaction. Sharif and colleagues reviewed the utility, theory, and evidence of extraclinical teaching (teaching away from the bedside), with its advantages being scale, asynchronous and tailored learning, democratization of teaching voices, and efficient renewal of resources (128). Finally, acknowledging the disparities made more apparent by COVID-19, medical students created a free and interactive website for kindergarten through 12th grade children to learn about COVID-19 in English, Spanish, and French to expand health literacy in vulnerable populations (128).

As we progress through 2021, significant progress has been made in understanding, treating, and preventing COVID-19 in 2020. The arrival of multiple efficacious vaccine candidates alongside national rollout programs provide hope. Our exit strategy through science was tested and is succeeding. We have gone from virus to vaccine in record time while developing an evidence base of multiple global clinical trials, all performed at breathtaking speed without compromising quality. As the race between infections and injections ensues, we continue to face important challenges, including emerging viral variants; the communication of appropriate and relatable information across media; and the understanding of vaccines, their long-term protection, and strategies for deployment and equity. Despite this, we can be hopeful that the dawn that always follows darkness is near. ■

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