Selected Bibliography of Recent Research in COVID-19

Benjamin D. Singer[1,2,3,4], Sanjay H. Chotirmall[5,6], Lindsay M. Leither[7,8], Oliver W. Meldrum[5], Anthony M. Joudi[1,3], Nitin Seam[9], Samuel M. Brown[7,8]*, and Başak Çoruh[10]*

[1]Department of Medicine, Division of Pulmonary and Critical Care Medicine, [2]Department of Biochemistry and Molecular Genetics, [3]Canning Thoracic Institute, and [4]Simpson Querrey Institute for Epigenetics, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [5]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [6]Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore; [7]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Intermountain Medical Center, Murray, Utah; [8]Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah; [9]Critical Care Medicine Department, National Institutes of Health, Bethesda, Maryland; and [10]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Washington, Seattle, Washington

ORCID IDs: 0000-0001-5775-8427 (B.D.S.); 0000-0003-0417-7607 (S.H.C.); 0000-0002-3442-2151 (O.W.M.); 0000-0003-1206-6261 (S.M.B.).

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continued throughout 2021. Highly effective vaccines became widely available in 2021, and basic, translational, and clinical knowledge about COVID-19 expanded at a rapid pace. This bibliography cites and summarizes publications from American Thoracic Society journals and others centered on the year 2021 that inform our understanding of the pathophysiology, clinical manifestations, vaccines, and treatment advances in COVID-19 while considering broader effects on society, healthcare delivery, and medical education.

Chotirmall SH, Martinez FJ, Schumacker PT, Cooke CR, Seam N, Brochard L, et al. Life at the editorial "COVID frontline". The American Thoracic Society Journal Family. Am J Respir Crit Care Med 2020; 201:1457–1459.

Pathophysiology

The biomedical community's grasp of the pathophysiology underlying the clinical spectrum of COVID-19, including basic, physiological, and environmental factors, grew in 2021.

National Institutes of Health. Clinical spectrum of SARS-CoV-2 infection. [accessed 29 Jan 2022]. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/.

For example, we have gained new insights into the biology of the SARS-CoV-2 viral receptor, ACE2 (angiotensin-converting enzyme 2). Murine ACE2 does not efficiently bind to the spike protein of most SARS-CoV-2 variants. Accordingly, techniques are emerging to sensitize mice to SARS-CoV-2 infection by expressing human ACE2 via an adenovirus delivery system, although these mouse models remain limited to a mild phenotype.

Han K, Blair RV, Iwanaga N, Liu F, Russell-Lodrigue KE, Qin Z, et al. Lung expression of human angiotensin-converting enzyme 2 sensitizes the mouse to SARS-CoV-2 infection. Am J Respir Cell Mol Biol 2021;64:79–88.

Harker JA, Johansson C. Rapidly deployable mouse models of SARS-CoV-2 infection add flexibility to the COVID-19 toolbox. Am J Respir Cell Mol Biol 2021; 64:7–9.

In humans, infant nasal epithelial cells exhibit interferon-stimulated ACE2

(Received in original form February 7, 2022; accepted in final form October 6, 2022)

*These authors contributed equally to this work.

Supported by the National Institutes of Health (NIH) awards R01HL149883, R01HL153122, P01HL154998, P01AG049665, and U19AI135964 (B.D.S.); the National Research Foundation Singapore under its COVID-19 Research Fund administered by the Singapore Ministry of Health's National Medical Research Council (MOH-000409 [S.H.C.]); the Singapore Ministry of Health's National Medical Research Council under its Clinician–Scientist Individual Research Grant (MOH-000141 [S.H.C.]); Clinician Scientist Award (MOH-000710 [S.H.C.]); the National Institutes of Health Clinical Center (N.S.); the Lee Kong Chian School of Medicine-Imperial College London Postdoctoral Fellowship (Grant#020458–00001 [O.W.M.]); LEARN Grant LEARN008 [O.W.M.]; NIH awards U01HL123018, OT2HL156812, and R01HL144624 (S.M.B.); and DoD award W81XWH-21–1-0050 (S.M.B.). The opinions expressed in this article are those of the authors and do not represent any position or policy of the National Institutes of Health, the U.S. Department of Health and Human Services, Department of Defense, or the U.S. government or any of their institutions.

Author Contributions: The following authors conceived and provided a first draft of each of the following sections: pathophysiology (O.W.M. and A.M.J.), clinical manifestations (B.D.S. and L.M.L.), vaccines (S.H.C. and B.Ç.), treatment (N.S. and S.M.B.), and societal effects (S.H.C. and B.Ç.). B.D.S., S.H.C., O.W.M., and B.Ç. conceived and drafted the figure and table. B.D.S. and S.H.C. conceived the overall project, coordinated the team, and planned and prepared the manuscript draft, including editing of all subsections, with assistance from all authors, who contributed to the editing of and approved the final submitted version of the manuscript.

Correspondence and requests for reprints should be addressed to Benjamin D. Singer, M.D., Northwestern University Feinberg School of Medicine, 303 E. Superior Street, Simpson Querrey, 5th Floor, Chicago, IL 60611. E-mail: benjamin-singer@northwestern.edu.

Am J Respir Crit Care Med Vol 206, Iss 12, pp 1548–1562, Dec 15, 2022

Originally Published in Press as DOI: 10.1164/rccm.202202-0277UP on October 6, 2022
Internet address: www.atsjournals.org

expression similar to adult cells, arguing against a prior hypothesis that a lack of interferon-stimulated ACE2 expression provides a protective advantage in younger individuals.

Salka K, Abutaleb K, Chorvinsky E, Thiruvengadam G, Arroyo M, Gomez JL, et al. IFN stimulates ACE2 expression in pediatric airway epithelial cells. Am J Respir Cell Mol Biol 2021;64:515–518.

Yepsen EN, Harrod KS. Influenza antiviral subversion: now the host is in on the act. Am J Respir Cell Mol Biol 2021;65:1–3.

Patients with chronic obstructive pulmonary disease have increased expression of *ACE2* and other genes encoding proteins that are predicted to mediate interactions between SARS-CoV-2 and human cells.

Agusti A, Sibila O, Casas-Recasens S, Mendoza N, Perea L, Lopez-Giraldo A, et al. Molecular interactions of SARS-CoV-2 in lung tissue of patients with chronic obstructive pulmonary disease. Ann Am Thorac Soc 2021;18:1922–1924.

These interactions can be blocked, representing a potential therapeutic strategy. Madan and colleagues demonstrated that a recombinant fragment of surfactant protein D reduces viral infectivity and replication *in vitro* by inhibiting the binding of SARS-CoV-2 spike protein to ACE2 in clinical samples.

Madan T, Biswas B, Varghese PM, Subedi R, Pandit H, Idicula-Thomas S, et al. A recombinant fragment of human surfactant protein D binds spike protein and inhibits infectivity and replication of SARS-CoV-2 in clinical samples. Am J Respir Cell Mol Biol 2021;65:41–53.

Finally, despite multivariate analyses revealing no association of serum ACE or ACE2 concentrations with mortality in COVID-19 acute respiratory distress syndrome (ARDS), manipulating the enzymatic function of ACE2 may be a therapeutic strategy in ARDS because of COVID-19 or other etiologies.

Reindl-Schwaighofer R, Hodlmoser S, Eskandary F, Poglitsch M, Bonderman D, Strassl R, et al. ACE2 elevation in severe COVID-19. Am J Respir Crit Care Med 2021;203:1191–1196.

Gerard L, Lecocq M, Bouzin C, Hoton D, Schmit G, Pereira JP, et al. Increased angiotensin-converting enzyme 2 and loss of alveolar type II cells in COVID-19-related acute respiratory distress syndrome. Am J Respir Crit Care Med 2021;204:1024–1034.

Collins SP, Chappell MC, Files DC. The renin-angiotensin-aldosterone system in COVID-19-related and non-COVID-19-related acute respiratory distress syndrome: not so different after all? Am J Respir Crit Care Med 2021;204:1007–1008.

Multiple studies have provided a mechanistic basis to explain the hypercoagulable state observed in patients with COVID-19.

Hernandez Cordero AI, Sin DD. Clotting in COVID-19: is it all in the genes? Am J Respir Cell Mol Biol 2021;64:647–649.

In human pulmonary microvascular endothelial cells, SARS-CoV-2 spike protein stimulates the expression of the prothrombotic molecule PAI-1 (plasminogen activator inhibitor 1).

Han M, Pandey D. ZMPSTE24 regulates SARS-CoV-2 spike protein-enhanced expression of endothelial PAI-1. Am J Respir Cell Mol Biol 2021;65:300–308.

Khan SS. The central role of PAI-1 in COVID-19: thrombosis and beyond. Am J Respir Cell Mol Biol 2021;65:238–240.

ZMPSTE24, an inhibitor of PAI-1, mediates ACE2 ectodomain shedding to generate SARS-CoV-2 decoy receptors. Its expression declines with age and inhalational injury, which may partially explain the thrombotic risk and poorer outcomes observed in older patients and those who smoke. KLF2 (Krüppel-like factor 2), which is downregulated in COVID-19 lung autopsy specimens, also inhibits PAI-1 while promoting the expression of antiviral genes and nitric oxide synthase *in vitro*.

Wu D, Lee TH, Huang RT, R DG, Schoettler N, Adegunsoye A, et al. SARS-CoV-2 infection is associated with reduced Kruppel-like factor 2 in human lung autopsy. Am J Respir Cell Mol Biol 2021;65:222–226.

Of note, patients with COVID-19 who experience anosmia demonstrate persistent elevations in nasal nitric oxide concentration up to 5 months after infection.

Hua-Huy T, Lorut C, Aubourg F, Morbieu C, Marey J, Texereau J, et al. Persistent nasal inflammation 5 months after acute anosmia in patients with COVID-19. Am J Respir Crit Care Med 2021;203:1319–1322.

Macrophages and damaged epithelial cells exert prothrombotic functions via the expression of plasminogen urokinase-localizing protein and tissue factor, respectively, together with PAI-2.

FitzGerald ES, Chen Y, Fitzgerald KA, Jamieson AM. Lung epithelial cell transcriptional regulation as a factor in COVID-19-associated coagulopathies. Am J Respir Cell Mol Biol 2021;64:687–697.

Elevated complement factors, specifically factor D, correlate with markers of endothelial injury and hypercoagulability, as well as poorer outcomes.

Ma L, Sahu SK, Cano M, Kuppuswamy V, Bajwa J, McPhatter JN, et al. Increased complement activation is a distinctive feature of severe SARS-CoV-2 infection. Sci Immunol 2021;6:eabh2259.

Host immune responses and the microbiome are associated with tissue pathology and outcomes. A pathological reticuloendothelial response characterized by infiltration of reactive plasma cells, iron-laden macrophages, and $MRP8^+$ mononuclear cells appears to be universal in severe and critical COVID-19. Notably, SARS-CoV-2 RNA and spike protein do not colocalize with these inflammatory changes.

Dorward DA, Russell CD, Um IH, Elshani M, Armstrong SD, Penrice-Randal R, et al. Tissue-specific immunopathology in fatal COVID-19. Am J Respir Crit Care Med 2021;203:192–201.

Welte T. SARS-CoV-2-triggered immune reaction: for COVID-19, nothing is as old as yesterday's knowledge. Am J Respir Crit Care Med 2021;203:156.

Monocyte-derived $CD68^+CD163^+$ macrophages adopt a damage response gene expression signature and profibrotic phenotype in severe SARS-CoV-2 pneumonia, potentially explaining the increased prevalence of fibroproliferative ARDS among patients with critical COVID-19.

Wendisch D, Dietrich O, Mari T, von Stillfried S, Ibarra IL, Mittermaier M, et al. SARS-CoV-2 infection triggers profibrotic macrophage responses and lung fibrosis. Cell 2021;184:6243–6261.e6227.

Lebreton G, Dorgham K, Quentric P, Combes A, Gorochov G, Schmidt M. Longitudinal cytokine profiling in patients with severe COVID-19 on extracorporeal membrane oxygenation and hemoadsorption. Am J Respir Crit Care Med 2021;203: 1433–1435.

Analysis of the upper respiratory tract microbiome in patients with COVID-19 supports the associations among microbiome composition, pathogen burden, and viral immune response.

Althuwaybi A, Al Quaimi M, Krishnan A, Jones R, Pearson J, Ward C. Hospitalization outcomes for COVID-19 in patients with interstitial lung disease: a potential role for aerodigestive pathophysiology? Am J Respir Crit Care Med 2021;203:521–522.

McGinniss JE, Collman RG. The upper airway microbiome and lung injury in COVID-19. Am J Respir Crit Care Med 2021;204:1353–1355.

Before death, but not on admission, hospitalized patients with COVID-19 carry a higher proportion of potential copathogens in their oropharyngeal microbiome, particularly *Enterococcus* spp. and *Candida* spp., compared with those who recover.

Ren L, Wang Y, Zhong J, Li X, Xiao Y, Li J, et al. Dynamics of the upper respiratory tract microbiota and its association with mortality in COVID-19. Am J Respir Crit Care Med 2021;204:1379–1390.

Several studies have expanded our understanding of respiratory system physiology in severe or critical COVID-19. Before the initiation of noninvasive ventilation, patients with COVID-19 exhibit a lower overall work of breathing and higher dynamic respiratory system compliance than patients with other causes of respiratory failure, which may limit the degree of self-inflicted lung injury.

Tonelli R, Busani S, Tabbi L, Fantini R, Castaniere I, Biagioni E, et al. Inspiratory effort and lung mechanics in spontaneously breathing patients with acute respiratory failure due to COVID-19: a matched control study. Am J Respir Crit Care Med 2021;204:725–728.

In contrast, time spent with a $Pa_{O_2}/FI_{O_2} < 100$ mm Hg and respiratory rate >greater than 25 breaths per minute before intubation is independently associated with increased driving pressure and elastance after initiation of mechanical ventilation.

Tsolaki VS, Zakynthinos GE, Mantzarlis KD, Deskata KV, Papadonta ME, Gerovasileiou ES, et al. Driving pressure in COVID-19 acute respiratory distress syndrome is associated with respiratory distress duration before intubation. Am J Respir Crit Care Med 2021;204:478–481.

A recruitment-to-inflation ratio greater than 0.7, as determined by lung ultrasound, identifies patients with potential for alveolar recruitment.

Stevic N, Chatelain E, Dargent A, Argaud L, Cour M, Guerin C. Lung recruitability evaluated by recruitment-to-inflation ratio and lung ultrasound in COVID-19 acute respiratory distress syndrome. Am J Respir Crit Care Med 2021;203:1025–1027.

Plasma concentrations of the soluble form of the receptor for advanced glycation end-products, a marker of lung alveolar epithelial injury, are elevated in COVID-19 ARDS and correlate with Pa_{O_2}/FI_{O_2}, ventilatory ratio, shunt fraction, RALE (Radiographic Assessment of Lung Edema) score, and mortality.

Kapandji N, Yvin E, Devriese M, de Margerie-Mellon C, Moratelli G, Lemiale V, et al. Importance of lung epithelial injury in COVID-19-associated acute respiratory distress syndrome: value of plasma soluble receptor for advanced glycation end-products. Am J Respir Crit Care Med 2021;204:359–362.

Hence, the soluble form of the receptor for advanced glycation end products may serve as a physiologically relevant biomarker of the severity of lung injury in COVID-19 ARDS.

Environmental factors and exposures are important risk factors for COVID-19 diagnosis and severity. People living in neighborhoods with higher concentrations of air pollution have an increased risk of dying from COVID-19.

Stieb DM, Evans GJ, To TM, Lakey PSJ, Shiraiwa M, Hatzopoulou M, et al. Within-city variation in reactive oxygen species from fine particle air pollution and COVID-19. Am J Respir Crit Care Med 2021;204:168–177.

Kim H, Bell ML. Air pollution and COVID-19 mortality in New York City. Am J Respir Crit Care Med 2021;204: 97–99.

Balmes JR. Stress is in the air: ambient reactive oxygen species and COVID-19. Am J Respir Crit Care Med 2021;204:118–120.

Data also demonstrate a dose-dependent correlation between alcohol consumption and the risk of developing ARDS during hospitalization for COVID-19.

Lassen MCH, Skaarup KG, Sengelov M, Iversen K, Ulrik CS, Jensen JUS, et al. Alcohol consumption and the risk of acute respiratory distress syndrome in COVID-19. Ann Am Thorac Soc 2021; 18:1074–1076.

High viral loads, which were associated with increased disease severity and odds of requiring intubation or death in the era before Omicron (B.1.1.529), increased the transmission of viral particles into the surrounding environment.

Zacharioudakis IM, Prasad PJ, Zervou FN, Basu A, Inglima K, Weisenberg SA, et al. Association of SARS-CoV-2 genomic load with outcomes in patients with COVID-19. Ann Am Thorac Soc 2021; 18:900–903.

Yang M, Li L, Huang T, Li S, Zhang M, Yang Y, et al. SARS-CoV-2 detected on environmental fomites for both asymptomatic and symptomatic patients with COVID-19. Am J Respir Crit Care Med 2021;203:374–378.

These transmission dynamics are important considerations when patients undergo aerosol-generating procedures.

Avari H, Hiebert RJ, Ryzynski AA, Levy A, Nardi J, Kanji-Jaffer H, et al. Quantitative assessment of viral dispersion associated with respiratory support devices in a simulated critical care environment. Am J Respir Crit Care Med 2021;203: 1112–1118.

Dhand R. Mitigating viral dispersion during respiratory support procedures in the ICU. Am J Respir Crit Care Med 2021; 203:1051–1053.

Clinical Manifestations

Reports describing mortality rates among patients receiving mechanical ventilation have exhibited high variability since the pandemic's beginning.

Angriman F, Scales DC. Estimating the case fatality risk of COVID-19 among mechanically ventilated patients. Am J Respir Crit Care Med 2021;203:3–4.

In a meta-analysis, Lim and colleagues estimated overall mortality in this population to be 45% (95% confidence interval, 39–52%) with substantial between-study heterogeneity.

Lim ZJ, Subramaniam A, Ponnapa Reddy M, Blecher G, Kadam U, Afroz A, et al. Case fatality rates for patients with COVID-19 requiring invasive mechanical ventilation. A meta-analysis. Am J Respir Crit Care Med 2021;203:54–66.

Temporal heterogeneity is also relevant, as highlighted by a retrospective cohort study in the United Kingdom that detected associations between caseload peaks and the makeup of the population of patients admitted to an ICU.

Pilcher D, Durie M. Learning from the first wave of the pandemic in England, Wales, and Northern Ireland. Am J Respir Crit Care Med 2021;203:532–534.

Doidge JC, Gould DW, Ferrando-Vivas P, Mouncey PR, Thomas K, Shankar-Hari M, et al. Trends in intensive care for patients with COVID-19 in England, Wales, and Northern Ireland. Am J Respir Crit Care Med 2021;203:565–574.

Churpek and colleagues studied hospital-level variation in the mortality of critically ill patients with COVID-19; whereas 38% of patients died by Day 28, there was significant variation between hospitals that was largely attenuated after adjusting for acute physiology, socioeconomic status, and caseload/census.

Teja B, Wunsch H. Pinpointing the cause of variation in mortality in COVID-19. Am J Respir Crit Care Med 2021;204: 381–382.

Churpek MM, Gupta S, Spicer AB, Parker WF, Fahrenbach J, Brenner SK, et al.; STOP-COVID Investigators. Hospital-level variation in death for critically ill patients with COVID-19. Am J Respir Crit Care Med 2021;204:403–411.

A retrospective cohort study of patients hospitalized with COVID-19 found that the most common causes of death were respiratory failure and septic shock with multiorgan dysfunction syndrome because of COVID-19 or a superinfecting pathogen, underscoring the paradigm that critical COVID-19 is best understood as severe community-acquired pneumonia.

Ketcham SW, Bolig TC, Molling DJ, Sjoding MW, Flanders SA, Prescott HC. Causes and circumstances of death among patients hospitalized with COVID-19: a retrospective cohort study. Ann Am Thorac Soc 2021;18:1076–1079.

Budinger GRS, Misharin AV, Ridge KM, Singer BD, Wunderink RG. Distinctive features of severe SARS-CoV-2 pneumonia. J Clin Invest 2021;131:e149412.

Nevertheless, important differences exist in comparing severe SARS-CoV-2 pneumonia with pneumonia owing to other pathogens, including influenza and other respiratory viruses.

Hardin CC. Influenza and COVID-19: times don't get no better. Ann Am Thorac Soc 2021;18:586–587.

A retrospective study found that patients admitted to the ICU with severe SARS-CoV-2 pneumonia experienced longer durations of mechanical ventilation than patients with severe influenza and were at greater risk for in-hospital mortality.

Cobb NL, Sathe NA, Duan KI, Seitz KP, Thau MR, Sung CC, et al. Comparison of clinical features and outcomes in critically ill patients hospitalized with COVID-19 versus Influenza. Ann Am Thorac Soc 2021;18:632–640.

Likewise, small observational cohort studies observed that patients with COVID-19 ARDS were similar to patients with non–COVID-19 ARDS except for experiencing longer durations of mechanical ventilation, exhibiting lower minute ventilation rates, and having lower blood concentrations of IL-6.

Sjoding MW, Admon AJ, Saha AK, Kay SG, Brown CA, Co I, et al. Comparing clinical features and outcomes in mechanically ventilated patients with COVID-19 and acute respiratory distress syndrome. Ann Am Thorac Soc 2021;18:1876–1885.

Bain W, Yang H, Shah FA, Suber T, Drohan C, Al-Yousif N, et al. COVID-19 versus non-COVID-19 acute respiratory distress syndrome: comparison of demographics, physiologic parameters, inflammatory biomarkers, and clinical outcomes. Ann Am Thorac Soc 2021;18:1202–1210.

In 2021, the literature expanded our understanding of short-term and long-term sequelae of COVID-19. An observational cohort study revealed short-term sequelae among survivors of COVID-19 who had been hospitalized, including a high prevalence of lung function deficits, functional impairment, and psychological symptoms.

Finney LJ, Doughty R, Lovage S, Spurr L, Mehta B, Kemp SV, et al. Lung function deficits and symptom burden in survivors of COVID-19 requiring mechanical ventilation. Ann Am Thorac Soc 2021;18: 1740–1743.

Indeed, peritraumatic dissociative symptoms and symptoms related to anxiety and depression also appear to be common during hospitalization for COVID-19 and during the early postacute recovery period in patients, family members, and healthcare workers.

Derry HM, Lief L, Woubeshet N, Schenck EJ, Kakarala S, LaFond E, et al. Peritraumatic stress symptoms during early post-intensive care unit recovery. Ann Am Thorac Soc 2021;18:364–367.

McPeake J, Shaw M, MacTavish P, Blyth K, Devine H, Fleming G, et al. Long-term outcomes after severe COVID-19 infection: a multicenter cohort study of family member outcomes. Ann Am Thorac Soc 2021;18:2098–2101.

Benedict C, Partinen M, Bjorvatn B, Cedernaes J. Sleep in female healthcare workers during COVID-19: a cross-sectional survey study in Sweden during the flattening of the first wave of the pandemic. Ann Am Thorac Soc 2021;18:1418–1420.

Rare postacute manifestations of COVID-19 continue to be reported, including angioedema weeks after symptom onset.

Batarseh E, Kersten BP, Pinelo AC, Nadler JN, Schwartz SA. Angioedema in African

American patients hospitalized for COVID-19. Am J Respir Crit Care Med 2020;202:1581–1584.

Chan ED, Majluf-Cruz A. Is the angioedema associated with COVID-19 a real entity, a mimic, or both? Am J Respir Crit Care Med 2021;203:645–646.

While still being defined, long COVID (formally postacute sequelae of SARS-CoV-2 infection [PASC]) refers to a constellation of signs and symptoms, including those attributable to neuromuscular, psychiatric, respiratory, cardiac, gastrointestinal, and other origins, that persist for weeks to months after acute COVID-19.

Gandotra S, Russell D. The long and the short of it: is "long COVID" more than slow resolution of the acute disease? Ann Am Thorac Soc 2021;18:948–950.

Investigators have reported PASC across the spectrum of acute COVID-19 severity.

Townsend L, Dowds J, O'Brien K, Sheill G, Dyer AH, O'Kelly B, et al. Persistent poor health after COVID-19 is not associated with respiratory complications or initial disease severity. Ann Am Thorac Soc 2021;18:997–1003.

Cohort studies have observed respiratory symptoms, reduced functional capacity, and impaired lung function, particularly gas exchange abnormalities, in survivors of COVID-19 3–4 months after acute illness that may persist for at least 1 year.

Mendez R, Latorre A, Gonzalez-Jimenez P, Feced L, Bouzas L, Yepez K, et al. Reduced diffusion capacity in COVID-19 survivors. Ann Am Thorac Soc 2021;18:1253–1255.

Abdallah SJ, Voduc N, Corrales-Medina VF, McGuinty M, Pratt A, Chopra A, et al. Symptoms, pulmonary function, and functional capacity four months after COVID-19. Ann Am Thorac Soc 2021;18:1912–1917.

Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021;398:747–758.

Among patients mechanically ventilated for COVID-19, most survivors exhibit abnormal respiratory physiology and imaging abnormalities 3 months after hospital discharge, with limited diffusion capacity, decreased lung volumes, and fibrosis characterizing the clinical syndrome.

van Gassel RJJ, Bels JLM, Raafs A, van Bussel BCT, van de Poll MCG, Simons SO, et al. High prevalence of pulmonary sequelae at 3 months after hospital discharge in mechanically ventilated survivors of COVID-19. Am J Respir Crit Care Med 2021;203:371–374.

As PASC is a syndrome associated with a novel pathogen, it may be years before we have robust, normative datasets regarding its course and outcomes.

Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Simons KS, et al. Clinical outcomes among patients with 1-year survival following intensive care unit treatment for COVID-19. JAMA 2022;327:559–565.

Numerous studies in 2021 evaluated diagnostics for SARS-CoV-2 and superinfection with other pathogens. Although some patients with SARS-CoV-2–induced respiratory failure will have negative PCR tests on samples obtained from their nasopharynx while testing positive on BAL samples, the accuracy of nasopharyngeal assessment remains approximately 90%.

Gao CA, Cuttica MJ, Malsin ES, Argento AC, Wunderink RG, Smith SB; NU COVID Investigators. Comparing nasopharyngeal and BAL SARS-CoV-2 assays in respiratory failure. Am J Respir Crit Care Med 2021;203:127–129.

Importantly, bronchoscopy performed using personal protective equipment for airborne infection isolation and aerosol-minimizing protocols can be accomplished in patients with severe SARS-CoV-2 pneumonia with a low infectious risk to bronchoscopists.

Centers for Disease Control and Prevention. Transmission-based precautions. [updated 2016 Jan 7; accessed 2022 Jan 20]. Available from: https://www.cdc.gov/infectioncontrol/basics/transmission-based-precautions.html#anchor_1564058235.

Gao CA, Bailey JI, Walter JM, Coleman JM, Malsin ES, Argento AC, et al. Bronchoscopy on intubated patients with COVID-19 is associated with low infectious risk to operators. Ann Am Thorac Soc 2021;18:1243–1246.

Accordingly, investigators have used bronchoscopy and other lower respiratory tract sampling procedures to guide antibacterial pharmacotherapy in patients with severe SARS-CoV-2 pneumonia.

Kitsios GD, Morris A. Seek and ye shall find: COVID-19 and bacterial superinfection. Am J Respir Crit Care Med 2021;204:875–877.

Musher DM. Bacterial coinfection in COVID-19 and influenza pneumonia. Am J Respir Crit Care Med 2021;204:498–500.

Bronchoscopy within 48 hours of intubation identified that up to 21% of patients recently intubated for severe SARS-CoV-2 pneumonia have a bacterial superinfection. The same study found a higher rate of ensuing ventilator-associated pneumonia than reported in other ICU populations.

Pickens CO, Gao CA, Cuttica MJ, Smith SB, Pesce LL, Grant RA, et al.; NU COVID Investigators. Bacterial superinfection pneumonia in patients mechanically ventilated for COVID-19 pneumonia. Am J Respir Crit Care Med 2021;204:921–932.

In a cohort study of patients with COVID-19 or influenza, sampling using primarily endotracheal aspirates detected an early superinfection rate of 10% in patients with critical COVID-19 and approximately 30% in patients with severe influenza.

Rouze A, Martin-Loeches I, Povoa P, Metzelard M, Du Cheyron D, Lambiotte F, et al.; coVAPid Study Group. Early bacterial identification among intubated patients with COVID-19 or influenza pneumonia: a European multicenter comparative cohort study. Am J Respir Crit Care Med 2021;204:546–556.

Although the literature supports an association between COVID-19 and invasive *Aspergillus*, evaluation of immunocompetent patients in French ICUs with severe SARS-CoV-2 pneumonia found a low rate of *Aspergillus* superinfection.

Baron A, Hachem M, Tran Van Nhieu J, Botterel F, Fourati S, Carteaux G, et al.

Bronchoalveolar lavage in patients with COVID-19 with invasive mechanical ventilation for acute respiratory distress syndrome. Ann Am Thorac Soc 2021;18: 723–726.

Wauters J, Lamoth F, Rijnders BJA, Calandra T. Invasive pulmonary aspergillosis goes viral again? Am J Respir Crit Care Med 2021;203:275–277.

Fekkar A, Lampros A, Mayaux J, Poignon C, Demeret S, Constantin JM, et al. Occurrence of invasive pulmonary fungal infections in patients with severe COVID-19 admitted to the ICU. Am J Respir Crit Care Med 2021;203:307–317.

Importantly, a cohort study demonstrated that patients with severe SARS-CoV-2 pneumonia remain susceptible to nosocomial infection via traditional routes such as indwelling devices.

Adelman MW, Bhamidipati DR, Hernandez-Romieu AC, Babiker A, Woodworth MH, Robichaux C, et al.; Emory COVID-19 Quality and Clinical Research Collaborative members. Secondary bacterial pneumonias and bloodstream infections in patients hospitalized with COVID-19. Ann Am Thorac Soc 2021;18:1584–1587.

Preexisting comorbidities, such as hypertension, cardiovascular disease, diabetes mellitus, obstructive sleep apnea (OSA), and lung disease, are risk factors for severe COVID-19.

Perger E, Soranna D, Pengo M, Meriggi P, Lombardi C, Parati G. Sleep-disordered breathing among hospitalized patients with COVID-19. Am J Respir Crit Care Med 2021;203:239–241.

Paradoxically, several studies suggest that the course of COVID-19 is less severe among patients with asthma; indeed, exacerbations of asthma requiring hospitalization decreased during 2020.

Chan KF, Kwok WC, Ma TF, Hui CH, Tam TC, Wang JK, et al. Territory-wide study on hospital admissions for asthma exacerbations in the COVID-19 pandemic. Ann Am Thorac Soc 2021;18: 1624–1633.

Terry PD, Heidel RE, Dhand R. Asthma in adult patients with COVID-19. Prevalence and risk of severe disease. Am J Respir Crit Care Med 2021;203: 893–905.

Beasley R, Hills T, Kearns N. Asthma and COVID-19: preconceptions about predisposition. Am J Respir Crit Care Med 2021;203:799–801.

Martinez FD. Asthma in the time of COVID-19. Am J Respir Crit Care Med 2021;203:785–786.

Likewise, patients with bronchiectasis experienced a significant reduction in exacerbations and hospitalizations when comparing 2019–2020 with baseline years.

Crichton ML, Shoemark A, Chalmers JD. The impact of the COVID-19 pandemic on exacerbations and symptoms in bronchiectasis: a prospective study. Am J Respir Crit Care Med 2021;204:857–859.

It is plausible that mitigation measures designed to decrease the spread of COVID-19, including self-imposed physical distancing, also decrease the transmission of other respiratory viruses that would otherwise contribute to exacerbations of chronic lung diseases.

Martinez FD. Asthma in the time of COVID-19. Am J Respir Crit Care Med 2021;203:785–786.

Metersky ML. Fewer bronchiectasis exacerbations during the "lockdown" for COVID-19: can we convert knowledge into action? Am J Respir Crit Care Med 2021;204:759–760.

Singer BD. COVID-19 and the next influenza season. Sci Adv 2020;6:eabd0086.

Previous studies found increased mortality among patients with interstitial lung disease (ILD) and COVID-19. Survival rates differ between types of ILD, with higher mortality among patients with fibrotic ILD compared with other types of ILD.

Gallay L, Uzunhan Y, Borie R, Lazor R, Rigaud P, Marchand-Adam S, et al. Risk factors for mortality after COVID-19 in patients with preexisting interstitial lung disease. Am J Respir Crit Care Med 2021;203:245–249.

Obesity and low lung function independently increase the risk of COVID-19.

Bui DS, Cassim R, Russell MA, Doherty A, Lowe AJ, Agusti A, et al. Lung function levels influence the association between obesity and risk of COVID-19. Am J Respir Crit Care Med 2021;204:1106–1108.

Adults at high risk for OSA have an increased risk for poor outcomes from COVID-19, and loud snoring predicts slow clinical improvement and the need for hospitalization, supplemental oxygen, and intensive care.

Peker Y, Celik Y, Arbatli S, Isik SR, Balcan B, Karataş F, et al. Effect of high-risk obstructive sleep apnea on clinical outcomes in adults with coronavirus disease 2019: a multicenter, prospective, observational clinical trial. Ann Am Thorac Soc 2021;18:1548–1559.

Overadjustment bias can occur when evaluating the effect of OSA on outcomes, and further studies are needed to understand causal relationships.

Mulla ZD, Pathak IS. Sleep apnea and poor COVID-19 outcomes: beware of causal intermediates and colliders. Am J Respir Crit Care Med 2021;203:1325–1326.

Immunocompromised patients, including those with a history of hematopoietic stem cell transplantation, tend to exhibit prolonged viral shedding and associated high mortality.

Roedl K, Heidenreich S, Pfefferle S, Jarczak D, Urbanowicz TT, Norz D, et al. Viral dynamics of SARS-CoV-2 in critically ill allogeneic hematopoietic stem cell transplant recipients and immunocompetent patients with COVID-19. Am J Respir Crit Care Med 2021;203:242–245.

Finally, data continue to support that pregnancy is a risk factor for morbidity and mortality associated with COVID-19.

Chinn J, Sedighim S, Kirby KA, Hohmann S, Hameed AB, Jolley J, et al. Characteristics and outcomes of women with COVID-19 giving birth at US academic centers during the COVID-19 pandemic. JAMA Netw Open 2021;4: e2120456.

Nevertheless, in a cohort of 32 critically ill pregnant women, all patients survived with no fetal deaths, and treatment outcomes were similar between pregnant and matched nonpregnant patients.

Easter SR, Gupta S, Brenner SK, Leaf DE. Outcomes of critically ill pregnant women with COVID-19 in the United States. Am J Respir Crit Care Med 2021;203: 122–125.

Vaccination

Approaches to COVID-19 vaccine development have included multiple platforms (Figure 1). BNT162b2 is an mRNA vaccine encoding a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. In the landmark efficacy trial of BNT162b2, a two-dose regimen in subjects at least 16 years old demonstrated 95% protection against COVID-19 with safety profiles comparable to other vaccines.

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al.; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020; 383:2603–2615.

Vaccine efficacy waned through 6 months of follow-up; however, BNT162b2 remained highly efficacious in preventing hospitalization and death because of COVID-19.

Thomas SJ, Moreira ED, Jr., Kitchin N, Absalon J, Gurtman A, Lockhart S, et al.; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. N Engl J Med 2021;385:1761–1773.

These results extended to 12- to 15-year-old recipients, who exhibited even greater immune responses than young adults.

Frenck RW, Jr., Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al.; C4591001 Clinical Trial Group. Safety, immunogenicity, and efficacy of the BNT162b2 COVID-19 vaccine in adolescents. N Engl J Med 2021;385:239–250.

Most recently, randomized trials reported positive safety, immunogenicity, and efficacy signals, including protection against severe illness, of a two-dose BNT162b2 regimen in children ages 5–11 years as well as in adolescents.

Walter EB, Talaat KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, et al.; C4591007 Clinical Trial Group. Evaluation of the BNT162b2 COVID-19 vaccine in children 5 to 11 years of age. N Engl J Med 2022;386:35-46.

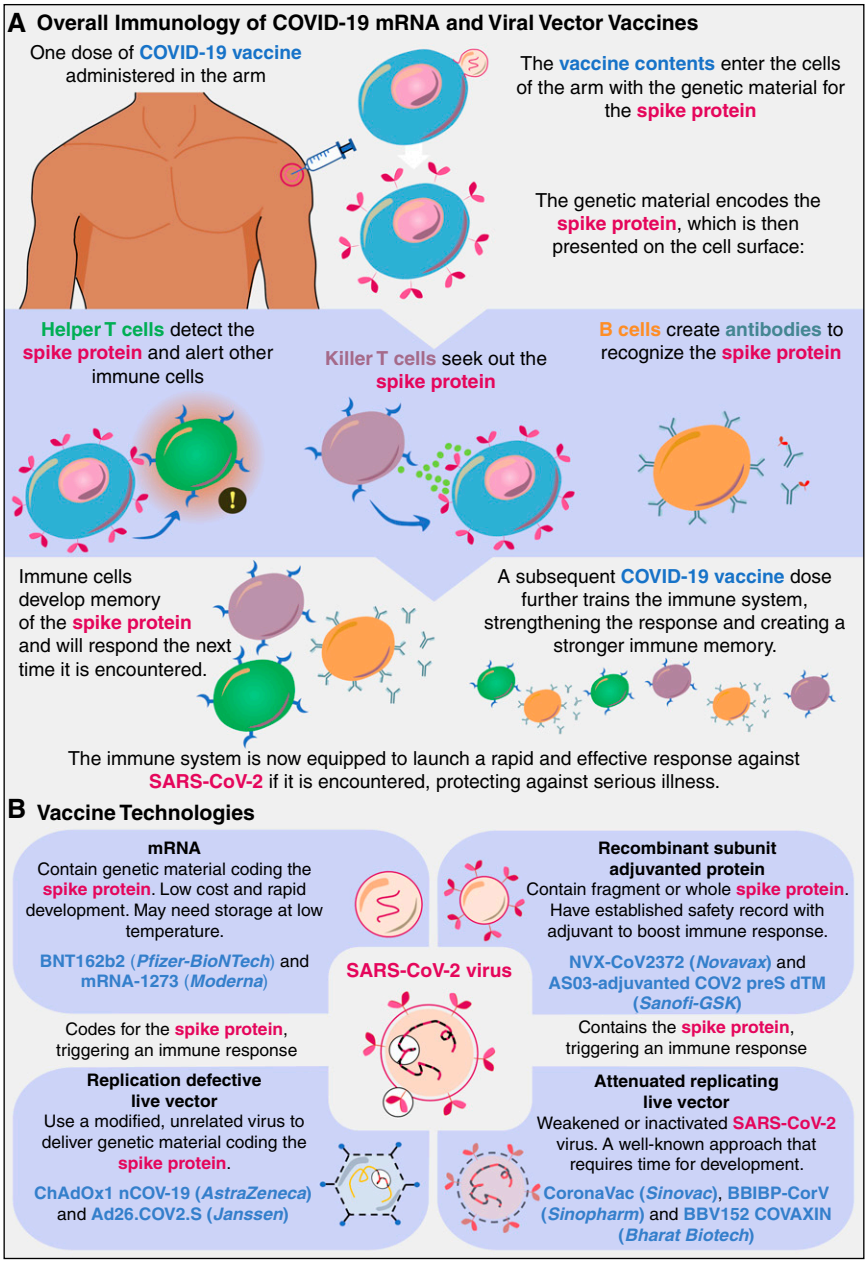

Figure 1. Vaccination against coronavirus disease 2019 (COVID-19). (*A*) Mechanisms of mRNA and viral vector vaccines. (*B*) Vaccine platforms in COVID-19. Examples of each category are listed. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Olson SM, Newhams MM, Halasa NB, Price AM, Boom JA, Sahni LC, et al.; Overcoming Covid-19 Investigators. Effectiveness of BNT162b2 vaccine against critical COVID-19 in adolescents. N Engl J Med 2022;386:713–723.

A different mRNA vaccine, mRNA-1273, demonstrated 94% efficacy in preventing COVID-19, including severe disease, with no significant safety signals in a randomized controlled trial.

Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al.; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–416.

At more than 5 months of follow-up, mRNA-1273 continued to have preventive efficacy against symptomatic COVID-19 with additive protection against asymptomatic infection.

El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al.; COVE Study Group. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med 2021;385:1774–1785.

Similar to BNT162b2, mRNA-1273 was found to be efficacious at preventing COVID-19 in healthy adolescents between 12 and 17 years of age with comparable immune responses to young adults.

Ali K, Berman G, Zhou H, Deng W, Faughnan V, Coronado-Voges M, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. N Engl J Med 2021;385:2241–2251.

Although rare and usually mild or moderate in severity, inflammatory heart disease has been reported after mRNA vaccination, mostly among young male recipients.

Verma AK, Lavine KJ, Lin CY. Myocarditis after Covid-19 mRNA vaccination. N Engl J Med 2021;385:1332–1334.

Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, et al. Myocarditis after BNT162b2 mRNA vaccine against COVID-19 in Israel. N Engl J Med 2021; 385:2140–2149.

Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, et al. Myocarditis after Covid-19 vaccination in a large health care organization. N Engl J Med 2021;385:2132–2139.

Alternative vaccine approaches, such as viral vectors and subunit proteins, provide similar protection against severe COVID-19 despite imparting less protection from symptomatic infection than mRNA vaccines.

Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al.; ENSEMBLE Study Group. Safety and efficacy of single-dose Ad26.COV2.S vaccine against COVID-19. N Engl J Med 2021; 384:2187–2201.

Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al.; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99–111.

Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al.; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2021;396:1979–1993.

Ad26.COV2.S is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding the SARS-CoV-2 spike protein. With a similar safety profile to other COVID-19 vaccines, a single dose protected against symptomatic and asymptomatic SARS-CoV-2 infection and was efficacious against severe disease, hospitalization, and death.

Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al.; ENSEMBLE Study Group. Safety and efficacy of single-dose Ad26.COV2.S vaccine against COVID-19. N Engl J Med 2021;384:2187–2201.

Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim results of a phase 1-2a trial of Ad26.COV2.S COVID-19 vaccine. N Engl J Med 2021;384:1824–1835.

Stephenson KE, Le Gars M, Sadoff J, de Groot AM, Heerwegh D, Truyers C, et al. Immunogenicity of the Ad26.COV2.S vaccine for COVID-19. JAMA 2021;325: 1535–1544.

A chimpanzee adenovirus-vector vaccine, ChAdOx1 nCoV-19 (AZD1222), demonstrated comparable immunogenicity across all age groups after a booster.

Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al.; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2021;396:1979–1993.

ChAdOx1 nCoV-19 was efficacious against symptomatic COVID-19, including the Alpha (B.1.1.7) variant; however, it did not impart protection against mild–moderate COVID-19 owing to Beta (B.1.351).

Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al.; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021; 397:99–111.

Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al.; COVID-19 Genomics UK consortium, AMPHEUS Project, Oxford COVID-19 Vaccine Trial Group. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet 2021;397:1351–1362.

Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al.; NGS-SA Group, Wits-VIDA COVID Group. Efficacy of the ChAdOx1 nCoV-19 COVID-19 vaccine against the B.1.351 variant. N Engl J Med 2021;384:1885–1898.

Concerns about the occurrence of a rare but clinically significant immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4 in recipients of the ChAdOx1 nCoV-19 and Ad26.COV2.S vaccines intermittently interrupted administration in some countries.

Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021; 384:2092–2101.

Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2202–2211.

Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. N Engl J Med 2021;384:1964–1965.

Shay DK, Gee J, Su JR, Myers TR, Marquez P, Liu R, et al. Safety monitoring of the Janssen (Johnson & Johnson) COVID-19

vaccine – United States, March-April 2021. MMWR Morb Mortal Wkly Rep 2021; 70:680–684.

Other COVID-19 vaccines, including Gam-COVID-Vac (Sputnik V), NVX-CoV2373, SCB-2019, BBV152, and inactivated whole-virion CoronaVac, provide a broad vaccine portfolio going into 2022.

Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al.; 2019nCoV-501 Study Group. Efficacy of NVX-CoV2373 COVID-19 vaccine against the B.1.351 variant. N Engl J Med 2021;384: 1899–1909.

Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al.; 2019nCoV-302 Study Group. Safety and efficacy of NVX-CoV2373 COVID-19 vaccine. N Engl J Med 2021;385:1172–1183.

Richmond P, Hatchuel L, Dong M, Ma B, Hu B, Smolenov I, et al. Safety and immunogenicity of S-Trimer (SCB-2019), a protein subunit vaccine candidate for COVID-19 in healthy adults: a phase 1, randomised, double-blind, placebo-controlled trial. Lancet 2021;397:682–694.

Tanriover MD, Doganay HL, Akova M, Guner HR, Azap A, Akhan S, et al.; CoronaVac Study Group. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 2021;398:213–222.

Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA 2021;326:35–45.

Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al.; COVAXIN Study Group. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. Lancet 2021; 398:2173–2184.

Heterologous vaccine schedules ("mix and match") may provide superior protection.

Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al.; Gam-COVID-Vac Vaccine Trial Group. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 2021;397:671–681.

Liu X, Shaw RH, Stuart ASV, Greenland M, Aley PK, Andrews NJ, et al.; Com-COV Study Group. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. Lancet 2021;398:856–869.

Indeed, in people vaccinated with a two-dose CoronaVac series, heterologous vaccination with an mRNA vaccine (BNT162b2) led to increased titers of neutralizing antibodies compared with a third CoronaVac dose.

Mok CKP, Chen C, Yiu K, Chan TO, Lai KC, Ling KC, et al. A randomized clinical trial using CoronaVac or BNT162b2 vaccine as a third dose in adults vaccinated with two doses of CoronaVac. Am J Respir Crit Care Med 2022;205:844–847.

Substantial challenges remain, including waning immunity, inequitable vaccine distribution, vaccine hesitancy, and higher rates of breakthrough infection with increasingly transmissible strains capable of evading host immunity.

Gupta RK, Topol EJ. COVID-19 vaccine breakthrough infections. Science 2021;374: 1561–1562.

Razai MS, Oakeshott P, Esmail A, Wiysonge CS, Viswanath K, Mills MC. COVID-19 vaccine hesitancy: the five Cs to tackle behavioural and sociodemographic factors. J R Soc Med 2021;114:295–298.

Waning vaccine efficacy remains greatest in older individuals and higher-risk groups.

Lin DY, Gu Y, Wheeler B, Young H, Holloway S, Sunny SK, et al. Effectiveness of COVID-19 vaccines over a 9-month period in North Carolina. N Engl J Med 2022;386:933–941.

Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of protection against mild and severe disease by COVID-19 vaccines. N Engl J Med 2022;386:340–350.

Alpha, Beta, Gamma (P.1), Delta (B.1.617.2), Epsilon (B.1.427/B.1.429), and Omicron have challenged vaccine efficacy. Although vaccine efficacy against some variants is reduced, vaccines continue to provide strong protection against severe disease.

Wu K, Werner AP, Koch M, Choi A, Narayanan E, Stewart-Jones GBE, et al. Serum neutralizing activity elicited by mRNA-1273 vaccine. N Engl J Med 2021;384:1468–1470.

Concerns over waning immunity and the emergence of more transmissible variants prompted consideration of an additional (booster) vaccine beyond the initial series. In a report from the United States, the administration of a third BNT162b2 dose between 7.9 and 8.8 months after the two-dose regimen to 23 study participants suggested improved COVID-19 protection.

Falsey AR, Frenck RW, Jr., Walsh EE, Kitchin N, Absalon J, Gurtman A, et al. SARS-CoV-2 neutralization with BNT162b2 vaccine dose 3. N Engl J Med 2021;385: 1627–1629.

Large datasets from Israel in individuals at least 16 years of age confirmed that rates of COVID-19 and, in particular, severe illness, are substantially lower among those boosted with a third dose of BNT162b2.

Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 vaccine booster against COVID-19 in Israel. N Engl J Med 2021;385:1393–1400.

Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against COVID-19 by BNT162b2 booster across age groups. N Engl J Med 2021;385:2421–2430.

The importance of a booster has become more apparent during the emergence of Omicron, with 100-fold higher neutralization efficiency achieved after a third dose. Even with three vaccine doses, overall neutralization efficacy against Omicron remains lower than that observed against Delta.

Collie S, Champion J, Moultrie H, Bekker LG, Gray G. Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. N Engl J Med 2022;386:494–496.

Nemet I, Kliker L, Lustig Y, Zuckerman N, Erster O, Cohen C, et al. Third

BNT162b2 vaccination neutralization of SARS-CoV-2 omicron infection. N Engl J Med 2022;386:492–494.

Sinha P, Furfaro D, Cummings MJ, Abrams D, Delucchi K, Maddali MV, et al. Latent class analysis reveals COVID-19-related acute respiratory distress syndrome subgroups with differential responses to corticosteroids. Am J Respir Crit Care Med 2021;204:1274–1285.

Going forward, intranasal and pansarbecovirus vaccines currently in development may address many of these challenges.

Tan CW, Chia WN, Young BE, Zhu F, Lim BL, Sia WR, et al. Pan-sarbecovirus neutralizing antibodies in BNT162b2-immunized SARS-CoV-1 survivors. N Engl J Med 2021;385:1401–1406.

Carmen JM, Shrivastava S, Lu Z, Anderson A, Morrison EB, Sankhala RS, et al. SARS-CoV-2 ferritin nanoparticle vaccine induces robust innate immune activity driving polyfunctional spike-specific T cell responses. NPJ Vaccines 2021;6:151.

Treatment

The primary message of COVID-19 therapeutics over the last year is the confirmation, with nuances related to the serological status, of the "two-phase" model proposed early in the pandemic. In general, it appears that virus-focused therapies are more effective in the early phase of illness, with host-focused therapies becoming more relevant later in the disease. Notwithstanding the methodological problems posed by substantial practice variation, the conceptual division into outpatient, inpatient, and intensive care continues to seem most useful for classifying therapies (Table 1). Key priorities for therapeutics in the coming year include grappling with fluctuations in the standards of evidence motivated by pandemic urgency, conducting strategy trials to manage the accumulating independent evidence for multiple therapies, and tailoring trials to relevant physiological subtypes.

Sinha P, Furfaro D, Cummings MJ, Abrams D, Delucchi K, Maddali MV, et al. Latent class analysis reveals COVID-19-related acute respiratory distress syndrome subgroups with differential responses to corticosteroids. Am J Respir Crit Care Med 2021;204:1274–1285.

Outpatient Therapy

The last year has witnessed transformational changes in outpatient care for COVID-19. Multiple neutralizing monoclonal antibody products have demonstrated efficacy for the treatment of early symptomatic disease, and some agents have demonstrated efficacy for preexposure (PROVENT [Prophylaxis Prevention] trial, NCT04625725) or postexposure prophylaxis.

O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan KC, Sarkar N, et al.; COVID-19 Phase 3 Prevention Trial Team. Subcutaneous REGEN-COV antibody combination to prevent COVID-19. N Engl J Med 2021;385:1184–1195.

Though this effect was not observed among patients treated in the emergency department with convalescent plasma, high-risk but less ill outpatients may have benefited from early administration of high-titer convalescent plasma.

Korley FK, Durkalski-Mauldin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, et al.; SIREN-C3PO Investigators. Early convalescent plasma for high-risk outpatients with COVID-19. N Engl J Med 2021;385:1951–1960.

Sullivan DJ, Gebo KA, Shoham S, Bloch EM, Lau B, Shenoy AG, et al. Early outpatient treatment for COVID-19 with convalescent plasma. N Engl J Med 2022;386:1700–1711.

A trial (NCT04910269) evaluating hyperimmune globulin among outpatients is ongoing. Given the expense, complexity of storage and administration, viral evolution limiting neutralization by established products, and ongoing constraints on supply, neutralizing monoclonal antibodies have generally been restricted to the highest-risk patients. Most available products have limited neutralization of the Omicron variant. Hence, these agents may need to be regularly updated and tested to cover new variants, similar to seasonal influenza vaccines. As we anticipate COVID-19 moving toward a more endemic state, a priority will be understanding how best to treat patients at the highest risk, particularly those with immune deficiency.

Table 1. Therapeutics Granted Emergency Use Authorization by U.S. Food and Drug Administration for COVID-19 through 2021

Outpatient
Passive immunity therapy
Monoclonal
Bamlanivimab–etesevimab*
Casirivimab–imdevimab*
Tixagevimab–cilgavimab*
Sotrovimab
Polyclonal
COVID-19 convalescent plasma
Direct antivirals
Nirmatrelvir–ritonavir
Molnupiravir
Remdesivir†
Inpatient
Immunosuppressants
Dexamethasone
Tocilizumab
Sarilumab
Baricitinib

*The Omicron (B.1.1.529) variant displays a markedly reduced susceptibility to therapy with these agents.
†Predominantly used in inpatient settings.
See Gottlieb and colleagues for trial results in outpatients.

It seems likely that a combination of passive immunity and complementary antiviral therapies will be useful in high-risk and immunocompromised patient populations.

Antivirals

The PINETREE (GS-US-540–9012) trial demonstrated a significant reduction in risk of hospitalization or death with a 3-day course of intravenous remdesivir in outpatients with an increased risk of severe COVID-19.

Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al.; GS-US-540-9012 (PINETREE) Investigators. Early remdesivir to prevent progression to severe COVID-19 in outpatients. N Engl J Med 2022;386:305–315.

Because remdesivir is a nucleoside analog, there may be better odds of it maintaining efficacy against new variants, although on-therapy resistance has been documented in an immunocompromised patient.

Gandhi S, Klein J, Robertson AJ, Pena-Hernandez MA, Lin MJ, Roychoudhury P, et al. De novo emergence of a remdesivir

resistance mutation during treatment of persistent SARS-CoV-2 infection in an immunocompromised patient: a case report. Nat Commun 2022;13:1547.

Through emergency use authorization, the U.S. Food and Drug Administration authorized the oral antivirals nirmatrelvir–ritonavir and molnupiravir for outpatient treatment of early COVID-19.

U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19. 2021 [accessed 2022 Jan 20]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19.

U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral for treatment of COVID-19 in certain adults. 2021 [accessed 2022 Jan 20]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain.

The pivotal trials for both agents (NCT04960202 and NCT04575597) were stopped early for efficacy, although final data for molnupiravir suggested modest efficacy, whereas nirmatrelvir–ritonavir exhibited higher efficacy in the final analysis cohort. Although oral drugs are sometimes hailed as "game-changing" in the popular press, adherence may be low, particularly with nirmatrelvir–ritonavir, given its side effect profile and potential for drug–drug interactions.

Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al.; EPIC-HR Investigators. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med 2022;386:1397–1408.

Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al.; Group MO-OS. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med 2022;386:509–520.

The antidepressant fluvoxamine has been studied as a treatment for COVID-19 because of its potential antiinflammatory properties. The TOGETHER trial in Brazil suggested a modest decrease in long emergency department stays or transfer to tertiary care hospitals for high-risk outpatients with COVID-19 treated with fluvoxamine (100 mg twice daily) compared with placebo; a small trial ($N = 153$) also suggested possible efficacy for fluvoxamine, albeit using an idiosyncratic primary endpoint (dyspnea, hospitalization, or hypoxemia) and a different dosing regimen.

Reis G, Moreira-Silva EAD, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al.; TOGETHER Investigators. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet Glob Health 2022;10:E36–E45.

Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA 2020;324:2292–2300.

Despite considerable partisan fervor, the clinical data supporting ivermectin are limited. The ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines)-6 trial (NCT04885530) is studying fluvoxamine as well as two dosing strategies for ivermectin in a pragmatic design.

Inpatient Therapy

For inpatients, remdesivir continues to be favored in the United States on the basis of findings of the ACTT (Adaptive COVID-19 Treatment Trial)-1 trial and less favored outside the United States because of a lack of mortality benefit in large pragmatic trials that were not designed to test time to recovery.

Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al.; ACTT-Study Group Members. Remdesivir for the treatment of COVID-19 – final report. N Engl J Med 2020;383:1813–1826.

Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al.; WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19—interim WHO solidarity trial results. N Engl J Med 2021;384:497–511.

Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Poissy J, Belhadi D, et al.; DisCoVeRy Study Group. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis 2022;22:209–221.

Dexamethasone or an equivalent glucocorticoid is a cornerstone therapy in SARS-CoV-2 pneumonia, although it has not demonstrated benefit in a placebo-controlled trial.

Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al.; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384:693–704.

Targeted antiinflammatory therapies have been studied with mixed results. Inhibition of the IL-6 receptor with tocilizumab or sarilumab is a complex story, with positive readouts from two unblinded pragmatic trials. A large ($N = 4,116$) trial of hospitalized patients found benefit of tocilizumab in patients requiring oxygen with evidence of systemic inflammation, and one moderately large ($N = 803$) trial of critically ill patients also found benefit of tocilizumab.

RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397:1637–1645.

Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al.; REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 2021;384:1491–1502.

Nevertheless, two moderately sized (total $N = 438 + 649 = 1,087$) placebo-controlled trials showed no benefit of tocilizumab.

Rosas IO, Brau N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. N Engl J Med 2021;384:1503–1516.

Rosas IO, Diaz G, Gottlieb RL, Lobo SM, Robinson P, Hunter BD, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med 2021;47:1258–1270.

The results of trials studying the JAK (Janus kinase) inhibitor baricitinib are somewhat clearer. ACTT-2 suggested a modest benefit for baricitinib without glucocorticoids, whereas ACTT-4 suggested no difference between dexamethasone and baricitinib, and trials with a background of glucocorticoids suggested efficacy for baricitinib (COV-BARRIER [A Study of Baricitinib (LY3009104) in Participants With COVID-19]) and tofacitinib (STOP-COVID [Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19]).

Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al.; COV-BARRIER Study Group. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021;9:1407–1418.

Guimaraes PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al.; STOP-COVID Trial Investigators. Tofacitinib in patients hospitalized with COVID-19 pneumonia. N Engl J Med 2021;385:406–415.

The efficacy signals were not large, and whether IL-6 receptor inhibition and JAK inhibition are interchangeable is unknown. Because the safety dataset for these agents in COVID-19 is not large, real-world pharmacovigilance will be important and will require methodological rigor to ensure that benefits continue to outweigh risks. Notably, nosocomial infections were more common in the placebo than in the tocilizumab groups in trials, although overall numbers of infections were low.

Rosas IO, Brau N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. N Engl J Med 2021;384:1503–1516.

Rosas IO, Diaz G, Gottlieb RL, Lobo SM, Robinson P, Hunter BD, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med 2021;47:1258–1270.

Although neutralizing monoclonal antibodies are not beneficial in unselected hospitalized patients, seronegative patients likely benefited from their administration, at least for the REGN-COV cocktail in the era before Omicron.

ACTIV-3/Therapeutics for Inpatients with COVID-19 Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis 2022;22:622–635.

Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, Sandkovsky U, et al.; ACTIV-3/TICO Bamlanivimab Study Group. Responses to a neutralizing monoclonal antibody for hospitalized patients with COVID-19 according to baseline antibody and antigen levels: a randomized controlled trial. Ann Intern Med 2022;175:234–243.

RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2022;399:665–676.

The United Kingdom approved the REGN-COV cocktail for inpatients with a pragmatic approach to serological testing. Another unknown is whether the most important signal is viral load (perhaps sampled in blood as serum antigen), serostatus, or both. Whether antibody-dependent enhancement drives pathology in COVID-19 is controversial. Hence, it seems prudent not to administer neutralizing monoclonal antibodies to seropositive patients unless or until there is evidence to suggest that certain seropositive patients, such as those with high viral loads, are likely to benefit.

Because COVID-19 is associated with a prothrombotic state, several trials have studied anticoagulation. Full-dose heparinoid-based anticoagulation in hospitalized patients with COVID-19–related acute illness who did not require ICU care and did not have venous thromboembolism was beneficial on the basis of the primary efficacy endpoint in a multiplatform trial.

Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al.; ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. N Engl J Med 2021;385:790–802.

Nevertheless, the interpretation is complex given the study design, with the primary effect being a decrease in progression from conventional oxygen to high-flow nasal oxygen. Smaller trials have provided confirmatory results, although inclusion criteria and beneficial outcomes differed somewhat from the multiplatform trial. The use of tissue plasminogen activator early in the pandemic was prominently discussed but had little clinical evidence supporting its administration.

Douin DJ, Shaefi S, Brenner SK, Gupta S, Park I, Wright FL, et al. Tissue plasminogen activator in critically ill adults with COVID-19. Ann Am Thorac Soc 2021; 18:1917–1921.

There is growing interest in treatments for patients during the convalescent phase, especially the use of thromboprophylaxis, a topic being addressed by the ACTIV-4c trial (NCT04650087), with encouraging early results from the Brazilian MICHELLE (Medically Ill Hospitalized Patients for COVID-19 THrombosis Extended ProphyLaxis With Rivaroxaban ThErapy) trial.

Ramacciotti E, Barile Agati L, Calderaro D, Aguiar VCR, Spyropoulos AC, de Oliveira CCC, et al.; MICHELLE Investigators. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet 2022;399:50–59.

Critically Ill Patients

The most important intervention in critically ill patients is high-quality, multidisciplinary supportive care. Specific to COVID-19, the mainstays of therapy remain glucocorticoids and probably secondary immune modulation. A multiplatform trial of full-dose anticoagulation suggested probable harm among patients receiving life support at the time of randomization.

Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, Gong MN, et al.; REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. N Engl J Med 2021;385:777–789.

On the totality of the evidence, it seems appropriate to stop full-dose anticoagulation and replace it with thromboprophylaxis for

patients transferred to the ICU with organ failure.

The best ventilatory strategy before invasive mechanical ventilation remains an open question. The largest trial, RECOVERY-RS (Randomized Evaluation of COVID-19 Therapy–Respiratory Support), suggests that early noninvasive ventilation (NIV) may be superior to early high-flow nasal oxygen or conventional oxygen.

Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al.; RECOVERY-RS Collaborators. Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: the RECOVERY-RS randomized clinical trial. JAMA 2022;327:546–558.

Nevertheless, the results of the RECOVERY-RS trial do not mean that NIV should be used as salvage therapy for patients who otherwise require intubation and invasive mechanical ventilation. Other investigators have explored NIV use outside the ICU.

Bellani G, Grasselli G, Cecconi M, Antolini L, Borelli M, De Giacomi F, et al. Noninvasive ventilatory support of patients with COVID-19 outside the intensive care units (WARd-COVID). Ann Am Thorac Soc 2021;18:1020–1026.

Despite an ongoing lack of clear evidence for efficacy from well-controlled trials, many centers have adopted extracorporeal membrane oxygenation as a centerpiece of their management for critical COVID-19.

Schmidt M, de Chambrun MP, Lebreton G, Hekimian G, Chommeloux J, Brechot N, et al. Extracorporeal membrane oxygenation instead of invasive mechanical ventilation in a patient with severe COVID-19-associated acute respiratory distress syndrome. Am J Respir Crit Care Med 2021;203:1571–1573.

Diaz RA, Graf J, Zambrano JM, Ruiz C, Espinoza JA, Bravo SI, et al. Extracorporeal membrane oxygenation for COVID-19-associated severe acute respiratory distress syndrome in Chile: a nationwide incidence and cohort study. Am J Respir Crit Care Med 2021;204:34–43.

Karagiannidis C, Strassmann S, Merten M, Bein T, Windisch W, Meybohm P, et al. High in-hospital mortality rate in patients with COVID-19 receiving extracorporeal membrane oxygenation in Germany: a critical analysis. Am J Respir Crit Care Med 2021;204:991–994.

Patient positioning has also been of interest, focusing on the implementation of prone positioning, which had low uptake in the United States before the pandemic.

Klaiman T, Silvestri JA, Srinivasan T, Szymanski S, Tran T, Oredeko F, et al. Improving prone positioning for severe acute respiratory distress syndrome during the COVID-19 pandemic. An implementation-mapping approach. Ann Am Thorac Soc 2021;18:300–307.

Among patients not undergoing mechanical ventilation, prone positioning and various other positions to improve oxygenation have been proposed, including one on the basis of Rodin's "The Thinker."

Taylor SP, Bundy H, Smith WM, Skavroneck S, Taylor B, Kowalkowski MA. Awake prone positioning strategy for nonintubated hypoxic patients with COVID-19: a pilot trial with embedded implementation evaluation. Ann Am Thorac Soc 2021;18:1360–1368.

Johnson SA, Horton DJ, Fuller MJ, Yee J, Aliyev N, Boltax JP, et al. Patient-directed prone positioning in awake patients with COVID-19 requiring hospitalization (PAPR). Ann Am Thorac Soc 2021;18:1424–1426.

Coppo A, Winterton D, Benini A, Monzani A, Aletti G, Cadore B, et al. Rodin's Thinker: an alternative position in awake patients with COVID-19. Am J Respir Crit Care Med 2021;204:728–730.

Societal Effects

COVID-19 continues to cause widespread impacts on society, healthcare delivery, the conduct of research, and medical education. Striking racial and ethnic disparities noted early in the COVID-19 pandemic have persisted. In a retrospective cohort study, Gershengorn and colleagues found that Black race and Hispanic ethnicity increased the odds of COVID-19 diagnosis and hospitalization, a finding largely mediated by socioeconomic factors.

Gershengorn HB, Patel S, Shukla B, Warde PR, Bhatia M, Parekh D, et al. Association of race and ethnicity with COVID-19 test positivity and hospitalization is mediated by socioeconomic factors. Ann Am Thorac Soc 2021;18:1326–1334.

The prognostic accuracy of mortality prediction models was also examined through an equity lens. The SOFA (Sequential Organ Failure Assessment) score and LAPS2 (Laboratory-based Acute Physiology Score) underestimated in-hospital mortality for White patients and overestimated mortality for Black patients, indicating that overreliance on SOFA scores for triage could divert resources away from Black patients.

Ashana DC, Anesi GL, Liu VX, Escobar GJ, Chesley C, Eneanya ND, et al. Equitably allocating resources during crises: racial differences in mortality prediction models. Am J Respir Crit Care Med 2021;204:178–186.

Interestingly, an examination of the effect of four different allocation frameworks on disparities demonstrated no significant racial differences in allocation scores and no effect from the use of equity-focused modifications.

Ross-Driscoll K, Esper G, Kinlaw K, Lee YH, Morris AA, Murphy DJ, et al. Evaluating approaches to improve equity in critical care resource allocation in the COVID-19 pandemic. Am J Respir Crit Care Med 2021;204:1481–1484.

Crisis standard-of-care plans were proposed but plagued by unresolved ethical debates, underappreciated practical issues with scoring systems, and the fear of legal liability.

Oxman D. The crisis in crisis standards of care. Ann Am Thorac Soc 2021;18:1283–1284.

The medical community was urged to consider principles of distributive justice, including the use of racial or socioeconomic correction factors, training on ethics and equity, and a system of checks and balances through hospital triage and ethics committees.

Tukpah AM, Moll M, Gay E. COVID-19 racial and ethnic inequities in acute care

and critical illness survivorship. Ann Am Thorac Soc 2021;18:23–25.

Ramnath VR, Lafree A, Staats K, Tomaszewski C. Promoting racial and health equity in COVID-19 by leveraging empathic interpreters, trained liaisons, and cross-institutional physician leadership. Ann Am Thorac Soc 2021;18:1262–1263.

Disruptions in the availability of personnel, equipment, and space continued through 2021. Alternative staffing from redeployment resulted in less supervision and lowered perceived quality and safety.

Hennus MP, Young JQ, Hennessy M, Friedman KA, de Vries B, Hoff RG, et al. Supervision, interprofessional collaboration, and patient safety in intensive care units during the COVID-19 pandemic. ATS Sch 2021;2:397–414.

Proposed strategies to maximize ventilator availability included using NIV and maximizing the existing supply of ventilators with operating room devices, supply from governments, and conversion of noninvasive devices to invasive ones.

Dar M, Swamy L, Gavin D, Theodore A. Mechanical-ventilation supply and options for the COVID-19 pandemic. Leveraging all available resources for a limited resource in a crisis. Ann Am Thorac Soc 2021;18:408–416.

With a scarcity of hospital beds and personnel, health systems also grappled with equity in resource allocation. Investigators used a simulated ventilator shortage to assess triage strategies for ventilator allocation and found that "color-blind" allocation exacerbated health inequities. Systematic triage algorithms saved more lives than a lottery system.

Bhavani SV, Luo Y, Miller WD, Sanchez-Pinto LN, Han X, Mao C, et al. Simulation of ventilator allocation in critically ill patients with COVID-19. Am J Respir Crit Care Med 2021;204:1224–1227.

Specific stakeholders in health care have been differentially affected by the pandemic. An observational cohort study of family members of severely ill patients with COVID-19 revealed high levels of anxiety, depression, and caregiver strain.

McPeake J, Shaw M, MacTavish P, Blyth K, Devine H, Fleming G, et al. Long-term outcomes after severe COVID-19 infection: a multicenter cohort study of family member outcomes. Ann Am Thorac Soc 2021;18:2098–2101.

With the media focus primarily on physicians, there was a call for attention to nursing shortages.

Lynch J, Evans N, Ice E, Costa DK. Ignoring nurses: media coverage during the COVID-19 pandemic. Ann Am Thorac Soc 2021;18:1278–1282.

Many summer research programs, including those for high school, college, and medical students, remained virtual. Nevertheless, investigators discovered that program objectives could be accomplished remotely.

Hardie WD. Evaluation of a summer medical student research program during a pandemic. ATS Sch 2021;2:172–175.

Berr AL, Ridge KM, Hu JY-S. Pivoting to a remote-learning summer student program during the COVID-19 pandemic. ATS Sch 2021;2:521–534.

Early-career physician–scientists remained disadvantaged during 2021 because of pandemic effects on research productivity, access to mentors, professional development opportunities, funding, and threats to wellness.

Burden M, Flores SC, Schwartz DA. COVID-19: a time to reinvest in our scientists. Am J Respir Crit Care Med 2021;203:1190–1191.

Kliment and colleagues proposed interventions to address these challenges.

Kliment CR, Barbash IJ, Brenner JS, Chandra D, Courtright K, Gauthier MC, et al. COVID-19 and the early-career physician-scientist. Fostering resilience beyond the pandemic. ATS Sch 2020;2: 19–28.

The pandemic has led to new approaches to clinical care that reflect requirements for physical distancing. Virtual focus groups supported qualitative research into these approaches.

Santhosh L, Rojas JC, Lyons PG. Zooming into focus groups: strategies for qualitative research in the era of social distancing. ATS Sch 2021;2:176–184.

In a qualitative study, clinicians and families reported that phone calls for routine updates and video calls for aligning clinician and family perspectives were somewhat effective communication tools.

Kennedy NR, Steinberg A, Arnold RM, Doshi AA, White DB, DeLair W, et al. Perspectives on telephone and video communication in the intensive care unit during COVID-19. Ann Am Thorac Soc 2021;18:838–847.

A national survey in the United Kingdom determined that virtual family visits decreased psychological distress for patients, reoriented those with delirium, and improved staff morale.

Rose L, Yu L, Casey J, Cook A, Metaxa V, Pattison N, et al. Communication and virtual visiting for families of patients in intensive care during the COVID-19 pandemic: a UK national survey. Ann Am Thorac Soc 2021;18:1685–1692.

Virtual peer support for ICU survivors was also valuable in promoting a greater understanding of illness management and improving quality of life.

Lassen-Greene CL, Nordness M, Kiehl A, Jones A, Jackson JC, Boncyk CS. Peer support group for intensive care unit survivors: perceptions on supportive recovery in the era of social distancing. Ann Am Thorac Soc 2021;18:177–182.

The COVID-19 pandemic has also provided opportunities to evaluate other processes of care.

Weissman GE. A bold first toe into the uncharted waters of evaluating proprietary clinical prediction models. Ann Am Thorac Soc 2021;18:1116–1117.

Investigators observed that the Epic Deterioration Index, a proprietary clinical prediction tool, possesses low sensitivity among patients with COVID-19, limiting its use as an early warning system.

Singh K, Valley TS, Tang S, Li BY, Kamran F, Sjoding MW, et al. Evaluating a widely implemented proprietary deterioration index model among hospitalized patients with COVID-19. Ann Am Thorac Soc 2021;18:1129–1137.

A study comparing no face mask with surgical- or N95-type face masks found similar

results on 6-minute-walk testing among patients undergoing evaluation for PASC.

Salles-Rojas A, Guzman-Valderrabano C, Madrid WA, Gonzalez-Molina A, Silva-Ceron M, Rodriguez-Hernandez C, et al. Masking the 6-minute walking test in the COVID-19 era. Ann Am Thorac Soc 2021;18:1070–1074.

Finally, in a United Kingdom-based ICU cohort in which the mean duration of mechanical ventilation was 19 days and 90% of patients received neuromuscular blockade, efforts to initiate rehabilitation were delayed by severe illness yet still resulted in increased mobility before ICU discharge.

McWilliams D, Weblin J, Hodson J, Veenith T, Whitehouse T, Snelson C. Rehabilitation levels in patients with COVID-19 admitted to intensive care requiring invasive ventilation. An observational study. Ann Am Thorac Soc 2021; 18:122–129.

Graduate medical education, particularly for pulmonary and critical care trainees, has experienced continued disruption because of the pandemic.

Lenz PH. Adding to the COVID-19 educational script. ATS Sch 2021;2:497–499.

In a survey of interventional pulmonary fellows, over half of respondents reported deployment to care for patients with COVID-19, although most educational activities were retained.

Kalchiem-Dekel O, Schwalk AJ, Patel NM, Lin IH, Beattie JA, Husta BC, et al. COVID-19 impact on interventional pulmonology training. ATS Sch 2021;2:236–248.

A U.S. survey of pulmonary and critical care fellowship program directors identified educational gaps resulting from the pandemic, including pulmonary function test interpretation, elective bronchoscopy, and outpatient encounters.

Matta A, Adamson R, Hayes MM, Carmona H, Soffler MI, Benzaquen S, et al. Impact of the COVID-19 pandemic on US pulmonary and critical care medicine fellowship training. ATS Sch 2021;2: 556–565.

Wahlster and colleagues' global survey of critical care trainees and attendings revealed an overall negative impact of the pandemic on critical care training.

Wahlster S, Sharma M, Çoruh B, Town JA, Lewis A, Lobo SM, et al. A global survey of the effect of COVID-19 on critical care training. ATS Sch 2021;2:508–520.

The pandemic also affected trainee recruitment. Educators shared their experiences of pivoting to virtual recruitment interviews with proposals for minimizing cognitive load in this new format.

Chaisson NF, Ashton RW. Virtual interviews and their effect on cognitive load for graduate medical education applicants and programs. ATS Sch 2021;2:309–316.

A survey of both applicants and interviewers regarding the virtual interview process revealed benefits (reduction in travel costs and time required off-service) and identified new challenges, including a lack of training for virtual interviewing and a shift in attention to program websites.

Strumpf Z, Miller C, Livingston D, Shaman Z, Matta M. Virtual interviews: challenges and opportunities for pulmonary disease and critical care medicine fellowship programs. ATS Sch 2021;2:535–543.

In considering curricular changes, Brotherton and colleagues highlighted crucial topics for training frontline providers in low-to-middle-income countries during a pandemic, emphasizing the need for human resources.

Brotherton BJ, Mbugua E, Halestrap P, Lee BW. COVID-19 and the need for global critical care training. Why ventilators alone are not the answer. ATS Sch 2020;2:13–18.

A university health system deployed a tele-ICU system that benefited local clinicians as well as residents and fellows, who learned about critical care in resource-limited settings.

Leverone NA, Ramnath VR, Munce D, Raphelson JR, Ma J, Akuthota P, et al. Critical care education in a pandemic through tele-ICU. ATS Sch 2020;2:29–33.

Jackson and colleagues described their approach to a hybrid model of remote and in-person ultrasound teaching.

Jackson R, Brotherston D, Jain A, Doufle G, Piquette D, Goffi A. Teaching ultrasound at the point of care in times of social distancing. ATS Sch 2021;2:341–352.

Others found that remote simulation resulted in a trend toward higher comfort across technical and cognitive domains and improved competency in leading cardiac resuscitation.

Lin E, You AX, Wardi G. Comparison of in-person and telesimulation for critical care training during the COVID-19 pandemic. ATS Sch 2021;2:581–594.

Critical appraisal of the literature became even more important with the deluge of information on COVID-19, and the American Thoracic Society's weekly COVID-19 Critical Care Training Forum provided a venue to address training and knowledge gaps.

Mazer AJ, Mazer MA, Meisenberg BR. Teaching deliberation and restraint in interpreting a tempest of COVID-19 "information." ATS Sch 2021;2:163–167.

Cypro A, McGuire WC, Rolfsen M, Jones N, Shah NG, Cribbs SK, et al. An international virtual COVID-19 critical care training forum for healthcare workers. ATS Sch 2021;2:278–286.

As we enter 2022, the threat of novel mutations creating variants with increased transmissibility and virulence continues to strain healthcare systems, research teams, medical education, and society at large. The advent of highly effective vaccines has changed the course of the pandemic, yet questions remain about how to maximize the benefit and equitable distribution of these preventives as well as novel therapeutics. Undoubtedly, we will continue to face social strife in the face of contagion; however, as we concluded the "Update in COVID-19" a year ago, we can remain hopeful that "the dawn that always follows darkness is near."

Chotirmall SH, Leither LM, Çoruh B, Chan LLY, Joudi AM, Brown SM, et al. Update in COVID-19 2020. Am J Respir Crit Care Med 2021;203:1462–1471. ■

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