The 2020 Pandemic

The Evolving Armamentarium of COVID-19 Therapeutics

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Multiple repositories have been created for the vast scientific outpouring of COVID-19 research. The NIH/PubMed created LitCovid, which currently indexes 69,724 publications (as of November 12) (asamonitor.pub/38xCPYD). Comprehensive lists of therapeutics and vaccines for COVID-19 have been curated by the Milken Institute (asamonitor.pub/3eJMpsI), *Genetic Engineering & Biotechnology News* (asamonitor.pub/3lkeGIB), and the Infectious Diseases Society of America (asamonitor.pub/35g8EmR). This review is based on the treatment guidelines put forward by the NIH (asamonitor.pub/3lnSgXg). Finally, the New York Times published an excellent review of COVID-19 treatment, classifying 22 treatments into the categories "FDA approved," "Widely Used," "Promising Evidence," "Tentative or Mixed Evidence," "Not Promising," and "Pseudoscience or Fraud" (asamonitor.pub/3kz1zSY).

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NIH guidelines

The NIH regularly updates its treatment guidelines (asamonitor.pub/3lnSgXg), which will be the primary reference for this review. To cut to the chase, there are only three drugs specifically recommended to treat COVID-19 in hospitalized patients: oxygen, remdesivir, and dexamethasone. *That's it!* As of this writing, bamlanivab (see below) is not on the NIH recommended list, but that may change in the weeks ahead following FDA Emergency Use Authorization.

There is no role for hydroxychloroquine. The NIH recommends against its use, with or without azithromycin, in any population (other than clinical trials) (asamonitor.pub/3lwAnW9). Quoting a recent editorial in JAMA (JAMA November 2020), "In the well-conducted clinical trials published to date, hydroxychloroquine has been evaluated in a wide variety of populations... These studies failed to show any beneficial effect of the drug."

Antiviral drugs

- **Remdesivir,** a prodrug of an adenosine analog (asamonitor.pub/3eR3qRF), was approved by the FDA for treatment of COVID-19 in hospitalized adults and pediatric patients. In 1,062 hospitalized patients with lower-respiratory tract infection, remdesivir was superior to placebo in shortening the time to recovery (*N Engl J Med* October 2020). Remdesivir reduced mortality at 28 days from 15% in the placebo group to 12% in the remdesivir group, a treatment that did not reach statistical significance. Remdesivir did not reduce mortality in the WHO SOLIDARITY trial (*medRxiv* October 2020). Remdesivir is particularly beneficial for patients who have shorter duration of symptoms and who do not have overactive immune response. For patients who require supplemental oxygen, the NIH recommends a five- to 10-day course of remdesivir, with or without dexamethasone. Guidelines for use of remdesivir in children have been suggested (*J Pediatric Infect Dis Soc* April 2020).
- Neither lopinavir nor ritonavir reduced mortality in the WHO solidarity trial (*medRxiv* October 2020), and the NIH recommends against their use.
- The NIH recommends against the use of ivermectin, an antiparasitic drug.

Immune-based therapy

- **Dexamethasone** has been the most effective drug to date for improving survival. In a meta-analysis of seven randomized trials of 1,703 patients, dexamethasone reduced the odds ratio for mortality to 0.64 (P = .001) (*N Engl J Med* July 2020; *JAMA* 2020;324:1330-41). The NIH recommends using dexamethasone 6 mg per day for up to 10 days for hospitalized patients who require supplemental oxygen, including mechanically ventilation. The NIH recommends against using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen. Corticosteroids used chronically for underlying conditions should be continued.
- **Bamlanivab** is a monoclonal antibody developed by Eli Lilly and AbCellera. The FDA issued an Emergency Use Authorization for bamlanivab for mild to moderate COVID-19 in patients at increased risk due to age >65 years or comorbidities. Bamlanivab should be administered as soon as possible and within 10 days of symptom onset. It is not authorized for hospitalized patients or those who require oxygen therapy. Bamlanivab was tested on 450 patients recently diagnosed with mild to moderate CoViD-19 (*N Engl J Med* October 2020). The duration of protection may be up to a month.
- **Convalescent** plasma recently failed to slow disease progression or reduce mortality in a study of 464 adults in India (*BMJ* 2020;371:m3939). The NIH does not recommend either for or against convalescent plasma because the data are insufficient to make a determination. The FDA issued an Emergency Use Authorization for convalescent plasma despite a recommendation from FDA reviewers that the data were insufficient. The New York Times also labeled convalescent plasma "mixed evidence."
- The NIH recommends against intravenous immunoglobins and mesenchymal stem cells.
- The NIH recommends against the use of interferon, which did not reduce mortality in the WHO SOLIDARITY trial (*medRxiv* October 2020). The NIH notes that a press release suggested efficacy of inhaled interferon, but the data remain unpublished as of this writing (asamonitor.pub/32PY44j).
- The NIH does not recommend for or against interleukin (IL-1) inhibitors (e.g., anakinra). A small cohort study suggested it might help severely ill patients (*Lancet Rheumatol* 2020;2:e393-e400), but no randomized controlled trials have been published.
- The NIH recommends against use of anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab), anti-IL-6 monoclonal antibodies (e.g., siltuximab), Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib), and Janus kinase inhibitors (e.g., baricitinib, ruxolitinib, tofacitinib).

Adjunctive therapy

COVID-19 increases the risk of thrombosis. The NIH recommends anticoagulant therapy any time thrombosis is suspected. Multiple studies suggest that anticoagulant and antiplatelet therapy may be beneficial in hospitalized patients (*Intensive Care Med* 2020;46:1089-98; *J Thromb Haemost* 2020;18:1094-9; *Thromb Haemost* 2020;120:1004-24). Although definitive randomized trials have not been reported, many institutions are using antithrombotic therapy empirically. Interestingly, unfrac-

tionated heparin binds the COVID-19 spike protein in vitro at clinically relevant concentrations (*Br J Pharmacol* October 2020). The NIH recommends that chronic anticoagulant or antiplatelet therapies for underlying conditions should be continued, and venous thromboembolism prophylaxis for both outpatients and inpatients should follow existing guidelines as for non-COVID-19 patients.

- The NIH does not recommend either for or against vitamin C, vitamin D, or zinc.

Miscellaneous

- The NIH recommends that angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and nonsteroidal anti-inflammatory drugs should be continued in patients with COVID-19.
- The NIH (and literally everyone else) strongly urges that everyone receive their annual influenza vaccination.

Monoclonal antibodies in development

Monoclonal antibodies may prove highly effective for immediate treatment of patients with worsening symptoms (*Nature* 2020;584:443-49), as documented in the curated data sources mentioned in the introduction (asamonitor.pub/38xCPYD; asamonitor.pub/3eJMpsI; asamonitor.pub/3lkeGIB; asamonitor.pub/35g8EmR). Novel techniques have been developed to rapidly isolate antibodies from the plasma or serum of individuals infected with SARS-CoV-2 (*Nat Med* 2020;26:1422-27). Bamlanivab has received an Emergency Use Authorization, as noted above. Several more appear poised for Emergency Use Authorization over the next few months

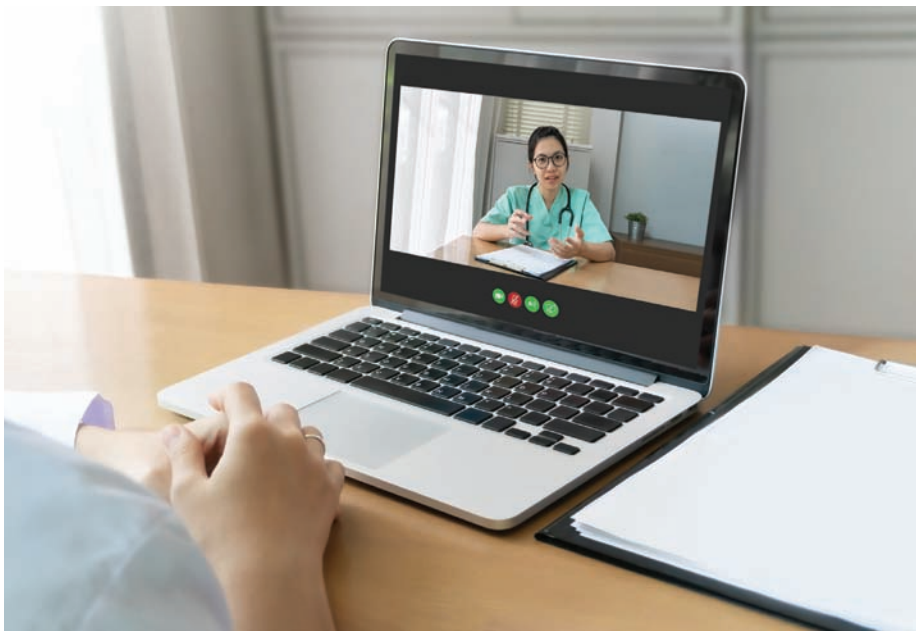
- **REGN-COV2** is a cocktail of two antibodies that bind non-competitively to the receptor-binding domain of the spike protein (*Science* 2020 October 2020). It is being developed by Regeneron. According to a company press release, in a study of 275 non-hospitalized patients, REGN-COV2 hastened alleviation of symptoms and reduced the nasopharyngeal viral load after seven days (asamonitor.pub/2UAzxeY). The data remain unpublished as of this writing. A second press release documented positive results in additional study of 524 patients (asamonitor.pub/38Ouyju). Neither of these studies has been published as of this writing. Regeneron has applied for Emergency Use Authorization from FDA.
- **AZD7442** is a cocktail of two monoclonal antibodies licensed by AstraZeneca from the monoclonal antibody discovery program and Vanderbilt University (*Nat Med* 2020;26:1422-27). The two antibodies interact synergistically at non-overlapping sites of the receptor-binding domain of the S protein. While AstraZeneca has published multiple press releases (asamonitor.pub/38OPk2i), there are no references to AZD7442 human studies in the peer-reviewed literature, bioRxiv, or MedRxiv at the time of this writing. Its protection may last for several months.
- **AeroNabs** is a completely synthetic "nanobody" developed by scientists at UCSF (*bioRxiv* August 2020). Although it is not a monoclonal antibody, functionally it behaves the same way and appears to be among the most potent SARS-CoV-2 antivirals discovered to date. AeroNabs strongly binds to the three receptor-binding domains (RBD) of the spike protein. It also prevents the spike protein from assuming an active state. Remarkably, it is a stable powder that can be self-administered through an inhaler (asamonitor.pub/3f58PVB). Clinical studies and commercial production are being pursued. Recently, FDA issued Emergency Use Authorization for baricitinib plus remdesivir as well as for casirivimab plus imdevimab. ■

Building Rapport in the COVID Era

Syed Sohaib Nasim, MD **Steven Minear, MD**

The COVID-19 pandemic has had a devastating impact on health care, and it has brought forth new challenges to the current system (*J Hosp Med* 2020;15:437-9). The communication process with patients and their families in the perioperative setting, especially during critical moments and critical illness, has changed significantly over the past few months, moving wherever possible to virtual platforms. Online or telephone appointments have become an expected aspect of care (*J Hosp Med* 2020;15:437-9).

During extended critical illness, this virtual setting is unsatisfactory for both patient and doctor. Building rapport with patients and their family members is crucial because it helps clinicians connect, and it improves patient care (*J Hosp Med* 2020;15:437-9). As patients continue through their perioperative course, especially patients in the ICU, these complicated treatment plans and their clinical implications cannot be easily translated to an episodic, virtual conversation (*J Hosp Med* 2020;15:437-39). Prior to stricter visiting policies, family would come frequently to visit, creating opportunities to interact with the care team. These frequent, casual, patient-family-doctor moments cements care team rapport: the feeling of being "on the same team" and present for families (*J Hosp Med* August 2020).



With multiple trips to the OR, rapid changes in clinical status, and the potential for eventual decline, palliative options and end-of-life conversations are made even more challenging due to necessarily strict hospital visiting policies in place (*J Hosp Med* August 2020). At times, the first instance physicians and family physically meet is for an end-of-life discussion. The unsung bystanders of the COVID pandemic are the families and care team of critically ill patients, who are missing that team dynamic, strengthened by many informal points of contact outside of the official "update."

The Centers for Disease Control and Prevention (CDC) has recommended that states limit visitation, allowing them in situations such as altered mental status or end-of-life settings (*J Hosp Med* August 2020). Hospitals by necessity are pressured to introduce strict policies, and consequently family members often could not visit patients even in non-COVID situations. This was done to limit COVID transmission while allowing clinicians the ability to provide compassionate care. However, it has raised challenges for communicating patient progress with family members (*J Hosp Med* August 2020).

There are feelings of isolation, and clinicians cannot communicate easily with different family members at the same time. This makes care discussion very challenging because family members are unable to witness patient progress, either to recovery or decline (*J Hosp Med* 2020;15:437-9; *J Hosp Med* August 2020). Moreover, there are challenges with discharge planning and education because family members are not present at critical moments, which can negatively affect care coordination. This is especially true for the ICU, where patients recovering from their illnesses may be expected to understand instructions about

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