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COVID-19 Therapeutics

Richard Simoneaux Steven L. Shafer, MD
Editor-in-Chief

As SARS-CoV-2 spread across the globe early last year, the WHO initiated the "Solidarity Trial" to efficiently see if existing drugs could be repurposed to treat COVID-19 (asamonitor.pub/3kj5hmV; asamonitor.pub/3zaBsJb). Fifty-two nations are participating in the WHO Solidarity Trial. Unfortunately, the first four drugs evaluated – remdesivir, hydroxychloroquine, lopinavir, and interferon – all had the same outcome: little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay (*N Engl J Med* 2021;384:497-511). Although the U.S. is not a participant in the Solidarity Trial, several therapies have received emergency use authorizations (EUAs) from the U.S. Food and Drug Administration. Even though effective vaccines are now available in the U.S., effective antiviral treatment remains an essential component of managing the COVID-19 pandemic (asamonitor.pub/2Z45MsR).

EUA therapies

Table 1 shows the antiviral therapies for COVID-19 that have been authorized for

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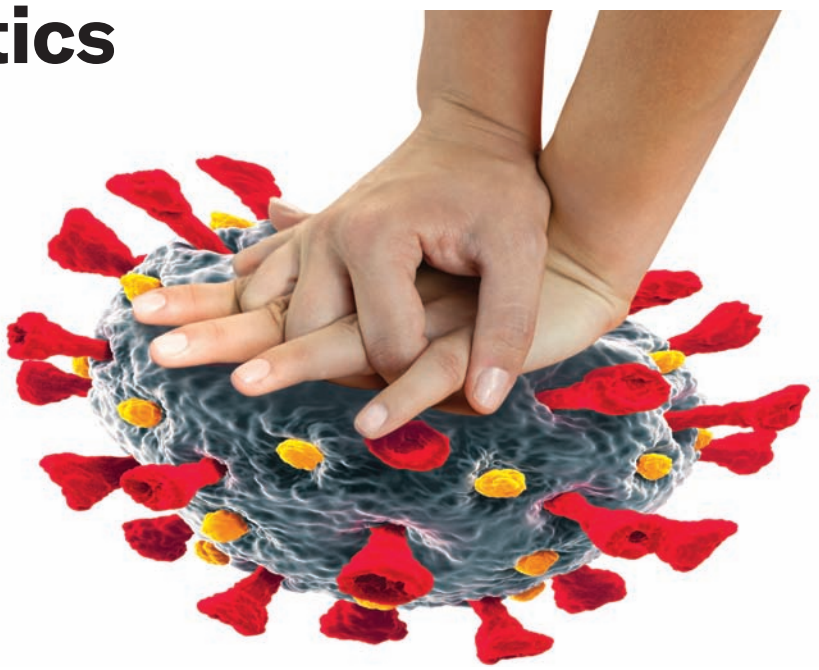

Perioperative Medicine and the Environment: Are We Obsessed with 'Clean' but Oblivious to 'Green'?

Zachary Deutch, MD, FASA Brian Chesebro, MD

Hello, everyone, and welcome to the November 2021 "Ask the Expert." This month, we are going to explore a topic with huge implications for the medical field and the planet, namely the environmental impact of perioperative medicine. All of us are familiar with the concepts of climate change, ozone layer depletion, and the push for sustainability in equipment/device production and utilization. But what do these things really mean to us as anesthesia professionals and physicians? Where should our priorities lie, and how should we conduct ourselves? There are no easy answers to these questions, but our Expert, ***Dr. Brian Chesebro,*** *will educate us, and thereby*

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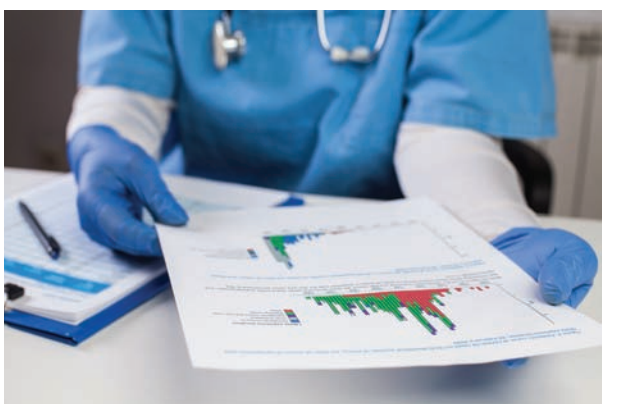
Impact of COVID-19 on Excess Mortality

Dibash Kumar Das, PhD



The COVID-19 pandemic has resulted in excess mortality. Excess mortality encompasses the total number of deaths from all causes during a crisis observed in a given period compared with what would have been expected based on past trends and seasonality. The confirmed deaths due to COVID-19 offer information about the cause of death. In contrast, excess mortality is important both for modeling the transmission dynamics of the disease as well as providing information about the burden of mortality potentially related to the pandemic.

Excess mortality is shaped by several drivers of all-cause mortality that correlate to the pandemic and the social distancing directives that came with the pandemic. These drivers include health care being delayed or deferred during the pandemic, racial and socioeconomic inequities, increase in mental health disorders, increased alcohol use, and increased opioid use. This all makes it clear that the two metrics –

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In the Know: Therapeutics

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clinical use under the EUA regulations. It hasn't been smooth sailing for these drugs. As noted above, the WHO Solidarity Trial found that the remdesivir did not improve outcome. Bamlanivimab was found to be ineffective as a monotherapy and needed to be given in combination with a second monoclonal antibody. Given the role of autoantibodies in the pathogenesis of severe COVID-19 disease, it is not surprising that two of the drugs – baricitinib and tocilizumab – are powerful immune modulators.

"Massive investment in research and development by government, industry, and academia has identified potential therapies with great promise for treating moderate or severe COVID-19. SARS-CoV-2 will likely join the four other endemic coronaviruses and be with us forever. However, the dozen approved vaccines combined with the addition of at least a dozen highly effective therapies will likely bring the great pandemic of 2020 to an end in 2022."

Non-EUA therapies

Table 2 lists several of the drugs used off-label to treat COVID-19. Dexamethasone was identified early in the course of the pandemic as an effective immune modulator for patients with moderate to severe disease and has been an off-label mainstay of therapy since. Hydroxychloroquine was found to be ineffective in the Solidarity Trial and seems to be of less interest now.

A great deal of misinformation has been put forward about ivermectin. A preprint published by Sapin Desai, founder of Surgisphere, reported a large reduction in COVID-19 mortality with ivermectin. The preprint was withdrawn along with the rest of Desai's COVID-19 studies for unreliable data (*Nature* 2020;582:160). Another preprint demonstrating ivermectin efficacy was withdrawn after data manipulation was identified by alert readers (*Nature* 2021;596:173-4; asamonitor.pub/3CgHmuc). Remarkably, this withdrawn preprint continues to be used in meta-analyses purporting to demonstrate benefit. As noted by Popp and colleagues, a common thread of meta-analyses purported to show benefit of ivermectin is the selective use of highly positive, low-quality studies (*BMJ Evid Based Med* August 2021). A recent narrative review advocating ivermectin went further, and evidently fabricated the epidemiologic data purporting to show benefit (*Am J Ther* 2021;28:e596-8). As usual, the highest-quality review is from the Cochrane Collaboration, and they report no compelling demonstration of benefit among well conducted trials (asamonitor.pub/3nzm9Yi).

Therapies under development

Nanobodies

As reported in *Nature News*, "nanobodies" are small antibodies, derived from camelids (e.g., llamas and camels), that can attach to epitopes in protein folds too narrow to be accessed by human antibodies (*Nature* 2021;595:176-8). In another paper in *Nature*, Xu et al. created camelid-based nanobodies (in mice – go figure) targeting the highly conserved portion of the receptor binding domain (RBD) of the SARS-CoV-2 spike protein (*Nature* 2021;595:278-82). The region is inaccessible to human antibodies because it is somewhat buried in the surface. Also, the region is outside of the ACE2-binding portion of the spike protein, so mutations that increase binding affinity (e.g., most of them) do not confer resistance to binding (*Nat Microbiol* 2021;6:1188-98). Despite being outside of the ACE2-binding region, binding of these nanobodies to the spike protein blocked ACE2-RBD interaction and prevented infection.

A similar study by Koenig et al. in *Science* isolated four nanobodies from camelids (one alpaca and one llama) inoculated with formalin-inactivated SARS-CoV-2 and the receptor binding domain of the SARS-CoV-2 spike protein (*Science* 2021;371:eabe6230). The nanobodies neutralized the ability of the spike protein to initiate fusion with target cells. The researchers created three multivalent nanobodies, each incorporating two nanobody binding sites. Binding multiple sites makes it exceptionally difficult for SARS-CoV-2 escape mutations to evolve. Additionally, because nanobodies are small, soluble molecules, the authors note that nanobodies are inexpensive to manufacture and amenable to intranasal delivery. They speculate that an intranasal dose could accompany a COVID-19 test in outpatients with symptoms. Additionally, since nanobodies lack the Fc fragment present in antibodies, engagement by phagocytes bearing Fc-receptors is prevented, thus avoiding a potential mechanism for antibody-dependent enhancement (ADE).

More recently, Güttler and colleagues published a library of 45 thermally stable and ultra-potent nanobodies (up to 95°C) (*EMBO J* August 2021). The isolated nanobodies displayed neutralized SARS-CoV-2 at concentrations ranging from 17 to 50 picomolar and were unaffected by any of the known variants.

Monoclonal antibodies

Preclinical studies performed by Ralph Baric's research group evaluated an engineered human monoclonal antibody that targeted a highly conserved epitope in the ACE2 binding site (*Science* 2021;371:823-9). Interestingly, their antibody construct bound tightly against all clade 1 SARS betacoronavirus spike protein RBDs, suggesting likely efficacy in both this and future coronavirus pandemics. The authors found that binding was only affected by four specific mutations (D405, G502, G504, and Y505), mutations that are not observed in nature. Murine studies showed that the antibody provided broad protection in both SARS and COVID-19 models.

Research performed by Zhengli Shi's group at the Wuhan Institute of Virology identified two potent human neutralizing anti-SARS-CoV-2 antibodies (*Nat Commun* 2021;12:4887). These antibodies, termed nCoVmab1 and nCoVmab2, target the RBD of SARS-CoV-2. As with the nanobodies described earlier, these antibodies are ultra-potent with neutralizing concentrations in the picomolar and nanomolar levels, respectively. The more potent antibody, nCoVmab1, reduced viral loads with both prophylactic and therapeutic administration in genetically modified mice expressing "humanized" ACE2.

Preclinical studies performed at the Utrecht University evaluated two human monoclonal antibodies isolated from "hu-

Table 1: COVID-19 therapies with FDA approval or emergency use authorization

Therapy	Class of Therapy	FDA Emergency Use Authorization	References
Remdesivir	Antiviral	FDA Approval: https://www.fda.gov/media/137564/download	*Rev Med Virol* 2021; 31:e2187; *JAMA Netw Open* 2021;4:e2114741
Baricitinib	Janus kinase inhibitor	https://www.fda.gov/media/143823/download (without remdesivir) https://www.fda.gov/media/144473/download (with remdesivir)	*N Engl J Med* 2021;384:795-807; *BMC Infect Dis* 2021;21:427; *Clin Infect Dis* 2021;72:1247-1250
Bamlanivimab	Anti-SARS-CoV-2 spike monoclonal antibody	EUA: https://www.fda.gov/media/144118/download Revocation: https://www.fda.gov/media/146272/download	*Lancet Microbe* 2021;2:e424; *JAMA* 2021; 325:632-44
Bamlanivimab plus Etesevimab	Anti-SARS-CoV-2 monoclonal antibody cocktail	https://www.fda.gov/media/146255/download	*N Engl J Med* July 2021; *JAMA Netw Open* 2021;4:e2114741
Casirivimab and Imdevimab (REGEN-COV)	Anti-SARS-CoV-2 monoclonal antibody cocktail	Original EUA: https://www.fda.gov/media/144468/download Revision: https://www.fda.gov/media/150165/download	*N Engl J Med* 2021;384:238-51
Tocilizumab	Anti-IL-6 monoclonal antibody	https://www.fda.gov/media/150748/download	*N Engl J Med* 2021; 384:1503-1516

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manized" genetically-modified mice (*Nat Commun* 2021;12:1715). The studied antibodies displayed significant cross-reactivity against the spike proteins of several betacoronaviruses, including SARS-CoV-1, SARS-CoV-2, MERS-CoV, and HC0V-OC43 (an endemic human coronavirus). Unlike antibodies that target the receptor binding domain, these antibodies targeted the stem helix portion of the S2 fusion subunit of the spike protein, preventing bound spike protein from fusing with the cell membrane. The antibodies also blocked infection with MERS-CoV, suggesting that the binding site is highly conserved.

Table 2: COVID-19 therapies without FDA emergency use authorization

Therapy	Class of Therapy	References
Acalabrutinib, Ibrutinib	Bruton's tyrosine kinase inhibitors	*Metabol Open* September 2021; *J Hematol Oncol* 2021;14:15; *Mol Cancer Res* 2021;19:549-54
Dexamethasone	Glucocorticoid	*N Engl J Med* 2021;384:693-704; *Lancet Respir Med* 2020; 8:1170-2
Fluvoxamine	Selective serotonin reuptake inhibitor	*JAMA* 2020;324:2292-300; *Front Pharmacol* April 2021
Proxalutamide	Antiandrogen	*Front Med (Lausanne)* 2021;8:668698; *Endocrinology* 2021; 162:bqab114
Ivermectin	Anthelminthic	*JAMA* 2021;325:1426-35; *Nat Med* September 2021
Hydroxychloroquine	Antimalarial	*N Engl J Med* 2020;383:2030-40; *N Engl J Med* 2020;383: 2041-52; *N Engl J Med* 2021;384:417-27; *N Engl J Med* 2020; 382:2411-8; *N Engl J Med* 2021;384:881-2; *Sci China Life Sci* 2020;63:1515-21; *Int J Antimicrob Agents* 2020;56:106144

Protease inhibitors

When SARS-CoV-2 infects cells, the positive-sense RNA is transcribed into two polyproteins and one active protein: a protease. The job of the protease is to split the polyproteins into 11 small proteins vital to viral replication. This protease, called M^{pro} or 3CL protease, is exceptionally highly conserved among coronaviruses. Indeed, among the studied coronaviruses, 12 of the 13 amino acids that comprise the catalytic site are identical between SARS, MERS, and SARS-CoV-2.

A recent review in *Current Opinion in Virology* looked at the potential for developing M^{pro} inhibitors (*Curr Opin Virol* 2021;49:36-40). Interestingly, Pfizer started work on an M^{pro} inhibitor, PF-00835231, 15 years earlier as a candidate treatment for SARS. The program was stopped when the SARS pandemic waned from aggressive containment measures. Pfizer recently identified PF-07304814, a phosphate prodrug of PF-00835231, and recently completed a phase 1b clinical trial evaluating its clinical utility in a phase Ib study in patients hospitalized with COVID-19 (NCT04535167).

Pfizer is also developing a second-generation M^{pro} inhibitor, PF-07321332, that will be administered orally (asamonitor.pub/3lwADFV). The oral M^{pro} inhibitor shows potent *in vitro* pan-coronavirus protease inhibition against alphacoronaviruses (229E and NL63) and betacoronaviruses (SARS-CoV-2, SARS-CoV-1, MERS-CoV, HKU1, and OC43). As of this writing there are 9 studies from phase 1 through phase 3 of PF-07321332 reported on clinicaltrials.gov. Efficacy and safety results from these trials are expected by the end of this year (asamonitor.pub/3AgU63l).

Probenecid

Probenecid (used to treat gout) may have activity against SARS-CoV-2 as strongly suggested by a recent report in *Nature Scientific Reports* (*Sci Rep* 2021;11:18085). The data strongly suggest that one dose/day would easily achieve the necessary concentration to inhibit SARS-CoV-2. Quoting the authors, "The major advantages of probenecid are that it is an FDA-approved therapeutic drug that has been on the market for >50 years, it can be administered orally with favorable pharmacokinetics, it operates at the host cell level, is refractory to viral mutation, and has the potential to treat multiple other viruses." Currently there are no registered trials at clinicaltrials.gov, but this will likely change since publication of the report.

In conclusion, science rocks. Massive investment in research and development by government, industry, and academia has identified potential therapies with great promise for treating moderate or severe COVID-19. SARS-CoV-2 will likely join the four other endemic coronaviruses and be with us forever. However, the dozen approved vaccines combined with the addition of at least a dozen highly effective therapies will likely bring the great pandemic of 2020 to an end in 2022. ■