Title

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SPECIAL ARTICLE

Developing Treatment Guidelines During a Pandemic Health Crisis: Lessons Learned From COVID-19

The development of the National Institutes of Health (NIH) COVID-19 Treatment Guidelines began in March 2020 in response to a request from the White House Coronavirus Task Force. Within 4 days of the request, the NIH COVID-19 Treatment Guidelines Panel was established and the first meeting took place (virtually–as did subsequent meetings). The Panel comprises 57 individuals representing 6 governmental agencies, 11 professional societies, and 33 medical centers, plus 2 community members, who have worked together to create and frequently update the guidelines on the basis of evidence from the most recent clinical studies available. The initial version of the guidelines was completed within 2 weeks and posted online on 21 April 2020. Initially, sparse evidence was available to guide COVID-19 treatment recommendations. However, treatment data rapidly accrued based on results from clinical studies that used various study designs and evaluated different therapeutic agents and approaches. Data have continued to evolve at a rapid pace, leading to 24 revisions and updates of the guidelines in the first year.

This process has provided important lessons for responding to an unprecedented public health emergency: Providers and stakeholders are eager to access credible, current treatment guidelines; governmental agencies, professional societies, and health care leaders can work together effectively and expeditiously; panelists from various disciplines, including biostatistics, are important for quickly developing well-informed recommendations; well-powered randomized clinical trials continue to provide the most compelling evidence to guide treatment recommendations; treatment recommendations need to be developed in a confidential setting free from external pressures; development of a user-friendly, web-based format for communicating with health care providers requires substantial administrative support; and frequent updates are necessary as clinical evidence rapidly emerges.

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When the first U.S. patients were diagnosed with COVID-19 in January 2020, clinicians faced the daunting task of managing a severe, life-threatening disease caused by a novel pathogen (SARS-CoV-2) about which little was known. As the pandemic surged in the United States from January to March 2020, information about treatment, mostly in the form of case reports and case series, began to appear on social media, in the popular press, through press releases, on preprint servers, and in medical literature. Specific therapies were championed by various medical and nonmedical sources, often with scant evidence for safety or efficacy. Subsequently, several countries and many U.S. health care institutions and organizations issued management guidelines that recommended–on the basis of limited evidence–various therapeutic options, including hydroxychloroquine, lopinavir–ritonavir, and interleukin-6 inhibitors.

In March 2020, the White House Coronavirus Task Force, through the Secretary of Health and Human Services, asked the National Institutes of Health (NIH) to develop evidence-based guidelines for the treatment of patients with COVID-19. Although the NIH rarely sponsors guidelines, NIH sponsorship of a COVID-19 guideline was warranted in this instance given the urgency of the public health emergency and the ability of NIH to immediately launch an adequately resourced response. The expectation was that the guidelines would provide recommendations that clinicians in the United States could use to guide their therapeutic decision making. The resulting recommendations were not and should not be considered mandates. It was also expected that the guidelines would be updated regularly as evidence about treatment evolved, providing confidence that the guidelines were current. Maintaining currency and meeting stakeholder expectations required considerable time by the COVID-19 Treatment Guidelines Panel (the "Panel") and extensive administrative support.

Treatment guidelines for COVID-19 were clearly needed: In the first 3 days after initial release, the NIH's COVID-19 Treatment Guidelines website received 840 000 page views. Each week since, it has had between 100 000 and 650 000 page views from the United States and abroad, with a total of approximately 17.2 million page views since inception.

Developing treatment guidelines for a pandemic health emergency proved to be very different from developing guidelines for nonpandemic medical conditions (**Appendix Table 1**, available at Annals.org). This article summarizes some of the lessons learned from the Panel's first year of work (1) (**Table**).

Initiating and Operationalizing the NIH COVID-19 Treatment Guidelines

The first meeting of the full Panel occurred virtually on 24 March 2020 (**Figure 1**), 4 days after the formal request to the NIH. The National Institute of Allergy and Infectious Diseases initiated the formation of the NIH COVID-19 Treatment Guidelines Panel by leveraging an infrastructure that had been put into place to develop guidelines in response to the HIV pandemic; the existing

See also:

Web-Only
Supplement

Table. Lessons Learned

Need for guidelines	During a pandemic, there is a compelling need for unbiased, accurate, and up-to-date treatment guidelines. Treatment recommendations must at times be made on the basis of scarce data or conflicting study results.
Multidisciplinary working groups	For complex, multisystem diseases, the Panel works more effectively and expeditiously when multiple relevant disciplines are represented. Biostatisticians and clinical trial experts are essential to ensure optimal interpretation of data.
Infrastructure and resources	Frequent updates require substantial administrative support to ensure currency, accuracy, and readability.
Data sources	Well-powered randomized clinical trials provide the most compelling evidence, although valuable information can be derived from well-designed observational studies. The Panel does not need to restrict its review to published data, although study results that are not peer-reviewed must be interpreted with caution.
EUAs	EUAs are an FDA mechanism to provide access to investigational drugs. The Panel's role is to provide the best treatment recommendations regardless of EUA status. There is not always concordance between the Panel's and the FDA's missions.
Effective, rapid communication	Recommendations need to be straightforward and consistent. Communication with stakeholders is facilitated by a user-friendly platform. Treatment guidelines must be revised frequently and quickly as new information about treatment emerges.
Outside pressure	The guideline process must be protected from outside pressure if its recommendations are to be credible and evidence-based.
Children and pregnant individuals	It is imperative to include treatment recommendations for populations often excluded in clinical trials, including pregnant individuals and children.
Collaboration	The guidelines process is enhanced by members who understand how to work effectively in groups. Collaboration and communication among different disciplines and with relevant government agencies and professional societies enhanced the quality of the guidelines.

EUA = emergency use authorization; FDA = U.S. Food and Drug Administration.

infrastructure included infectious disease experts who were active in COVID-19 patient care, program management, and/or research. Additional members were chosen on the basis of their relevant expertise; experience with the conduct and analysis of clinical trials; experience with the guideline process; record of working effectively in group settings; and established working relationships with colleagues, governmental agencies, and professional societies. Biostatisticians were especially important members of the Panel from the onset given the complexity of the data to be analyzed and the trial designs reviewed. The Panel currently comprises 57 individuals representing 6 governmental agencies, 11 professional societies, and 33 medical centers, plus 2 community members (Appendix, available at Annals.org).

Professional societies were asked to nominate representatives to the Panel but were not requested to endorse Panel recommendations because time-consuming negotiations with multiple other entities would preclude rapid Panel decisions. New members were subsequently added when it became evident that additional areas of clinical expertise were needed, including in clotting disorders, immunomodulatory therapy, and viral resistance. In many cases, members of the Panel concurrently served on other guidelines panels that were convened by health care systems or professional societies and focused on COVID-19 or other relevant topics; however, no formal process was implemented to harmonize recommendations. When appropriate, links were provided to other COVID-19–related guidelines. The Society of Critical Care Medicine also graciously permitted the adaptation of considerable material from their initial COVID-19 guidelines document (2) for use in the NIH guidelines.

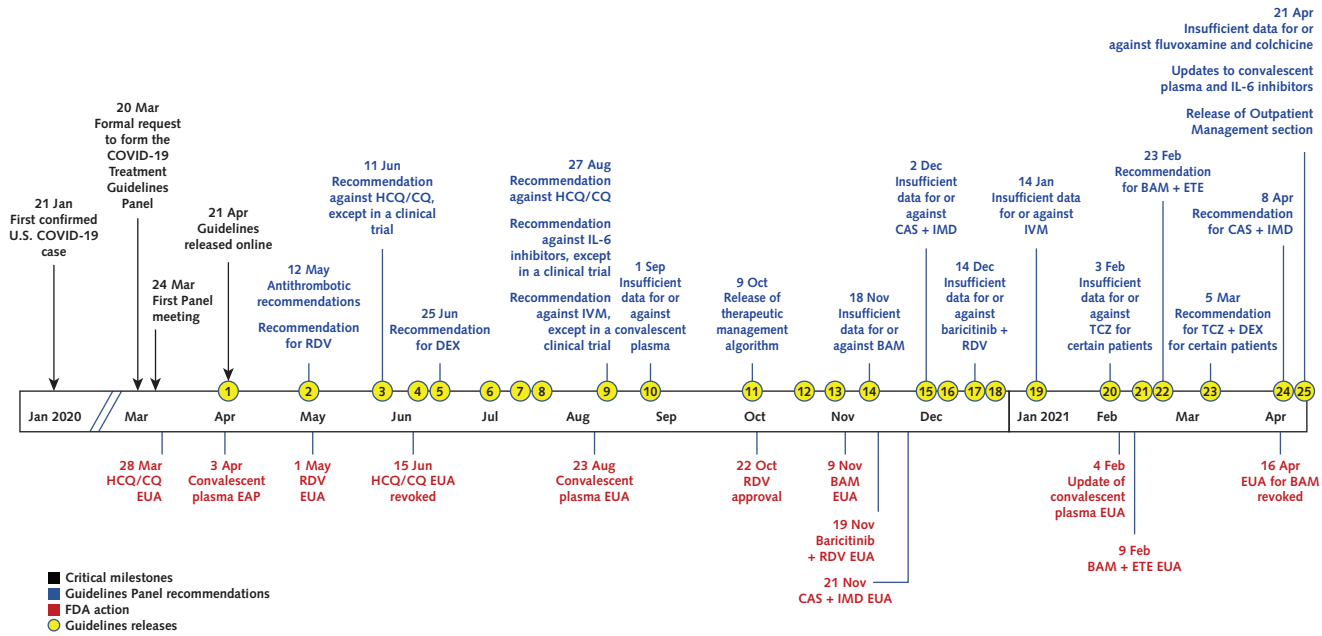
Panel co-chairs included 1 nongovernment and 2 government physician-scientists, each of whom had extensive clinical, research, and guideline experience. All nongovernment Panel members served as volunteers and received no compensation for this activity. Government employees served as part of their official duties. Each member submitted financial disclosures that were reviewed by Panel co-chairs biannually to determine suitability for membership and were updated in the interim as appropriate. The Panel was divided into teams to focus on key content areas, including overview, clinical spectrum, outpatient management, and prevention; antiviral therapies; immunomodulators; and critical care. Panel recommendations were determined by majority vote using electronic polling, with each voting member having an equal vote. Virtual meetings were coordinated by NIH staff, who served as facilitators and carried out executive secretary roles. The editing of content and posting of updates were facilitated by contract support staff, who provided editorial, website development, graphic design, and social media management services.

Data Quality and Challenges With Interpretation

Early in the pandemic, because of the severity and high mortality associated with COVID-19, many clinicians felt compelled to repurpose available drugs for prevention or treatment of COVID-19 despite a lack of adequate evidence to support their safety or efficacy. A deluge of observational data ranging from anecdotes to case series appeared almost daily. However, there were few convincing, well-controlled clinical studies on which to base early recommendations. Panel members and staff attempted to collect data from all available credible sources and make such data easily accessible to all Panel members (**Appendix Figure**, available at Annals.org).

The Panel believed strongly that well-powered randomized clinical trials were the most reliable sources of evidence to guide therapeutic recommendations. Observational cohorts provided important information

Figure 1. NIH COVID-19 treatment guidelines: the first year.



BAM = bamlanivimab; CAS = casirivimab; CQ = chloroquine; DEX = dexamethasone; EAP = Expanded Access Program; ETE = etesevimab; EUA = emergency use authorization; FDA = Food and Drug Administration; HCQ = hydroxychloroquine; IL-6 = interleukin-6; IMD = imdevimab; IVM = ivermectin; NIH = National Institutes of Health; RDV = remdesivir; TCZ = tocilizumab.

as well, with the caveat that unrecognized confounders could bias the results of even well-designed observational studies. Case series reports or poorly controlled studies were also considered, particularly early in the pandemic when data were scarce, but they were interpreted with caution. As the pandemic progressed, more credible data from randomized trials became increasingly available (**Figure 2**).

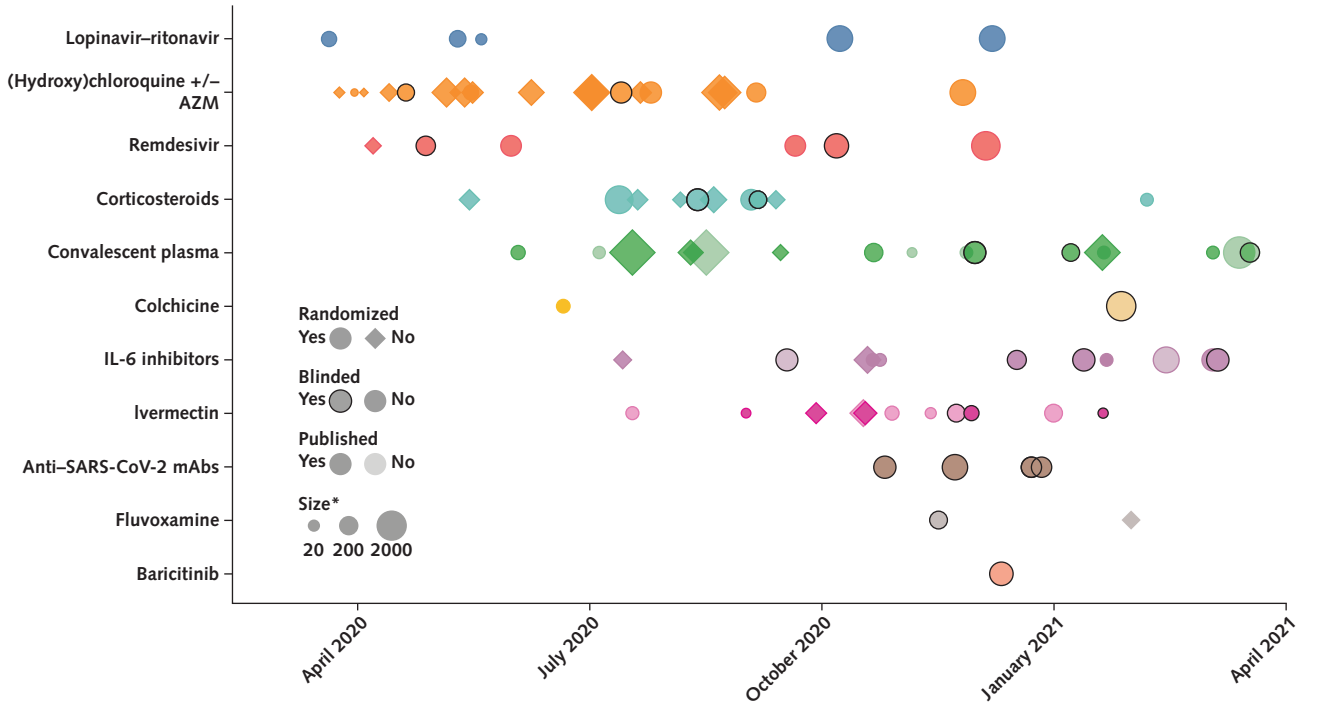
Studies required considerable analysis. The efficacy and safety of any intervention for the treatment of COVID-19 depend on many variables, including patient age and comorbid conditions, the stage of illness when the intervention was initiated, concurrent drug treatment, and standards of supportive care. Studies done in different patient populations, in different settings, or with different study end points often resulted in conflicting conclusions and interpretations.

In an attempt to identify the ideal time to intervene with a specific therapy (in the setting of different severities of COVID-19), some trials narrowed the eligible population–for example, limiting enrollment to patients in the intensive care unit in the first 24 hours after admission (3, 4)–whereas others tested the intervention across disease stages and then provided subgroup analyses according to baseline COVID-19 severity (5–7). Evaluating the studies and making appropriate recommendations required synthesizing information on different outcomes and often resulted in individualized recommendations for subgroups of patients according to disease characteristics.

Primary study outcomes varied among trials, ranging from viral RNA shedding to clinical progression to overall mortality. The Panel needed to compare trials with a wide range of sample sizes and trial designs and paid particular attention to randomized clinical trials that were adequately powered to detect well-defined, meaningful clinical end points, especially mortality (**Figure 2**). To achieve adequate power in a short time, many trials took pragmatic approaches that facilitated rapid enrollment. The RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial in the United Kingdom, for instance, used an open-label design with simple eligibility criteria and simultaneously randomly assigned patients into 1 of several treatment groups, with mortality as the primary outcome (8). RECOVERY was launched on 19 March 2020, rapidly enrolled many participants across numerous institutions, and consequently was generalizable to various clinical practice settings. The trial provided answers expeditiously to certain treatment questions but lacked the granularity needed for detailed assessments of safety and efficacy, including determining effects within subgroups (for example, patients receiving different levels of oxygen support). Despite these limitations, RECOVERY has been one of the most critical and influential studies during the pandemic. For example, it supported the efficacy of dexamethasone and tocilizumab in certain patients and provided important negative results about hydroxychloroquine and lopinavir–ritonavir in all patient groups evaluated.

Interpreting the generalizability of trials was an important consideration for the Panel because management strategies and standards of care evolved rapidly during the first year of the pandemic. Criteria to hospitalize or intubate

Figure 2. Key clinical studies for developing treatment recommendations for COVID-19.



This figure is not inclusive of all studies that informed recommendation statements or of all drugs for which there are recommendation statements. For published articles, dates reflect e-publication if applicable. For unpublished reports, dates reflect the posted date at the time of Panel review. Size of symbol corresponds to approximate study size. AZM = azithromycin; IL-6 = interleukin-6; mAbs = monoclonal antibodies.
* Proportional to the $\log_{10}$ of the number of participants in the target drug group.

patients or transfer them to intensive care units differed by locale and frequently changed on the basis of evolving knowledge, clinical experience, and hospital capacity. Moreover, many studies included several concurrent therapies, which substantially influenced and complicated the interpretation of the results. For instance, the standard of care changed abruptly after dexamethasone was shown to be safe and effective in reducing mortality for severe and critical COVID-19 (6). This defined a new standard of care for COVID-19 treatment and changed the Panel's interpretation of older studies where corticosteroids were less often used or use was imbalanced among study groups. For example, older studies of tocilizumab with sparse concomitant use of corticosteroids led to different outcomes and conclusions from more recent studies of tocilizumab with routine concomitant use of corticosteroids.

The Panel's work has been facilitated by the willingness of key national and international research study teams and government experts to accept ad hoc invitations to present data to the Panel. Panelists had the opportunity to review the most current data available and discuss the interpretation of such data with experts from multiple disciplines as well as the teams that were generating those data.

To ensure clear communication to stakeholders about what the Panel was recommending, it provided 4 types of recommendations, each supported by a written rationale and often supported by summary tables (**Appendix Table 2**, available at Annals.org). The following standard recommendations were used: recommend for, insufficient data to recommend for or against, recommend against except in a clinical trial, or recommend against. Most guidance initially fell into the second category.

The Panel rated recommendations on both the strength of the recommendation (A, B, or C, with A being strongest) and the quality of the supporting evidence (I, IIa, IIb, or III, with I being the highest-quality data and III being expert opinion) using a relatively simple system (**Appendix Table 2**). The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (9) was not used because the urgency of the pandemic required that the guideline be launched expeditiously, and there was insufficient time to train the full Panel on how to apply the GRADE framework.

Providing timely updates was a challenge. Reviewing the rapidly expanding literature thoroughly and analyzing evidence thoughtfully took considerable time and administrative support (**Appendix Figure** and **Supplement**, available at Annals.org). Although some new or revised recommendations could be made expeditiously, more often updates required lengthy analyses and deliberations (for example, when the volume of studies was large, studies conflicted, studies required more intensive review, or consensus was more difficult to achieve). However, in every instance the Panel understood the importance of maintaining the currency of the guidelines.

Navigating U.S. Food and Drug Administration Emergency Use Authorizations

Emergency use authorization (EUA) authority allows the U.S. Food and Drug Administration (FDA) to facilitate rapid access to medical products and diagnostics during a public health emergency; an EUA may only be issued after the Secretary of Health and Human Services has declared that it is appropriate. In particular, EUAs are important for providing clinicians with access to investigational products that cannot otherwise be prescribed. Most Panelists, despite extensive collective experience writing treatment guidelines, as well as many guideline users, were unfamiliar with the FDA's EUA authority before the COVID-19 pandemic.

Whereas FDA approval of a product requires substantial evidence of effectiveness, the level of evidence required for EUA is considerably lower. The criteria for issuing an EUA include the following: The public health concern must be serious or life-threatening; sufficient evidence must exist that the agent "may be effective"; the known and potential benefits of the agent outweigh the known and potential risks of its use; and no adequate, approved alternatives are available (10). As is true outside a pandemic, the FDA's decision making may be informed by data not available to the Panel or the public.

The first EUA issued for an unapproved drug was for peramivir for treatment of 2009 H1N1 influenza (11), and no other EUAs for unapproved agents were issued for treatment indications before 2020. Since the beginning of the COVID-19 pandemic, however, the FDA has issued 8 EUAs for COVID-19 treatments (as of May 2021). Two were later withdrawn (hydroxychloroquine and bamlanivimab monotherapy), and another subsequently became the first FDA-approved drug for the treatment of COVID-19 (remdesivir). Several of the remaining EUAs have been modified. These EUAs have had substantial influence on prescriber options for treating COVID-19. Understanding this authorization mechanism has been essential for using these agents appropriately and for writing clear guidelines.

The Panel's assessment of the strength and quality of available data supporting EUAs did not always lead to Panel endorsement of these agents, sometimes giving an impression of discordance between the Panel and the FDA. In several cases, the Panel endorsed an agent available through EUA but recommended its use in a more limited patient population than authorized by the EUA (for example, remdesivir and baricitinib in combination with remdesivir). In other cases, the Panel determined that evidence was insufficient to support a treatment recommendation (for example, convalescent plasma) or recommended against the use of an agent initially available through EUA (such as chloroquine and hydroxychloroquine).

It should be noted that the FDA and the Panel have discrete missions. By issuing EUAs, the FDA provides access to potentially promising investigational therapies, whereas the Panel recommends the appropriate clinical use of those therapies. In reviewing the evolution of COVID-19 treatments over the past year, the FDA and the Panel played complementary roles in the medical response to the pandemic. This collaboration and communication was constructive and beneficial for the missions of both entities.

Children and Pregnant Individuals

Children and pregnant individuals each have historically been designated as "vulnerable populations" in the context of clinical research (12). This well-intentioned classification has led to systematic exclusion of these populations from many clinical trials, and the resulting delays in the availability of data for these groups may compromise maternal and child health. During the COVID-19 pandemic, the Panel believed that despite the absence of data, it was imperative to include recommendations for treating COVID-19 in children and pregnant individuals. This was particularly true as data emerged showing that pregnant women were at increased risk for severe disease (13, 14). To achieve this goal, the Panel included members with appropriate expertise and worked closely with pediatric and obstetric professional societies.

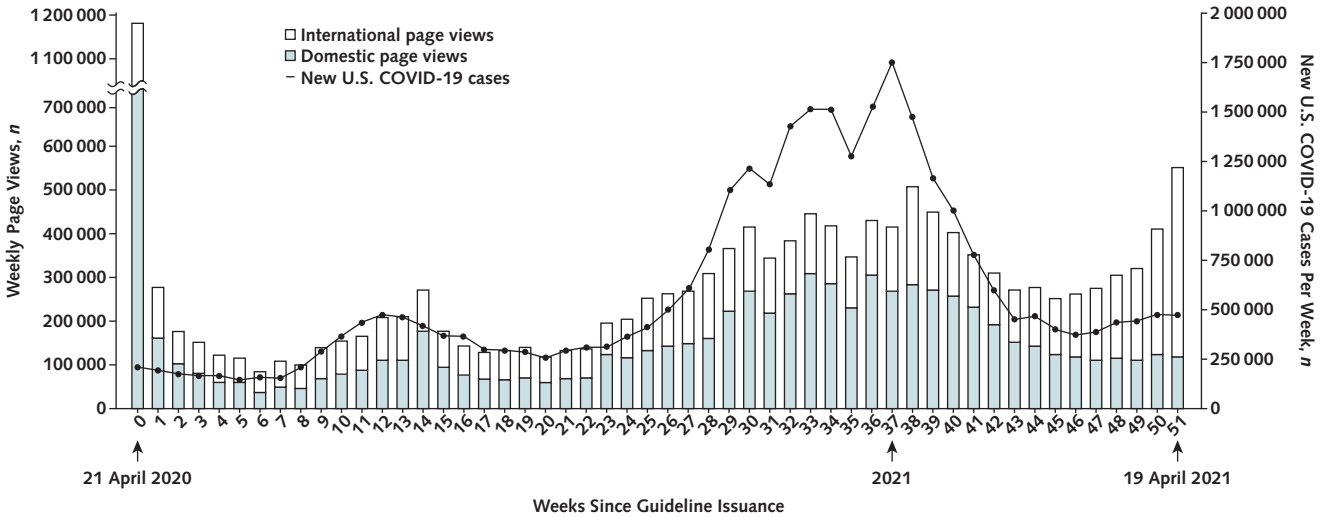
To make recommendations for children and pregnant individuals, the Panel needed to balance the potential risk with the potential benefit of therapies. Despite a paucity of data on safety, efficacy, pharmacokinetics, and pharmacodynamics, several EUAs were issued for the treatment of COVID-19 that included use in children (15, 16). For example, the EUA for baricitinib in combination with remdesivir allows for use in children as young as 2 years despite there being no data on efficacy and safety in this population; however, the Panel did not believe that a recommendation for use was indicated given that data are insufficient. In other instances, the Panel recommended that potentially effective or even life-saving treatments for COVID-19 should not be withheld from pregnant individuals because of theoretical concerns related to the safety of therapeutic agents for the fetus. In the case of dexamethasone, the mortality benefit for the pregnant person outweighed the theoretical fetal concerns, which were not well supported by current data. The Panel made this recommendation with the support of the American College of Obstetricians and Gynecologists.

Communicating With Stakeholders: Clinicians and the Public

The guidelines aimed to communicate recommended treatments to clinicians in a concise, straightforward, and clear manner. Recognizing that some stakeholders would focus primarily on recommendation summaries, the Panel provided a therapeutic management figure and boxed summaries of key recommendations for rapid overview. Tables summarizing key studies and descriptive text were provided for readers interested in more detail.

The overall communication strategy was to promptly alert the target audience to the content in the guidelines while presenting that content in a user-friendly manner. Recognizing that this document would need to be updated regularly, the Panel followed the precedent set by other governmental and professional society guidelines in publishing exclusively online, although this

Figure 3. NIH COVID-19 treatment guidelines weekly page views and new U.S. COVID-19 cases.



The data on new COVID-19 cases were downloaded from the Centers for Disease Control and Prevention COVID Data Tracker on 19 April 2021. Domestic and international weekly page views through 19 April 2021 were obtained from Google Analytics on 4 May 2021. NIH = National Institutes of Health.

guideline was established with the expectation that updates would occur with unprecedented frequency. The website was developed using an existing NIH platform (17), which allowed it to be established rapidly and reduced the likelihood of unexpected delays and technical problems.

The guidelines were announced by an NIH press release on 21 April 2020 (18). During the first week, most viewers came directly to the website using its URL. A minority were referred from other websites and social media. During the first week, the website had just over 1.1 million page views; subsequently, there were 100 000 to 650 000 page views per week. Since inception, the website has had more than 17.2 million page views (Figure 3). Of note, the number of international page views has increased substantially in recent months, coincident with the spike of cases in India, emphasizing that although the guidelines are intended for a U.S. audience, they are accessed frequently worldwide.

Most users accessed the guidelines using a mobile device (58%), whereas 39% used desktop computers and 3% used tablets—an observation that may be of interest to developers of future guidelines. E-mails regarding new updates were available to persons who signed up for the guideline listserv.

In addition to clinicians, it quickly became apparent that members of the public, press, pharmaceutical industry, and governmental agencies were also interested in the Panel's recommendations. The most-accessed pages varied according to where changes were being made in the guidelines and what treatments were being discussed in the medical literature and on traditional and social media. Media attention to certain drugs seemed to influence web traffic.

A Twitter account (@NIHCOVIDTxGuide) was established in May 2020, and communications were issued regularly. The site's visibility was further improved by use of search engine optimization principles and by referrals from such sources as the U.S. Centers for Disease Control and Prevention and major medical and nonmedical news media. Initially, only 3% of users came from popular search engines (such as Google). More recently, 75% of users have come from these search engines.

Outside Pressure

At times, medical and societal pressures to "do something to prevent people from dying" competed with the need for recommendations to be evidence-based. The Panel recognized its specific mission to issue recommendations based on careful interpretation of scientific evidence, even when such information was incomplete or even contradictory. Furthermore, it was clearly stated that the guidelines provided treatment recommendations—but not mandates—with the understanding that providers and other stakeholders were free to make their own decisions.

Sources of outside pressure included colleagues involved in patient care, patients and family members, groups and individuals advocating for specific drugs, members of the news media, the pharmaceutical industry, and various branches of government. This pressure took multiple forms, including telephone calls, e-mails, social media posts, blog posts, and even Congressional hearings, and was directed to both individual Panel members and the NIH as a whole. Despite outside pressure, NIH leadership ensured that there was no interference with the scientific independence of the Panel.

Limitations

These guidelines were developed for the United States by a panel of experts from the United States. As such, the

recommendations are not relevant to all areas of the world. Although the Panel attempted to collect and evaluate all relevant studies to inform its recommendations, the rapid escalation in number of studies worldwide made it impossible to read and thoroughly evaluate every publication and communication. The Panel operated without yielding to outside political or other pressure, despite the guidelines being developed in a national atmosphere of strong opinions within and outside the government and academia.

Conclusions

As the COVID-19 pandemic unfolded, health care providers needed credible, evidence-based guidelines. In the setting of rapidly expanding clinical information about a new disease, coordinated synthesis and dissemination of credible information was of critical importance. As a convening body, NIH had the scientific credibility and the resources to recruit experts in multiple clinical disciplines to establish a panel to meet this need.

Practitioners, professional societies, and governmental agencies worked efficiently together even when facing enormous challenges. Choosing members who were subject matter experts and also experienced at working effectively in groups was beneficial. Access to the best published and unpublished information required substantial support staff. Members needed to be assured that their deliberations were confidential and free from outside pressure. Communication and website development expertise and administrative support were essential. The lessons learned during this process will inform such efforts during future health emergencies.

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Appendix Table 1. Adaptations Made to Typical Guideline-Writing Process During the Pandemic

Guideline Development Domain	Typical Guideline Processes	Pandemic Modifications to Guideline Processes	Ongoing Challenges	Panel Suggestions for Pandemic Guideline Process
Member recruitment, chair identification, COI resolution	Assembly of multidisciplinary team with specific content expertise	No existing expertise in COVID-19, initial reliance on HIV/ID and critical care experts who pivoted to COVID-19 Multidisciplinary expertise (e.g., rheumatology, hematology) and community advocates added as the clinical landscape evolved	Ongoing, significant time commitment of volunteer Panel members	Encourage evolution of scope of Panel expertise over time to mirror new scientific findings Review COI regularly
Identification of clinical scope for guideline	Development of a set of a priori–defined PICO questions	Questions and management strategies rapidly added as information about disease and treatment landscape evolved Bedside clinical lessons and experimental observations about pathogenesis considered on an ongoing basis	Exponential growth of COVID-19 knowledge with newly defined sequelae and treatments, not the relative steady state of other clinical problems Pressure from clinicians, politicians, academia, and the public to provide immediate guidance on a wide range of clinical issues Challenge of determining how often and how rapidly to revise scope	Continuously revise and expand guideline scope to meet urgent clinical and public needs Ensure that guideline content responds to communities' need for guidance Establish a strong supportive infrastructure to meet these needs
Use of available evidence; use of a standardized scheme for grading evidence and strength of recommendations	Systematic review of peer-reviewed manuscripts Discussion of data at scientific meetings before publication	In addition to published data, multiple sources of evidence, including preprints, press releases, and primary data presentations, are reviewed urgently as available	Explosion of literature of uneven quality Non–peer-reviewed publications (presubmission publications, press releases) commonplace Urgency to issue recommendations in face of multiple randomized clinical trials with conflicting results Differing populations included in studies (e.g., different COVID-19 severity) Confounding interventions (e.g., varying degrees of corticosteroid use)	Establish a simple scheme (e.g., standard set of 4 recommendations) to rate strength of recommendations (Appendix Table 1) Establish procedures for timely and rigorous review of evidence, including communicating directly with study investigators Perform reviews with a multidisciplinary team of experts, including biostatisticians Acknowledge and clearly communicate uncertainty Directly address misinformation
Assessment of relative importance of clinical outcomes	A defined set of clinical outcomes are examined and prioritized	A range of outcomes are considered because end points used in trials evolve over time	Ordinal scales not standardized across clinical trials Timing of study outcomes not standardized (e.g., 7 d vs. 28 d) Challenges with determining relative weight to give evolving end points	Incorporate a variety of outcomes into recommendations Prioritize outcomes that are most important during the pandemic (e.g., mortality and time to discharge in setting of overwhelmed health systems)
Volume and pace of new data	Set cutoff dates for systematic literature reviews Predefined and typically limited volume	Weekly evaluations of new evidence Large and unpredictable volume of data available in a very fast pace	Potential for selection bias among panel members as they became aware of new reports New data can delay and/or require changes to guideline updates	Construct Panel teams and choose section leads to continually review emerging evidence Plan for infrastructure support to conduct literature reviews and liaise with study teams

Continued on following page

Appendix Table 1–Continued

Guideline Development Domain	Typical Guideline Processes	Pandemic Modifications to Guideline Processes	Ongoing Challenges	Panel Suggestions for Pandemic Guideline Process
			under development Frequent external contacts of Panel members by investigators globally	
Urgency to make recommendations	Urgency is typically moderate to low Slow guideline uptake into clinical practice	Urgency is high Rapid guideline uptake into clinical practice	Recommendations may have implications for ongoing trials Recommendations may have to change rapidly on the basis of newly released data Recommendations may have to be based on incomplete and non–peer-reviewed data	Establish pathways, such as periodic concise Panel statements, to rapidly update and disseminate recommendations to clinicians and the public Be prepared to modify recommendations as new data emerge that warrant a change
External demands and/or pressure placed on Guidelines Panel	Peer-reviewed evidence of FDA-approved drugs; fewer external influences	Rapid response needed to non–FDA-approved diagnostics and therapeutics Response needed to FDA EUA	Overwhelming need of providers and community for timely answers Overconfidence of community and investigators that newly touted therapy works without any sound evidence FDA EUAs state that products "may be effective," which may be misunderstood by public as endorsement of benefit	Ensure a careful and continuous scientific review process that is protected from political or other external pressures
Publication and distribution	Journals, scientific meetings, and web posting used to disseminate guidelines	Web posting used to continuously update and disseminate guidelines Social media and e-mails to alert users of new updates	Rapidly changing recommendations require frequent announcements of updates	Move guidelines to an entirely web-based format with community updates via social media to rapidly disseminate recommendations

COI = conflict of interest; EUA = emergency use authorization; FDA = U.S. Food and Drug Administration; ID = infectious disease; PICO = population, intervention, comparison, outcomes.

Appendix Table 2. Rating Scheme for Recommendations Used in the NIH COVID-19 Treatment Guidelines

General Panel Recommendation Category	Comments
The Panel recommends using [blank] for the treatment of COVID-19 (rating)	Evidence from clinical trials or large cohort studies demonstrating clinical or virologic efficacy of a therapy The potential benefits of the therapy outweigh the potential risks
There are insufficient data for the Panel to recommend either for or against the use of [blank] for the treatment of COVID-19 (no rating)	Cases with insufficient data to make a recommendation No rating is given for this statement because this is not a recommendation
The Panel recommends against the use of [blank] for the treatment of COVID-19, except in a clinical trial (rating)	For interventions that have not demonstrated efficacy in treatment of COVID-19 and/or have potential safety concerns
The Panel recommends against the use of [blank] for the treatment of COVID-19 (rating)	Cases when well-designed studies have shown that the intervention has no benefit for the treatment of COVID-19 and/or the available data show a safety concern

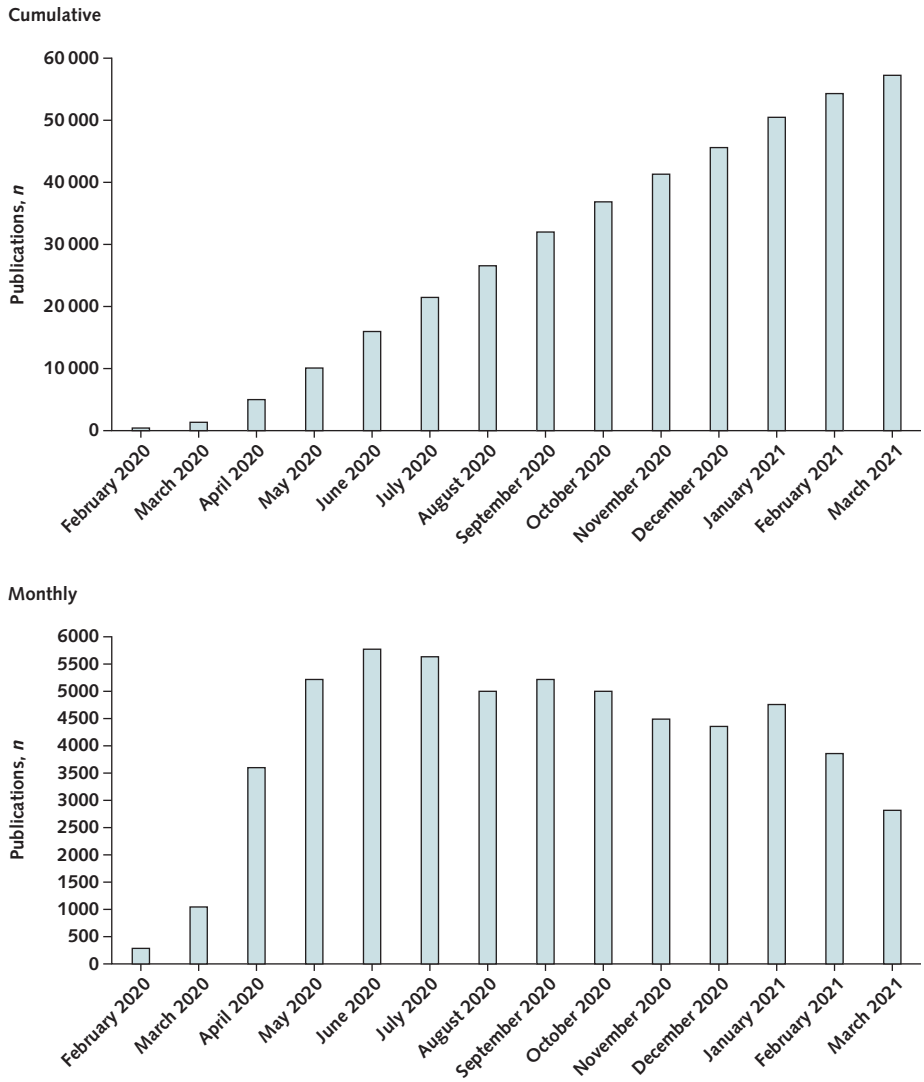
Strength of Recommendation
A: Strong recommendation
B: Moderate recommendation
C: Optional recommendation

Quality of Evidence	
Before November 2020	**After November 2020***
I: One or more randomized trials with clinical outcomes and/or validated laboratory end points	I: One or more randomized trials without major limitations
II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes	IIa: Other randomized trials or subgroup analyses of randomized trials IIb: Nonrandomized trials or observational cohort studies
III: Expert opinion	III: Expert opinion

NIH = National Institutes of Health.

* The rating scale was changed to acknowledge that some randomized trial data may have limitations, specifically that subgroup analyses provide less reliable evidence than the primary analysis in the full study population (e.g., guidelines for individual subgroups on the use of remdesivir based on ACTT-1 [ACCT-1 = Adaptive COVID-19 Treatment Trial 1] or dexamethasone based on RECOVERY [Randomised Evaluation of COVID-19 Therapy]), that the study population may not be clearly defined or is not generalizable, and that trials may be underpowered for the most relevant clinical end points (e.g., mortality).

Appendix Figure. COVID-19 treatment publications on PubMed.



For a detailed explanation of the search strategy, please see the Supplement.