

**Creation and maintenance of a table for assessment of evolving evidence for COVID-19–
related treatments**

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Purpose. This report describes the development and maintenance of a table to present an assessment of evidence for treatments used in patients with coronavirus disease 2019 (COVID-19).

Summary. AHFS Drug Information (AHFS DI) (American Society of Health-System Pharmacists, Bethesda, MD) is ASHP's evidence-based drug compendium that contains drug monographs written for pharmacists and other healthcare professionals. The professional editorial and analytical staff of pharmacists critically evaluate published evidence to develop drug monographs for AHFS DI. In response to the global COVID-19 pandemic, these skills were applied to assess emerging evidence for COVID-19–related treatments, and the information was compiled into a new resource for pharmacists and other healthcare professionals to use at the point of care. A list of therapies was developed and prioritized based on review of scientific and public discussions on the use of these therapies in patients with COVID-19; certain therapies used for supportive care and therapies that might theoretically be harmful to patients with COVID-19 also were considered for inclusion. Potential treatments were identified, and the evidence for use in patients with COVID-19 was assessed and summarized in a table format. Information presented for each therapy included the rationale for use, summaries of clinical trials or experience, trial registry numbers, and dosage regimens. Comments on safety and efficacy, including limitations of available data, were presented along with recommendations from recognized authorities. The editorial team continued to add new therapies to the table and update existing entries as new evidence emerged.

Conclusion. A comprehensive table that summarized available evidence for potential treatments for patients with COVID-19 was developed. The table format enabled the drug

information editorial staff to provide ongoing updates as new information emerged during the pandemic.

Keywords: COVID-19, COVID-19 drug treatment, drug information, evidence-based practice, pandemics

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The worldwide outbreak of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a global pandemic on March 11, 2020,¹ and by the end of March more than 750,000 cases and more than 36,000 deaths had already been reported worldwide (including more than 140,000 cases and more than 2,300 deaths in the United States).² New information with respect to the clinical characteristics and clinical course of COVID-19 and possible strategies for management of the disease was emerging daily. At that time, treatment consisted mostly of supportive care while a variety of investigational agents and therapeutic strategies were being explored. Multiple clinical trials were already in progress and many more were being initiated to evaluate a number of potential, but unproven, therapies.^{3,4,6-8} News media widely disseminated stories of various therapies that were being used or suggested as potential treatments; however, that information was often lacking in appropriate context and evidentiary support.^{5,8} Healthcare professionals were faced with the challenge of monitoring a rapidly expanding volume of clinical research findings that often were based on uncontrolled, unpublished, and/or non-peer-reviewed studies. There was a clear need for reliable and evidence-based information on drugs and other therapies that could be used appropriately for the management of COVID-19 and its complications.³⁻⁹

To support pharmacists and other healthcare professionals in making informed decisions about the use of various drugs and other treatments in patients with COVID-19, the drug information staff of an evidence-based drug information compendium decided to create a concise quick-reference document that would summarize the emerging evidence. The goal was to provide a succinct compilation of the existing evidence to provide nuance and perspective to early information being disseminated from various sources. Later efforts were directed at maintaining and enhancing the summaries as new information emerged.

Background

AHFS Drug Information (AHFS DI) (American Society of Health-System Pharmacists, Bethesda, MD) is ASHP's evidence-based drug compendium that contains drug monographs written for pharmacists and other healthcare professionals. The mission of AHFS DI is to provide an evidence-based foundation for safe and effective drug therapy. The professional editorial and analytical staff of pharmacists critically evaluates published evidence on various drugs and biologics to develop monographs for AHFS DI. The well-established editorial processes of AHFS DI were used to inform an assessment of evolving evidence related to therapies under consideration for the treatment of COVID-19; the goal was to provide a succinct summary of the evidence that clinicians could use as a quick resource guide when making treatment decisions or responding to queries about possible COVID-19 treatments.

Developing an initial list of COVID-19–related treatments

To select drugs and biologics for inclusion in AHFS's initial Assessment of Evidence for COVID-19-Related Treatments Table that was published online at the ASHP COVID-19 Resource Center on March 21, 2020, the AHFS DI editorial staff collectively compiled a list of various therapies that were being investigated for use in patients with COVID-19. The editorial staff decided to address therapies used in the earliest stages of the pandemic as well as therapies with potential or confirmed in vitro antiviral activity against SARS-CoV-2, certain supportive care agents, and drugs that theoretically might be harmful to patients with COVID-19. Compilation of the list of drugs included in the first iteration of the table was informed by initial case reports and small studies of early experience with COVID-19 in

China, information from the World Health Organization (WHO) regarding possible COVID-19 treatments, and previous treatment experience with other coronaviruses. In addition, therapies that were being discussed in the context of COVID-19 in prominent news stories from both medical and general media outlets, as well as among the members of ASHP, also were considered. Because knowledge regarding the pathogenesis and optimum management of COVID-19 was rapidly evolving, some of the therapies were prioritized for inclusion in the evidence table based only on biologically plausible, but unproven, mechanisms and/or anecdotal observations or widespread discussion. The initial list of drugs was viewed as a starting point for this new resource, and the evidence table was designed as a living document that could be updated and expanded as needed to ensure currency and relevance, reflecting the evolving changes in therapeutic perspectives.

Research and evidence assessment

Potential therapies identified for inclusion in the initial evidence table were divided among the AHFS DI editorial team, primarily based on each individual's therapeutic areas of expertise. Each individual was given the responsibility of researching, assessing, and creating table entries to summarize the available information for their assigned table entries. Members of the team also were responsible for continuously monitoring emerging evidence and updating their table entries as well as recommending additional therapeutic agents that should be added to the table. Members of the team worked collaboratively when information sources applied to multiple table entries. All table entries were written by the AHFS DI professional editorial and analytical staff and were then reviewed for accuracy against the cited references by other members of the group before publication.

The data collection strategy used for the initial table entries and subsequent table revisions consisted of traditional literature searches of the US National Library of Medicine's PubMed database to identify pertinent published articles using keywords related to COVID-19 and the index drug name; topic-specific terms related to the drug's mechanism of action or use in critical care or for treatment of other respiratory viral illnesses also were used. Although not a customary practice when evaluating data for AHFS DI drug monographs, inclusion of information based on selected preprint (non-peer-reviewed) articles in the table was allowed if considered necessary for timely dissemination of information. Searches of the National Library of Medicine clinical trials database (ClinicalTrials.gov) were conducted to identify clinical trial protocols indicating that a potential treatment was being investigated. Other sources included the Food and Drug Administration (FDA) and expert recommendations from the National Institutes of Health (NIH), WHO, US Centers for Disease Control and Prevention (CDC), and other professional organizations such as the Infectious Diseases Society of America (IDSA), American Heart Association (AHA), and Society for Critical Care Medicine (SCCM). In addition, selected news media sources (eg, press releases) and manufacturer websites were monitored; in most cases, such secondary sources were used to inform the evidence rather than as cited references. During the early stages of the pandemic, information also was sought from trial registries in other countries (eg, China, Japan) and treatment protocols issued in other countries (eg, those published by the National Health Commission in China).

The merits of the information retrieved were evaluated, and the totality of the evidence was considered. Peer-reviewed publications of well-designed clinical trials and recommendations from FDA, NIH, and other authoritative organizations were prioritized as primary references. If initial information was limited to clinical trial protocols, press

releases, news reports, or preliminary (non–peer-reviewed) articles and was considered acceptable for the purposes of the evidence table, such sources were replaced as soon as published studies became available.

Evidence table format and content

Selection of a table format for presentation of the evidence summaries enabled presentation of information succinctly while still allowing inclusion of important details about clinical trial protocols and results, including limitations; this format also facilitated creation of a living document that could be easily expanded and updated as additional evidence accrued. A 6-column format was adopted as the most efficient way to organize and present information in the evidence table. The column headings and corresponding information presented are described below.

Drug (or Biologic) Name. Drugs usually were listed individually; however, some entries were for groups of drugs when a class effect was discussed (eg, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers).

AHFS Class. This column indicated the usual classification of the drug(s) within the AHFS Pharmacologic-Therapeutic Classification system (eg, Antivirals 8:18, Antimalarials 8:30.08, HIV Protease Inhibitors 8:18.08.08, Adrenals 68:04, Antineoplastic Agents 10:00, Disease-modifying Antirheumatic Drugs 92:36). Classifications also were provided for drugs that were included but not approved in the United States to give additional therapeutic perspective.

Rationale. To provide context, particularly when evidence was preliminary or the proposed use was based on untested hypotheses, a brief description of the rationale for exploring the drug's use or possible adverse effects in patients with COVID-19 was provided.

Trials or Clinical Experience. The type of information (eg, case study or series; retrospective, observational study; randomized, controlled, comparative trial) available was presented. In many cases, trials that were in the planning or recruiting stages were listed or, in some cases, described, and the trial registry number was provided. Results of trials were presented; evidence based on preliminary results or interim analysis was presented when available but identified as preliminary. Major limitations of studies were noted. If initial evidence was related to clinical experience or studies in patients with other infections, such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), or other conditions that might provide relevant insights, such as sepsis and acute respiratory distress syndrome (ARDS), the information was described as such. Data from studies that were later retracted were identified.

Dosage. Dosages presented were those used in selected clinical studies or that were being investigated in selected registered studies. Dosages used in these trials often varied. If an emergency use authorization (EUA) was issued by FDA, that dosage was included.

Comments. Conclusions and other comments on safety and efficacy of the drug(s) in patients with COVID-19, including limitations of available data, were presented. Recommendations from recognized authorities, including statements from FDA (eg, MedWatch alerts, EUAs), NIH (eg, recommendations of the COVID-19 Treatment Guidelines Panel), WHO, CDC, IDSA, and the Surviving Sepsis Campaign, were included.

References. A separate list of references for each drug or drug class was provided in each edition of the COVID-19 evidence table. When available, the citations included digital object identifiers (DOIs), PubMed IDs (PMIDs), or URLs for the published articles to enable the user to easily find and retrieve the references. Citations for early-release articles were

updated as the articles proceeded to final publication. Articles that publishers identified as not yet having undergone peer review were noted as such in the reference citation. Articles that were later retracted were identified.

Evidence table updates and maintenance

The first version of the Assessment of Evidence for COVID-19-Related Treatments table was published on the ASHP COVID-19 Resource Center on March 21, 2020. Revisions to update the information began almost immediately, and the second version was published 3 days later. Subsequent table revisions were published as frequently as needed to add new table entries and revise existing entries to maintain currency.

Because the information on COVID-19 was evolving at such a rapid pace, the AHFS DI editorial team continued to monitor the evidence on a regular basis, sometimes daily, and promptly assessed and incorporated emerging evidence. Ongoing developments and research were monitored by reviewing new information from FDA, NIH, WHO, CDC, and IDSA, as well as the PubMed database, study protocols from ClinicalTrials.gov, and other sources as detailed in the “Research and Evidence Assessment” section. Selected news media also were included in the surveillance of information to provide insights into emerging interest in other therapies that might be added to the list. In addition, queries and discussions within the membership of ASHP informed the monitoring process.

The editorial team updated the evidence table as new information was identified. New therapies were added using essentially the same criteria that were used for the first iteration of the table, and existing entries were updated by the assigned editorial team member. The goal was to keep up with the current state of knowledge for each therapy as understanding of the COVID-19 disease process progressed. New information generally was

added to an existing entry (rather than entirely replacing existing text) to provide a comprehensive narrative of the evolving evidence related to the role of the therapeutic agent in treating patients with COVID-19. Each entry included the date on which it was last revised.

The most recent version of the Assessment of Evidence for COVID-19-Related Treatments table can be accessed at <https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx> within the ASHP COVID-19 Resource Center.

As of August 20, 2020, the 34th edition of the evidence table had been published. The 34th edition included 37 table entries, compared with 15 in the original version. The median number of references per drug or drug class had increased from 5.5 (range, 1-14) in the original version to 14 (range, 3-61) in the 34th edition.

Conclusion

A comprehensive table was developed to provide a summary of available evidence for various therapies being investigated or used in patients with COVID-19 to inform and support pharmacists and other clinicians as they make therapeutic decisions while caring for patients with the disease. The evidence table format enabled the AHFS DI staff to provide ongoing updates as new information became available during the pandemic.

Given the fluid nature of the COVID-19 pandemic, the conclusion for most drugs assessed to date was that additional research is required to definitively establish the safety and efficacy of any given therapy.

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Disclosures

At the time of this project, Ms. Snow was editor-in-chief of AHFS Drug Information, ASHP, and has since retired. Dr. Miller is senior associate editor of AHFS Drug Information, ASHP. Ms. Kester is associate editor of AHFS Drug Information, ASHP. Dr. Mendham is associate editor of AHFS Drug Information, ASHP. Ms. Heydorn is assistant editor of AHFS Drug Information, ASHP. Dr. Huang is assistant editor of AHFS Drug Information, ASHP. Dr. Leu is oncology specialist assistant editor of AHFS Drug Information, ASHP. Dr. Kohoutek is assistant editor for injectables for the Handbook on Injectable Drugs, ASHP. Dr. Rosanelli is senior drug information analyst for AHFS Drug Information, ASHP. At the time of this project, Dr. Harves was drug information analyst for AHFS Drug Information, ASHP.

Key Points

- During the initial phase of the COVID-19 pandemic in the United States, information on appropriate therapies was often incomplete or apparently based on preliminary information.
- The professional editorial and analytical staff of AHFS Drug Information (AHFS DI) evaluated available information and created an evidence assessment table that summarized the findings, including research in progress, limitations of available data, and recommendations from recognized authorities.

- The drug information editorial staff continued to update the table as new information emerged during the pandemic.

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