

# Open-source institutional guideline recommendations during the COVID-19 pandemic

**Curtis D. Collins, PharmD, MS,**  
Department of Pharmacy Services, St.  
Joseph Mercy Health System, Ann Arbor,  
MI

**Jean Huang, PharmD,** Department of  
Pharmacy Services, St. Joseph Mercy  
Health System, Ann Arbor, MI

**Brian A. Potoski, PharmD,**  
Departments of Pharmacy and  
Therapeutics and Medicine, University of  
Pittsburgh, Pittsburgh, PA

**Purpose.** The global coronavirus disease 2019 (COVID-19) pandemic and the search for ways in which to provide the best available care have created unprecedented times in terms of rapidly evolving reports of available treatment options. The primary objective of our analysis was to categorize online, open-source guidance to determine how US institutions approached their recommendations for management of patients with COVID-19 in the early weeks of the pandemic.

**Methods.** A search for open-source, online institutional guidelines for the treatment of COVID-19 was conducted using predefined criteria. The search was limited to the United States and conducted from April 12 through 14, 2020, and again on April 22, 2020. Searches were conducted at 2 points in time in order to identify changes in treatment recommendations due to evolving literature or institutional experience. Treatment recommendations, including guidance on antiviral therapy, corticosteroid and interleukin-6 inhibitor use, and nutritional supplementation were compared.

**Results.** Of the 105 institutions that met initial screening criteria, 14 institutions (13.3%) had online COVID-19 guidance available. Supportive care and clinical trial enrollment were the primary recommendations in all evaluated guidance. Recommendations to consider antimicrobial and adjunctive therapy varied. Eighty-six percent of guidelines contained recommendations for use, or consideration of use, of hydroxychloroquine. Guidance from 2 institutions mentioned use of hydroxychloroquine and azithromycin in combination. Of the 13 institutions listing hydroxychloroquine dosing recommendations, 62% recommended maintenance dosing of 200 mg twice daily. Infectious diseases or other specialty consultation was required by 89% of institutions using interleukin-6 inhibitors for COVID-19 management.

**Conclusion.** Overall, the analysis revealed variability in treatment or supplemental pharmacologic therapy for the management of COVID-19.

**Keywords:** antimicrobial stewardship, COVID-19, guidelines, pandemic, pharmacy

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Address correspondence to Dr. Collins  
([curtis.collins@stjoeshealth.org](mailto:curtis.collins@stjoeshealth.org)).

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The global coronavirus disease 2019 (COVID-19) pandemic and the search for ways in which to provide the best available care have created unprecedented challenges in terms of the rapidly evolving reports of available treatment options. Reports have emerged from traditional and nontraditional sources and across multiple outlets.<sup>1</sup> During the early course of the disease response

in the United States, there was a lack of consensus guidelines and varying recommendations existed in international and early-emerging society guidance.<sup>2,3</sup>

Without clear evidence to guide clinicians in management of COVID-19, institutions were strained to quickly evaluate this onslaught of evidence to develop facility-specific guidance. Decision makers often turn

to the infectious diseases (ID) community at large to gauge how peers are interpreting literature. The lack of published consensus guidelines and limited amount of high-quality evidence have, perhaps now more than ever, prompted institutions to augment their expert interpretations with online and available resources. The primary objective of the analysis described here was to categorize online, open-source guidance to determine how institutions have approached their recommendations for management of patients with COVID-19.

## Methods

A Web search for open-source, online institutional guidelines on the treatment of COVID-19 published by institutions currently holding the Infectious Diseases Society of America (IDSA) Antimicrobial Stewardship Center of Excellence designation<sup>4</sup> was conducted. Search queries consisted of each identified center's name plus "antimicrobial stewardship" or "COVID-19." This search was supplemented by a review of institutional COVID-19 guidelines listed on the popular website IDStewardship.com, as well as the Society for Healthcare Epidemiology of America's list of institutional guidelines for COVID-19 and links to institutional antimicrobial stewardship resources.<sup>5,6</sup> The search was limited to US facilities and conducted from April 12 through April 14, 2020, and again on April 22, 2020. The second analysis was limited to institutions identified as having open-source guidance available during the first review period. Searches were conducted at 2 points in time in order to identify changes in treatment recommendations due to evolving literature or institutional experience. Several notable publications were released during the analysis. IDSA guidelines on the treatment and management of patients with COVID-19 were published online on April 11, 2020, and COVID-19 treatment guidelines were published by the National Institutes of Health (NIH) on April 21, 2020.<sup>7,8</sup> We theorized that the April 11 release would not impact

## KEY POINTS

- Online, open-source guidelines were evaluated to determine how institutions approached their recommendations for management of patients with coronavirus disease 2019 (COVID-19) at an early peak of the pandemic in the United States.
- Results of the analysis showed that outside of supportive care and clinical trial enrollment, recommendations to consider antimicrobial and adjunctive therapies varied.
- Variability in treatment or supplemental pharmacologic therapy recommendations underscored the challenges faced by decision makers early in the COVID-19 pandemic.

results of our first search (on April 12-14) and that institutional guidelines might change prior to the second review. Similarly, we theorized that any updates following the NIH document release on April 21 would not yet be reflected in our April 22 analysis. Document update dates were confirmed upon review at both time points. Both reviews occurred prior to release of the Food and Drug Administration drug safety communication regarding hydroxychloroquine and chloroquine on April 24, 2020.<sup>9</sup> Summary categorizations were from the first review time period, and changes between time periods were noted.

In order to gauge the availability of clinical trial enrollment at identified institutions, a registry search of ClinicalTrials.gov was performed to review institutions enrolled in clinical trials in the United States focused on COVID-19. Search terms included drug names (ie, hydroxychloroquine, remdesivir, tocilizumab, sarilumab, and lopinavir/ritonavir) plus "coronavirus";

and "convalescent plasma." The date of trial enrollment and whether an institution was enrolling patients during the study time period were noted. The institution listing for a trial of sarilumab (ClinicalTrials.gov identifier, NCT04315298) was undetermined and thus excluded from the analysis.<sup>10</sup> The study was determined to be exempt from institutional review board review.

Institutional treatment recommendations (including the need for ID or other provider authorization for use) for antiviral, corticosteroid, and interleukin-6 inhibitor therapy, as well as recommendations on use of antimicrobials, procalcitonin monitoring, and nutritional supplementation and accompanying recommendations, were compared. Categorization of guidance (ie, whether an action was to be considered vs recommended) was based on whether consideration was specifically listed either in summary for the entire guideline or specifically for individualized therapy. The dosing recommendations for hydroxychloroquine were noted due to uncertainty in standard dosing recommendations for use in COVID-19. Procalcitonin monitoring was included as the lone laboratory testing-related item of interest because of early discussion of its potential utility in guiding antimicrobial use for treatment of patients with COVID-19.

## Results

One-hundred five institutions designated as IDSA antimicrobial stewardship Centers of Excellence were identified. Of these, 14 institutions (13.3%) had guidance for COVID-19 available (Table 1). A majority of the 14 institutions (86%) were academic medical centers, with an average reported bed count of 900<sup>11</sup>; 8 institutions were IDSA-designated Centers of Excellence. The guidance provided by all institutions stated that supportive care was preferred, that there was little evidence to guide treatment, and that assessment of patients with COVID-19 for clinical trial enrollment was recommended. Twelve institutions (86%) were enrolled in at least 1 registered

**Table 1. Summary of Institutional Guideline Recommendations on COVID-19 Management**

Variable	No. (%) of Institutions in Study Cohort (n = 14)
Institution bed capacity <sup>11</sup>	900 (242.4) <sup>a</sup>
Institution teaching affiliation	
Academic	12 (86)
Community teaching hospital	2 (14)
Supportive care primary recommendation	14 (100)
ID consultation	
Required	2 (14)
Encouraged	8 (57)
Not specified	4 (29)
Therapy recommendations	
Evaluate for clinical trial enrollment	14 (100)
Hydroxychloroquine or chloroquine monotherapy <sup>b</sup>	
Available evidence did not support use	2 (14)
Recommended based on clinical criteria	2 (14)
Consider with ID or other party approval/discussion	5 (36)
Consider based on clinical severity; no ID approval required	3 (21)
Recommended based on clinical criteria in combination with azithromycin	2 (14)
Hydroxychloroquine and azithromycin combination	
Not recommended or not mentioned	11 (79)
Consider based on clinical criteria	1 (7)
Consider based on clinical criteria with ID consultation	1 (7)
Alternative to hydroxychloroquine monotherapy with ID discussion	1 (7)
Hydroxychloroquine dosing <sup>c</sup>	
400 mg twice daily for 1 day, then 200 mg twice daily	8 (62)
400 mg twice daily for 1 day, then 400 mg daily	3 (23)
Multiple options, including 200 mg 3 times daily for maintenance dosing	2 (15)
Hydroxychloroquine duration <sup>c</sup>	
5 days	10 (77)
5 to 7 or 5 to 10 days	3 (23)
Remdesivir clinical trial	12 (86)
Lopinavir/ritonavir	
Not recommended or only as part of a clinical trial	7 (50)
Not mentioned or information only	3 (21)
Alternative to hydroxychloroquine with ID approval	3 (21)
Alternative to hydroxychloroquine	1 (7)
Interleukin-6 inhibitors	
Consideration within guidance	9 (64)
ID or other specialist consultation recommended or required	8 (57)

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Variable	No. (%) of Institutions in Study Cohort (n = 14)
Not recommended or only in context of a clinical trial	4 (29)
Not mentioned	1 (7)
Corticosteroids	
Not recommended for routine use without additional indications <sup>2</sup>	9 (64)
Not mentioned or no decision	3 (21)
Consider if sudden decline in patient status	2 (14)

Abbreviation: ID, infectious diseases.

<sup>a</sup>Expressed as mean (SD).

<sup>b</sup>Four institutions listed chloroquine as an alternative to hydroxychloroquine.

<sup>c</sup>Among 13 institutions listing dosing recommendations.

COVID-19–related clinical trial. Four institutions (29%) were enrolled in and recruiting for hydroxychloroquine trials. Twelve (86%) and 2 institutions (14%) were enrolled in and recruiting in remdesivir and tocilizumab trials, respectively. No institutions were identified as enrolled in and recruiting for studies of either lopinavir/ritonavir or convalescent plasma. ID consultation for COVID-19 management was recommended or required in guidelines from 10 institutions (71%).

Two institutions (14%) had determined that available evidence did not support use of hydroxychloroquine outside of a clinical trial; another 2 institutions (14%) recommended use based on clinical severity. Consideration of hydroxychloroquine use with approval by a designated party (eg, an ID physician) was recommended by 5 institutions (36%), while 3 (21%) recommended consideration based on clinical severity without the need for authorization. Chloroquine was listed as an alternative to hydroxychloroquine by 3 institutions (21%).

Eight institutions (57%) recommended against utilization of the combination of hydroxychloroquine and azithromycin, and 3 (21%) did not mention the combination. One institution (7%) listed combination therapy with hydroxychloroquine and azithromycin as a primary recommendation when

antiviral agents were used based on clinical criteria, and another institution recommended consideration of hydroxychloroquine in combination with azithromycin or zinc in conjunction with ID consultation; 1 institution (7%) listed the combination as an alternative following discussion with an ID provider.

Of the 13 institutions listing hydroxychloroquine dosing recommendations, 8 (62%) recommended a maintenance dose of 200 mg administered twice daily. Ten institutions (77%) listed a hydroxychloroquine therapy duration of 5 days, and 3 institutions (23%) recommended courses of 5 to 7 or 10 days.

Lopinavir/ritonavir was listed as an alternative treatment in guidance from 4 institutions (29%). Interleukin-6 inhibitors were not recommended or were recommended only in the context of a clinical trial in 4 guidelines (29%) and not mentioned in 1 guideline (7%). In the remaining 9 institutions (64%), ID or other specialty consultation was required by all but 1 institution. Corticosteroids were not recommended as a part of COVID-19 treatment guidance without additional indications for use in 9 institutions (64%). Two institutions (14%) recommended consideration of corticosteroids to prevent rapid COVID-19 progression.

In all evaluated guidance, antibiotics were not recommended outside of use for suspected or confirmed infections. Five institutions (36%) mentioned procalcitonin monitoring. Of these, 1 institution (7%) recommended procalcitonin testing as part of daily laboratory monitoring, while the remaining institutions recommended it in consideration of existing guidance. Nutritional supplementation was not addressed in 57% of guidance documents. Ascorbic acid was recommended for routine use by 1 institution (7%), and use of zinc was recommended in 2 facilities (14%).

Ten institutions (71%) updated guidance and 1 link became unavailable between the 2 evaluation periods. Updates included expansion of clinical trial availability ( $n = 3$ ), inclusion of additional nutritional supplementation information ( $n = 3$ ), revised criteria for interleukin-6 inhibitor initiation ( $n = 2$ ); 1 institution that initially recommended use of hydroxychloroquine in combination with azithromycin changed to recommending hydroxychloroquine alone.

## Discussion

The COVID-19 pandemic and associated clinical course of disease have presented several significant challenges to the medical community. One challenge is whether infected and

symptomatic patients should receive more than supportive care to possibly mitigate poor patient outcomes due to COVID-19. Overall, the data presented here represent a snapshot of recommendations across institutions, revealing some variability in treatment or supplemental pharmacologic therapy.

In addition to open-source institutional guidance, decision makers also were supported by professional societies such as the American Society of Health-System Pharmacists and the Society of Infectious Diseases Pharmacists, which provided timely expert review of available literature and emerging practices. Society support, online resources such as the aforementioned IDStewardship.com website, and the professional and social networks that are a hallmark of the pharmacy and medical communities, all undoubtedly facilitated institutional recommendations early in the pandemic. Often, these organizations were unable to provide definitive recommendations for emerging treatment options outside of supportive care as standard therapy due to a lack of high-quality evidence. Our analysis provides perspective on how evidence across the continuum was evaluated and implemented by institutions locally.

Our analysis had several limitations. First, it was beyond the scope of the study to determine actual utilization, adherence to recommendations, or the volume of clinical trial enrollment. Whether guidance significantly drove use is unknown. Another limitation was that interpretation of guideline recommendations was left to the authors, who had to gauge the intent and meaning of the recommendations. Interpretation of guideline recommendations from an outsider's perspective lacked the additional insights provided by internal communications clarifying the intended direction of recommendations within a particular institution; thus our categorization of ambiguous recommendations at a limited number of decision points was an acknowledged limitation. It is also unknown whether there were delays in updating

open-source guidelines, which consequently may not reflect changes communicated through other mechanisms internally. We feel this was somewhat mitigated by our follow-up snapshot review. It is also likely that guidance was formulated prior to the availability of associated adverse drug event data in the setting of COVID-19 that would otherwise change the risk/benefit determination.<sup>9</sup> That said, the majority of recommendations did not change following publication of IDSA guidelines; however, guidelines may have significantly changed in subsequent weeks following completion of our review.<sup>7</sup>

Those limitations aside, the observed variability in guidelines could potentially reflect the challenges institutions faced during a forced rapid decision-making process. In the face of low-quality evidence, preprint releases including interim analyses, or other non-peer-reviewed data that may impact practice when the perceived risk/benefit relationship is undefined and poorly informed, it is likely that risk/benefit calculations conventionally focused on objectivity were influenced to some degree. It is also likely that given the high visibility of COVID-19 and the desire for health systems to truncate the disease course with the hope for positive outcomes while avoiding overwhelming local hospital resources, it was difficult for institutions to “don't just do something, stand there.”<sup>12</sup>

As experience and high-quality data accrue over time, a robust and ongoing retrospective evaluation should be undertaken by institutions and professional societies alike. Collective discourse on the pros and cons of utilizing, or not utilizing, therapies with potentially beneficial (or harmful) consequences amongst all the challenges mentioned previously is warranted. This evaluation will allow for the identification of opportunities for improvement in both initial and adaptive responses to unproven therapeutic interventions, given the timeline of available information and their acknowledged limitations. It is in this way that we stand to be best prepared in the

future, given the potential parallels that may exist in the next epidemic.

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## Disclosures

Dr. Collins reports a consulting arrangement with ASHP Consulting. The other authors have declared no potential conflicts of interest.

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