

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Authors

Adarsh Bhimraj¹, Rebecca L. Morgan², Amy Hirsch Shumaker³, Valery Lavergne⁴, Lindsey Baden⁵, Vincent Chi-Chung Cheng⁶, Kathryn M. Edwards⁷, Rajesh Gandhi⁸, Jason Gallagher⁹, William J. Muller¹⁰, John C. O'Horo¹¹, Shmuel Shoham¹², M. Hassan Murad¹³, Reem A. Mustafa¹⁴, Shahnaz Sultan¹⁵, Yngve Falck-Ytter³

Affiliations

¹Department of Infectious Diseases, Cleveland Clinic, Cleveland, Ohio

²Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario

³VA Northeast Ohio Healthcare System, Case Western Reserve University School of Medicine, Cleveland, Ohio

⁴Department of Pathology and Laboratory Medicine, Vancouver General Hospital, Vancouver, British Columbia, Canada

⁵Brigham and Women's Hospital, Boston, Massachusetts

⁶Queen Mary Hospital, Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

⁷Division of Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee

⁸Infectious Diseases Division, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

⁹Department of Pharmacy Practice, Temple University, Philadelphia, Pennsylvania

¹⁰Division of Pediatric Infectious Diseases, Northwestern University, Chicago, Illinois

¹¹Division of Infectious Diseases, Joint Appointment Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota

¹²Johns Hopkins University School of Medicine, Baltimore, Maryland

¹³Division of Preventive Medicine, Mayo Clinic, Rochester, Minnesota

¹⁴Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas

¹⁵Division of Gastroenterology, Hepatology, and Nutrition, University of Minnesota, Minneapolis VA Healthcare System, Minneapolis, Minnesota

Corresponding Author: Adarsh Bhimraj

Panel Members: Adarsh Bhimraj (lead), Lindsey Baden, Vincent Chi-Chung Cheng, Kathryn M. Edwards, Rajesh Gandhi, Jason Gallagher, William J. Muller, John C. O’Horo, Shmuel Shoham, Amy Hirsch Shumaker

Methodologists: Yngve Falck-Ytter (lead), Rebecca L. Morgan, Valery Lavergne, M. Hassan Murad, Reem A. Mustafa, Shahnaz Sultan

Abstract

Background: There are many pharmacologic therapies that are being used or considered for treatment of coronavirus disease 2019 (COVID-19). There is a need for frequently updated practice guidelines on their use, based on critical evaluation of rapidly emerging literature.

Objective: Develop evidence-based rapid guidelines intended to support patients, clinicians and other health-care professionals in their decisions about treatment and management of patients with COVID-19.

Methods: In March 2020, the Infectious Diseases Society of America (IDSA) formed a multidisciplinary guideline panel of infectious disease clinicians, pharmacists, and methodologists with varied areas of expertise. The process followed a rapid recommendation checklist. The panel prioritized questions and outcomes. Then a systematic review of the peer-reviewed and grey literature was conducted. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence and make recommendations.

Results: On April 11, 2020, [IDSA released online](#) initial treatment recommendations and narrative summaries of other treatments under evaluation. Since that time, the guideline panel and methodologists have continued to monitor the literature and issue updates and addendums to these guidelines in response to evolving research.

Conclusions: Since the inception of its work, the panel has expressed the overarching goal that patients be recruited into ongoing trials, which would provide much needed evidence on the efficacy and safety of various therapies for COVID-19, given that we could not make a determination whether the benefits outweigh harms for most treatments.

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Executive Summary

Coronavirus disease 2019 (COVID-19) is a pandemic with a rapidly increasing incidence of infections and deaths. Many pharmacologic therapies are being used or considered for treatment. Given the rapidity of emerging literature, the Infectious Diseases Society of America (IDSA) identified the need to develop living, frequently updated evidence-based guidelines to support patients, clinicians and other health-care professionals in their decisions about treatment and management of patients with COVID-19.

Summarized below are the recommendations with comments related to the clinical practice guideline for the treatment and management of COVID-19. A detailed description of background, methods, evidence summary and rationale that support each recommendation, and research needs can be found online in the full text. In brief, per Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, recommendations are labeled as “strong” or “conditional”. The word “recommend” indicates strong recommendations and “suggest” indicates conditional recommendations. In situations where promising interventions were judged to have insufficient evidence of benefit to support their use and with potential appreciable harms or costs, the expert panel recommended their use in the context of a clinical trial. These recommendations acknowledge the current “knowledge gap” and aim at avoiding premature favorable recommendations for potentially ineffective or harmful interventions.

Recommendation 1. Among patients with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine only in the context of a clinical trial. (Knowledge gap)

Recommendation 2. Among patients with COVID-19, the IDSA guideline panel suggests against hydroxychloroquine/chloroquine plus azithromycin outside of the context of a clinical trial. (Conditional recommendation, Very low certainty of evidence)

Recommendation 3. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir only in the context of a clinical trial. (Knowledge gap)

Recommendation 4. Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence)

Recommendation 5. Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap)

Recommendation 6. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap)

Recommendation 7. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial. (Knowledge gap)

Recommendation 8. Among hospitalized patients with severe* COVID-19, the IDSA panel suggests remdesivir over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence)

- *Remark:* For consideration in contingency or crisis capacity settings (i.e. limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in

those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or extracorporeal mechanical oxygenation (ECMO).

Recommendation 9. Among patients with severe COVID-19 on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, Low certainty of evidence)

- *Remark:* In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.

*Severe illness is defined as patients with $SpO_2 \leq 94\%$ on room air, including patients on supplemental oxygen, on mechanical ventilation and ECMO.

Recommendation 10. Among hospitalized patients with severe COVID-19, the IDSA panel suggests against famotidine use for the sole purpose of treating COVID-19 outside of the context of a clinical trial. (Conditional recommendation, Very low certainty of evidence)

Since the inception of its work, the panel has expressed the overarching goal that patients be recruited into ongoing trials, which would provide much needed evidence on the efficacy and safety of various therapies for COVID-19. The panel has determined that when an explicit trade-off between highly uncertain benefits and known putative harms of these therapeutic agents were considered, a net positive benefit was not reached and could possibly be negative (risk of excess harm). The panel acknowledges that enrolling patients in randomized controlled trials (RCTs) might not be feasible for many frontline providers due to limited access and infrastructure. Should lack of access to clinical trials exist, we encourage setting up local or collaborative registries to systematically evaluate the efficacy and safety of drugs to contribute to the knowledge base. Each clinician can play a role in advancing our understanding of this disease through a local registry or other data collection efforts.

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Background

The first cases of COVID-19 were reported from Wuhan, China in early December 2019 [1], now known to be caused by a novel beta-coronavirus, named as Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Within a span of months, COVID-19 has become pandemic due to its transmissibility, spreading across continents with the number of cases and deaths rising daily [2]. Although most infected individuals exhibit a mild illness (80%+), 14% have serious and 5% have critical illness. Approximately 10% will require hospital admission due to COVID-19 pneumonia, of which approximately 10% will require ICU care, including invasive ventilation due to acute respiratory distress syndrome (ARDS) [3]. While mortality appears to be more common in older individuals and those with comorbidities, such as chronic lung disease, cardiovascular disease, hypertension and diabetes, young people with no comorbidities also appear to be at risk for critical illness including multi-organ failure and death.

There has been an expanding number of studies rapidly published online and in academic journals; however, some of these may be of limited quality and are pre-published without sufficient peer-review. Critical appraisal of the existing studies is needed to determine if the existing evidence is sufficient to support currently proposed management strategies.

Given the rapid global spread of SARS CoV-2 and the difficulty for the overburdened front-line providers and policymakers to stay up to date on emerging literature, IDSA has recognized the necessity of developing a rapid guideline for the treatment of COVID-19. The guideline panel is using a methodologically rigorous process for evaluating the best available evidence and providing treatment recommendations. Two additional guidelines on diagnostic testing and infection prevention also have been developed. These guidelines will be frequently updated as substantive literature becomes available and are accessible on an easy to navigate web and device interface at <http://www.idsociety.org/covid19guidelines>.

There continue to be several ongoing trials evaluating therapeutic agents for the treatment of COVID-19. As data becomes available from these trials and if there is a preponderance of evidence to suggest the use of a therapeutic agent even in the context of clinical trials is no longer warranted it will be removed from future updates of the guideline

(and the removal will be noted in the updated guidelines). If there is emerging evidence on the efficacy or safety of a therapeutic agent not mentioned in the current version of the guideline it will be included in future updates of the guideline.

These recommendations are intended to inform patients, clinicians, and other health professionals by providing the latest available evidence.

Methods

This guideline was developed using the GRADE approach for evidence assessment. In addition, given the need for an urgent response to a major public health crisis, the methodological approach was modified according to the Guidelines International Network/McMaster checklist for the development of rapid recommendations [4].

Panel composition

The initial guideline panel assembled in March 2020 was composed of nine members including infectious diseases specialists as well as experts in public health as well as other front-line clinicians, specializing in pharmacology, pediatrics, medical microbiology, preventive care, critical care, hepatology, nephrology and gastroenterology. Organizational representatives were included from the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS). In May 2020, an additional panel member was included as a representative from the Society of Infectious Diseases Pharmacists (SIDP). The Evidence Foundation provided technical support and guideline methodologists for the development of this guideline.

Disclosure and Management of Potential Conflict of Interest

The conflict of interest (COI) review group for this guideline includes two representatives from IDSA who are responsible for reviewing, evaluating and approving all disclosures. All members of the expert panel have complied with the COI process for reviewing

and managing conflicts of interest, which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict, regardless of relevancy to the guideline topic. The assessment of disclosed relationships for possible COI is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The COI review group has ensured that the majority of the panel and chair is without potential relevant (related to the topic) conflicts for the duration of their term on the panel. The chair and all members of the technical team have been determined to be unconflicted.

Question generation

Clinical questions included in this guideline were developed into a PICO format (Population, Intervention, Comparison, Outcomes) [5] and prioritized according to available evidence that met the minimum acceptable criteria (i.e., the body of evidence reported on at least a case-series design, case reports were excluded). Panel members prioritized patient-important outcomes such as mortality, development of ARDS (need for non-invasive or invasive ventilation) and clinical improvement (such as disease-oriented outcomes inferred by radiological findings or virologic cure), and severe adverse events (SAE) leading to treatment discontinuation. Serious adverse events are death, life threatening reactions, those that require hospitalization, result in disability or permanent damage or require an intervention to prevent permanent impairment [6]. Additional drug specific harms were evaluated when clinically relevant, including possible drug-drug reactions, if applicable.

Search strategy

The National Institute for Health and Care Excellence (NICE) highly-sensitive search was reviewed by the methodologist in consultation with the technical team information specialist and was determined to have high sensitivity [7]. An additional term, COVID, was added to the

search strategy used in addition to the treatment terms identified in the PICO questions (**Table s1**). Ovid Medline and Embase were searched from 2019 through June 18, 2020. Horizon scans have been performed regularly during the evidence assessment and recommendation process to locate additional grey literature and manuscript pre-prints. Reference lists and literature suggested by panelists were reviewed for inclusion. No restrictions were placed on language or study type.

Screening and study selection

Two reviewers independently screened titles and abstracts, as well as eligible full-text studies. When acceptable RCTs of effectiveness were found, no additional non-randomized studies or non-comparative evidence (i.e., single arm case series) were sought. Evidence from single arm studies reporting on non-comparative rates of outcomes of interest were included if a historical control event rate could be estimated from the literature. Reviewers extracted relevant information into a standardized data extraction form.

For several interventions, no direct evidence was available other than case reports or mechanistic considerations. The panel either decided to include plausible indirect evidence and make a recommendation (e.g., from studies of SARS-CoV) or to provide a short narrative discussion of the intervention.

Data collection and analysis

Data extracted from the available evidence included: mortality, clinical progression or improvement as reported in the studies, virologic clearance, and adverse events. Where applicable, data were pooled using random effects model (fixed effects model for 2 or less trials or pooling of rates) using RevMan [8].

Risk of bias and certainty of evidence

Risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs and the Risk of Bias Instrument for Non-randomized Studies – of Interventions (ROBINS-I) [9, 10]. The certainty

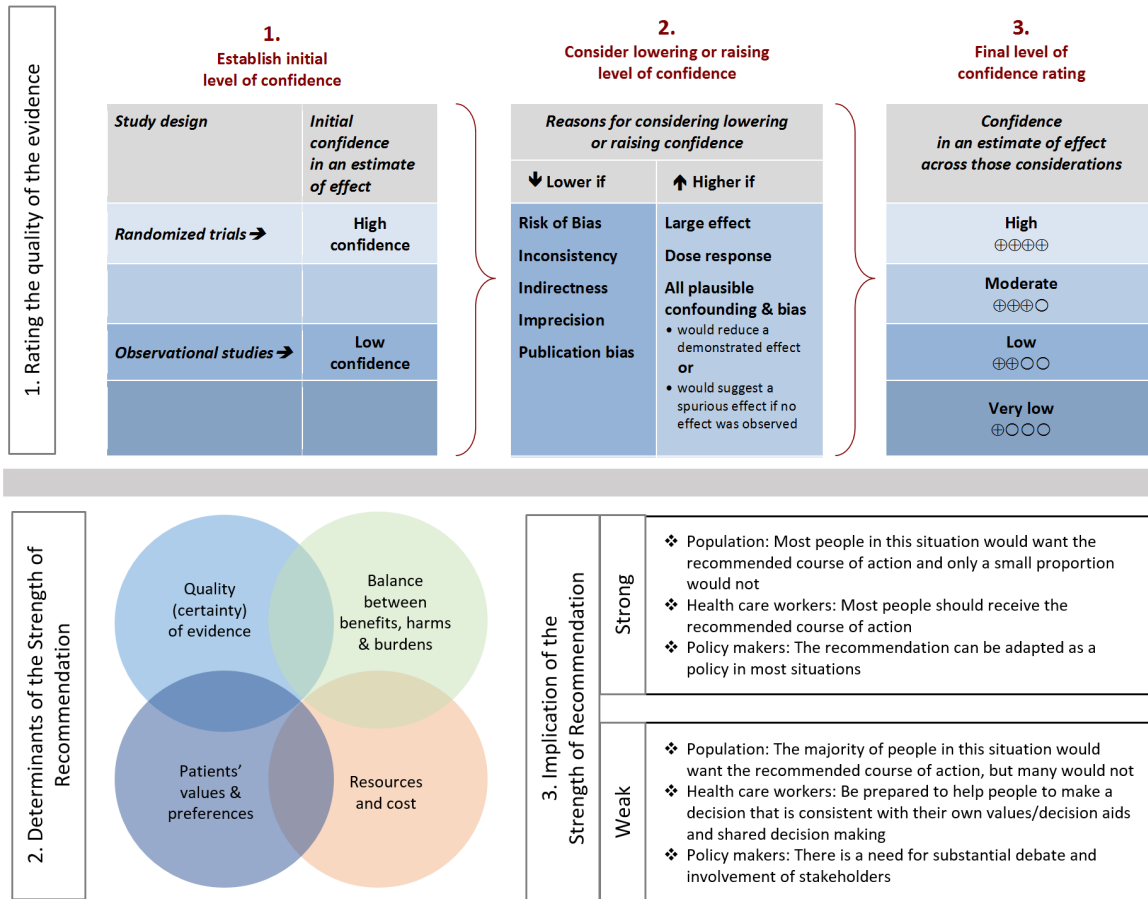
of evidence was assessed using the GRADE approach [11]. Within GRADE, the body of evidence across each outcome is assessed for domains that may reduce or increase one's certainty in the evidence. Factors that may reduce one's certainty include risk of bias (study limitations), inconsistency (unexplained heterogeneity across study findings), indirectness (applicability or generalizability to the research question), imprecision (the confidence in the estimate of an effect to support a particular decision) or publication bias (selective publication of studies). One's certainty in the evidence may be strengthened if the following considerations are present: large or very large magnitude of effect, evidence of a dose-response gradient, or opposing residual confounding. GRADE summary of findings tables were developed in GRADEpro Guideline Development Tool [12].

Evidence to recommendations

The panel considered core elements of the GRADE evidence in the decision process, including Certainty of evidence and balance between desirable and undesirable effects. Additional domains were acknowledged where applicable (feasibility, resource use, acceptability). For all recommendations, the expert panelists reached consensus. Voting rules were agreed on prior to the panel meetings for situations when consensus could not be reached.

As per GRADE methodology, recommendations are labeled as “strong” or “conditional”. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. [Figure 1](#) provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and healthcare policymakers. For recommendations where the comparators are not formally stated, the comparison of interest is implicitly referred to as “not using the intervention”. These recommendations acknowledge the current “knowledge gap” and aim at avoiding premature favorable recommendations for their use and to avoid encouraging the rapid diffusion of potentially ineffective or harmful interventions. Detailed suggestions about the specific research questions that should be addressed are found in the table (see **Table s2**).

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network)



Review process

This guideline has been rapidly reviewed and approved by the IDSA Board of Directors Executive Committee external to the guideline development panel. SHEA, SIDP and PIDS have reviewed and provided endorsement of its contents.

Updating process and terminology

Regular, frequent screening of the literature will take place to determine the need for revisions based on the likelihood that any new data will have an impact on the recommendations. When necessary, the entire expert panel is reconvened to discuss potential changes.

Changes to these guidelines will fall into one of two categories: update or amendment. An update involves a search for new studies, and if any new studies are found, they will be critically appraisal and the pertinent section will be removed and replaced with the updated section. An amendment involves a change or correction to the document, without any search for new studies and their appraisal. It will also involve changes made to clarify or explain a section based on “living” feedback from the readers.

Guideline revisions may result in major, minor, or “patch” version changes, defined as follows:

- Major version (e.g., 1.0.0): Synonymous with a newly published version in the journal. This is usually called a "breaking version", i.e. prior recommendations may not be valid anymore.
- Minor version (e.g., 1.1.0): Includes new information, maybe even added PICO's, but not a breaking version, i.e. existing recommendations are still valid, although new recommendations may be available.
- Patch version (e.g., 1.0.1): Small changes, i.e., typos, adding words, removing words, but there are no material changes to the document or changes in recommendations.

Results

Systematic review and horizon scan of the literature identified 2030 references of which 48 informed the evidence base for these recommendations (**Figure s1**). Characteristics of the included studies can be found in **Tables s3a-s3h**.

Hydroxychloroquine/Chloroquine; Hydroxychloroquine/Chloroquine plus Azithromycin

Section last reviewed and updated 6/18/20

Recommendation 1. Among patients with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine only in the context of a clinical trial. (Knowledge gap)

Recommendation 2. Among patients with COVID-19, the IDSA guideline panel suggests against hydroxychloroquine/chloroquine plus azithromycin outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)

The last literature search was conducted on June 18, 2020 and we identified three RCTs and two non-randomized studies in OVID. Two new non-indexed RCTs were available.

Why are hydroxychloroquine and hydroxychloroquine plus azithromycin considered for treatment?

Hydroxychloroquine (HCQ) and chloroquine are 4-aminoquinoline drugs developed in the mid-20th century for the treatment of malaria [13]. Hydroxychloroquine differs from chloroquine only in the addition of a hydroxyl group and is associated with a lower incidence of adverse effects with chronic use [13]. These drugs have been used in the treatment of autoimmune diseases for their immunomodulatory effects through effects on several cytokines, including IL-1 and IL-6 [13]. It has been known that they have antiviral properties against many different viruses, including the coronaviruses that cause SARS and Middle Eastern Respiratory Syndrome (MERS) [14, 15]. They have *in vitro* activity against SARS-CoV-2, and though half maximal effective concentration (EC50) values range considerably between studies, they are generally within the range of predicted achievable tissue concentrations [14, 16-18]. The *in vitro* activity of HCQ, the history of use for other conditions, and widespread availability of generic versions of the drug made it a potentially attractive option for the treatment of COVID-

19. Interest in combinations of HCQ with azithromycin (AZ) began when investigators in a small, uncontrolled study of HCQ use for COVID-19 noticed a higher frequency of patients achieving virologic response in the six subjects who received AZ to prevent bacterial infection [19]. Azithromycin, widely utilized as an antibacterial agent, has been shown to have antiviral activity *in vitro* against a number of viruses [20-22]. While the exact mechanism of antiviral activity is unknown, possible mechanisms include inhibiting endocytosis thereby limiting viral replication [23] and the ability to induce interferon responses [22, 24]. Macrolides have also been shown to have anti-inflammatory activity [25, 26].

Summary of the evidence

Our search identified three RCTs and six comparative cohort studies of hospitalized patients with confirmed COVID-19 treated with HCQ reporting on mortality, clinical progression or clinical improvement, and adverse events [27-35] (**Table s3a**) ([Table 1](#)).

In addition, we identified three comparative cohort studies and one case-control study reporting adjusted analyses of hospitalized patients with confirmed COVID-19 treated with HCQ plus AZ reporting on the outcomes of mortality, failure of virologic clearance (assessed with polymerase chain reaction [PCR] test), and adverse events (i.e., significant QT prolongation leading to treatment discontinuation) [29, 31, 33, 34] (**Table s3a**) ([Table 2](#)).

Benefits

Hydroxychloroquine

No mortality events were reported from 180 patients receiving either HCQ or no HCQ treatment across two RCTs [27, 29]. Five non-randomized studies failed to identify an association between persons treated with HCQ (compared to those not receiving HCQ) and mortality: Geleris 2020 reported an adjusted hazard ratio (HR) of 1.00 (95% confidence interval [CI]: 0.76, 1.32); Ip 2020 reported an adjusted HR of 1.02 (95% CI: 0.83, 1.27); Magagnoli reported in an adjusted HR in a subset after propensity score adjustment of 0.99 (95% CI: 0.50, 1.92); Mahévas 2020 reported a weighted HR of 1.20 (95% CI: 0.40, 3.30); Rosenberg 2020

reported an adjusted HR of 1.08 (95% CI: 0.63, 1.85) [30-33, 35]. One non-randomized study reported a decrease in mortality among persons treated with HCQ (adjusted HR: 0.36; 95% CI: 0.18, 0.75) [34].

The currently available best evidence failed to demonstrate or to exclude a beneficial effect of HCQ on clinical progression of COVID-19 (as inferred by radiological findings; risk ratio [RR]: 0.61; 95% CI: 0.26, 1.43; see **Figure s2a**), or on viral clearance by PCR tests (RR: 2.00; 95% CI: 0.02, 20.00; see **Figure s2b**), although a somewhat higher proportion in the HCQ group experienced clinical improvement (RR: 1.47; 95% CI 1.02, 2.11) (**Table 1**). However, the certainty in the evidence was rated as very low mainly due to small sample sizes (sparse data), co-interventions, and risk of bias due to methodological limitations.

Hydroxychloroquine + Azithromycin

Three non-randomized studies failed to identify an association between treatment with HCQ + AZ and mortality: Ip reported an adjusted HR of 0.98 (95% CI: 0.75, 1.28); Magagnoli reported an adjusted HR in a subset after propensity score adjustment of 0.89 (95% CI: 0.45, 1.77); Rosenberg 2020 reported an adjusted HR of 1.35 (95% CI: 0.79, 2.40) [31, 33, 35].

Harms

Hydroxychloroquine

Four recent or ongoing RCTs did not show a harm signal among persons with or without COVID-19 receiving treatment with HCQ [37-40], as well as two larger observational studies [30, 33]. Across the body of evidence from three RCTs, treatment with HCQ may increase the risk of experiencing adverse events (RR: 3.14; 95% CI: 1.58, 6.24; Very low CoE); however, the evidence is uncertain [27-29]. Two non-randomized comparative studies suggest increased risk of QT prolongation among patients receiving HCQ compared to those not receiving HCQ (RR: 2.89; 95% CI: 1.62, 5.16; Very low CoE) [32, 33]. In addition, Rosenberg 2020 reported 16% of patients in the HCQ arm experienced arrhythmias compared with 10% in the non-HCQ arm (RR: 1.56; 95% CI: 0.97, 2.50).

In another prospective cohort study in 224 COVID-19 uninfected patients with systemic lupus erythematosus (SLE) who received either chloroquine or HCQ for routine care, gastrointestinal side effects occurred in 7% of patients [41].

While the 4-aminoquinolines, chloroquine and HCQ, have not been demonstrated to cause hemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency [42, 43], case reports of hemolysis have emerged when these agents have been used for the treatment of COVID-19 [44-46]. It is possible that infection itself, specifically in cases of SARS CoV-2 infection, may trigger hemolysis in G6PD deficient individuals in the absence of a 4-aminoquinolone, however it may be prudent to exercise caution in administering these agents to G6PD deficient individuals with COVID-19, particularly if used for extended durations.

Renal clearance accounts for 15-25% of total clearance of HCQ; however, dose adjustments are not recommended with kidney dysfunction according to package labeling. Chloroquine and HCQ are metabolized by cytochrome P450 isoenzymes 2C8, 2D6, and 3A4 [47], therefore inhibitors and inducers of these enzymes may result in altered pharmacokinetics of these agents.

Hydroxychloroquine + Azithromycin

Two studies described significant QT prolongation in 10 of 95 patients treated with HCQ+AZ, either resulting in an QT increase to over 500 ms or discontinuation of the HCQ+AZ treatment, illustrating the high risk for clinically relevant arrhythmias with this treatment [48, 49]. In addition, several case reports of QT prolongation related to HCQ have also been published [50-53]. A case-control study of persons with COVID-19 treated with HCQ+AZ compared to healthy untreated controls reported higher values of minimum (415 vs 376 ms), mean (453 vs 407 ms) and maximum QTc-interval (533 vs 452 ms) among COVID-19 cases (n=22) than controls (n=34) [36].

Several case reports have been published citing the risk of a prolonged QT prolongation, torsades de pointes, and ventricular tachycardia in patients without COVID-19 receiving AZ alone. In a large cohort study, patients taking a five-day course of AZ had an increased risk of

sudden cardiac death with a HR of 2.71 (1.58-4.64) vs. 0.85 (0.45-1.60), compared to patients receiving no antibiotic or amoxicillin, respectively [54]. Given the cumulative effect on cardiac conduction seen with HCQ and AZ, if this combination was to be used in the context of a clinical trial, baseline and follow-up echocardiogram (ECG) monitoring would be indicated, as well as careful surveillance for other concomitant medications known to prolong the QT interval.

Providers are encouraged to visit resources such as the newly created website, <https://www.covid19-druginteractions.org/>, to aid in the evaluation and management of drug interactions with current and emerging investigational agents for COVID-19.

Azithromycin has a low risk for cytochrome P450 interactions [55]; however additional pharmacologic adverse events including gastrointestinal effects and QT prolongation need to be carefully considered particularly in the outpatient setting where frequent ECG monitoring is not feasible.

Other considerations

The panel agreed that the overall certainty of evidence was very low due to concerns with risk of bias, inconsistency, indirectness, imprecision, and publication bias. When considering the addition of AZ, the panel recognized the greater concern with the toxicity.

Conclusions and research needs for this recommendation

The guideline panel recommends that, because of uncertainty regarding its risks and benefits, the use of HCQ should be only in the context of a clinical trial. Because of the potential for toxicity, the panel suggests against HCQ+AZ combination outside of a clinical trial. This recommendation does not address the use of AZ for secondary bacterial pneumonia in patients with COVID-19. Additional RCTs and prospective outcome registries are needed to inform research for treatment with HCQ alone or in combination with AZ for patients with COVID-19 (**Table s2**).

Table 1. GRADE evidence profile, PICO 1

Question: Hydroxychloroquine compared to no hydroxychloroquine for hospitalized patients with COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine	no HCQ	Relative (95% CI)	Absolute (95% CI)		

Mortality (RCTs) (follow up: 14 days)

2 ^{1,2,a}	randomized trials	serious ^b	not serious	not serious	very serious ^c	none	0/90 (0.0%)	0/90 (0.0%)	not estimable		⊕○○○ VERY LOW	CRITICAL
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Mortality (NRS) (follow up: range 21 days to 60 days)

6 ^{3,4,5,6,7,8}	observational studies	very serious ^d	not serious ^e	not serious	serious ^f	none	Five non-randomized studies failed to identify an association between persons treated with HCQ and mortality: Geleris 2020 reported an adjusted HR of 1.00 (95% CI: 0.76, 1.32); Ip 2020 reported an adjusted HR of 1.02 (95% CI: 0.83, 1.27); Magagnoli reported in an adjusted HR in a subset after propensity score adjustment of 0.99 (95% CI: 0.50, 1.92); Mahévas 2020 reported a weighted HR of 1.20 (95% CI: 0.40, 3.30); Rosenberg 2020 reported an adjusted hazard ratio (HR) of 1.08 (95% CI: 0.63, 1.85) and (Geleris 2020, Ip 2020, Magagnoli 2020, Mahévas 2020, Rosenberg 2020). One study reported a decrease in mortality among persons treated with HCQ (adjusted HR: 0.36; 95% CI: 0.18, 0.75)(Yu 2020).				⊕○○○ VERY LOW	CRITICAL
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Clinical progression (as inferred by radiological/CT scan progression) (follow up: range 3 days to 6 days; assessed with: CT Scan)

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine	no HCQ	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,9}	randomized trials	serious ^b	not serious	serious ^g	serious ^f	none	5/46 (10.9%)	11/46 (23.9%)	RR 0.61 (0.26 to 1.43)	93 fewer per 1,000 (from 177 fewer to 103 more)	⊕○○○○ VERY LOW	CRITICAL

Clinical improvement (as inferred by CT scan findings) (follow up: 6 days)

1 ⁹	randomized trials	serious ^b	not serious	serious ^g	serious ^h	none	25/31 (80.6%)	17/31 (54.8%)	RR 1.47 (1.02 to 2.11)	258 more per 1,000 (from 11 more to 609 more)	⊕○○○○ VERY LOW	CRITICAL
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Failure of virologic clearance (follow up: 7; assessed with: PCR)

1 ¹	randomized trials	serious ^b	not serious	serious ⁱ	very serious ^f	none	2/15 (13.3%)	1/15 (6.7%)	RR 2.0 (0.2 to 20.0)	67 more per 1,000 (from 53 fewer to 1,000 more)	⊕○○○○ VERY LOW	IMPORTANT
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Adverse events, any

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine	no HCQ	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,2,9}	randomized trials	serious ^b	not serious	not serious	very serious ^f	none	27/116 (23.3%) ⁱ	9/126 (7.1%) ^k	RR 3.14 (1.58 to 6.24)	153 more per 1,000 (from 41 more to 374 more)	⊕○○○ VERY LOW	IMPORTANT

QT prolongation

2 ^{5,6}	observational studies	very serious ^{d,l}	not serious	not serious	serious ^h	none	46/355 (13.0%)	13/311 (4.2%)	RR 2.89 (1.62 to 5.16)	79 more per 1,000 (from 26 more to 174 more)	⊕○○○ VERY LOW	IMPORTANT
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Arrhythmias

1 ⁶	observational studies	very serious ^d	not serious	not serious	very serious ^{f,h}	none	44/271 (16.2%)	23/221 (10.4%)	RR 1.56 (0.97 to 2.50)	58 more per 1,000 (from 3 fewer to 156 more)	⊕○○○ VERY LOW	CRITICAL
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine	no HCQ	Relative (95% CI)	Absolute (95% CI)		
GRADE Working Group grades of evidence												
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect												
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different												
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect												
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect												
Risk of bias: Study limitations												
Inconsistency: Unexplained heterogeneity across study findings												
Indirectness: Applicability or generalizability to the research question												
Imprecision: The confidence in the estimate of an effect to support a particular decision												
Publication bias: Selective publication of studies												

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. Chen Z 2020 did not explicitly report on deaths
- b. Did not report on blinding (including outcome adjudication committee), sequence generation or allocation concealment; Chen J 2020: all patients received nebulized alpha-interferon, 80% vs. 67.7% of subjects received Abidiol in the hydroxychloroquine vs. placebo arm, respectively. Two subjects in the control arm received lopinavir/ritonavir.
- c. Zero events
- d. Concerns with unmeasured and residual confounding. Multiple co-interventions received across arms.
- e. While Yu 2020 reports a decrease in mortality, the concerns with risk of bias may contribute to this spurious finding.
- f. The 95% CI includes the potential for both benefit and harm.
- g. Radiological progression is an intermediary for worsening to ARDS, need for intubation, and death
- h. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
- i. Viral clearance is a surrogate for clinical improvement, such as worsening to ARDS, intubation, and death
- j. Chen J 2020: 4 AEs include diarrhea, fatigue and transient AST elevation. Chen Z 2020: 1 rash, 1 headache. Tang 2020: 21 AEs include disease progression (1%), URI (1%), diarrhea (10%), vomiting (3%).
- k. 3 AEs reported in 2 patients include: AST elevation, creatinine elevation and anemia

- I. Mahévas 2020 does not report on AEs in the comparator arm.

References

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4. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. *Med* **2020**.
5. Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. *MedRxiv* **2020**.
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7. Yu B, Li C, Chen P, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. *Sci China Life Sci* **2020**.
8. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* **2020**.
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Table 2. GRADE evidence profile, PICO 2

Question: Hydroxychloroquine and azithromycin compared to no hydroxychloroquine/azithromycin for hospitalized patients with COVID-19

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine and azithromycin	no HCQ/azithromycin	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3 ^{1,2,3}	observational studies	very serious ^a	not serious	not serious	serious ^b	none	Three non-randomized studies failed to identify an association between persons treated with HCQ + AZ and mortality: Ip reported an adjusted HR of 0.98 (95% CI: 0.75, 1.28); Magagnoli reported an adjusted HR in a subset after propensity score adjustment of 0.89 (95% CI: 0.45, 1.77); Rosenberg 2020 reported an adjusted hazard ratio (HR) of 1.35 (95% CI: 0.79, 2.40). ^{1,2,3}				⊕○○○ VERY LOW	CRITICAL
Virologic Failure (follow up: range 5 days to 6 days; assessed with: PCR Test)												
2 ^{4,5,6}	observational studies	very serious ^c	serious ^d	serious ^e	serious ^f	none	29/71 (40.8%) ^g	12/12 (100.0%) ^h	not estimable		⊕○○○ VERY LOW	CRITICAL
Significant QT prolongation												
2 ^{6,7}	observational studies	very serious ^c	not serious	serious ⁱ	serious ^f	none	10/95 (10.5%) ^j	-	-	-	⊕○○○ VERY LOW	IMPORTANT
Adverse events												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine and azithromycin	no HCQ/azithromycin	Relative (95% CI)	Absolute (95% CI)		
0	observational studies	serious ^k	not serious	not serious	serious ^k	none	Several case reports of QT prolongation related to hydroxychloroquine have been published. In another prospective cohort study in 224 patients with SLE who received either chloroquine or hydroxychloroquine, gastrointestinal side effects occurred in 7% of patients. ⁸ Several case reports have been published citing the risk of a prolonged QT prolongation, torsades de pointes, and ventricular tachycardia in patients receiving azithromycin. In a large cohort study, patients taking a 5 day course of azithromycin had an increased risk of sudden cardiac death with a hazard ratio of 2.71 (1.58-4.64) vs. 0.85 (0.45-1.60), compared to no antibiotic or amoxicillin, respectively. ⁹ Given that both medications have QT prolonging effects, any combination is likely to substantially increase the risk of clinically relevant harmful effects. ^{8,9}				⊕○○○ VERY LOW	IMPORTANT
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine and azithromycin	no HCQ/azithromycin	Relative (95% CI)	Absolute (95% CI)		
<p>Risk of bias: Study limitations</p> <p>Inconsistency: Unexplained heterogeneity across study findings</p> <p>Indirectness: Applicability or generalizability to the research question</p> <p>Imprecision: The confidence in the estimate of an effect to support a particular decision</p> <p>Publication bias: Selective publication of studies</p>												

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio

Explanations

- Concerns with unmeasured and residual confounding. Multiple co-interventions received across arms.
- The 95% CI includes the potential for both benefit and harm.
- No contemporaneous control groups; no adjustment for baseline severity, resulting in high risk for residual confounding
- 2 case series from France showed divergent results
- Surrogate marker for mortality or resolution of COVID-19.
- A very small number of events. Optimal information size not met.
- Gautret reported 21/61 patients as positive at day 6 (estimate from supplied graph); Molina reported 8/10 patients positive at day 5 or 6. Pooled rates of virologic failure using fixed effects inverse variance method resulted in a 43% failure rate (95% CI, 32% to 54%)
- Gautret reported on a historical viral clearance rate in symptomatic patients from a separate hospital. Criteria for selection of patient remains unclear, as presumably a sizable number of untreated patients could have been available with data on viral clearance.
- Azithromycin and hydroxychloroquine can independently cause QT prolongation. Used together there can be an additive effect. Caution should be exercised with other agents known to prolong the QT interval.
- Molina 2020: 1/11 leading to treatment discontinuation; Chorin 2020: 9/84 with significant QTc prolongation of more than 500 ms
- Case reports

References

- Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *Jama* **2020**.
- Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. *Med* **2020**.
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5. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. [Pre-print - not peer reviewed]. **2020**.
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Lopinavir/Ritonavir

Section last reviewed 6/22/20; no updates made

Recommendation 3. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir only in the context of a clinical trial. (Knowledge gap)

Summary of the evidence

One RCT and two case studies reported on treatment with combination lopinavir/ritonavir for hospitalized patients with COVID-19 [56-58] ([Table 3](#)). Cao et al. randomized 199 hospitalized patients with severe COVID-19 to receive treatment with lopinavir/ritonavir in addition to standard of care (n=99) or standard of care alone (n=100) for 14 days. The trial reported on the following outcomes: mortality, failure of clinical improvement (measured using a 7-point scale or hospital discharge), and adverse events leading to treatment discontinuation.

Benefits

Based on a modified intention to treat analysis, treatment with lopinavir/ritonavir failed to show or exclude a beneficial effect on mortality (RR: 0.67; 95% CI: 0.38, 1.17), although failure of clinical improvement was lower in the lopinavir group (RR: 0.78; 95% CI: 0.63, 0.97; ITT analysis).

Harms

Nearly 14% of lopinavir/ritonavir recipients were unable to complete the full 14-day course of administration due primarily to gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse episodes of acute gastritis. Two recipients also had self-limited skin eruptions. The risk of hepatic injury, pancreatitis, severe cutaneous eruptions, QT prolongation, and the potential for multiple drug interactions due to CYP3A inhibition, are all well documented with this drug combination.

Other considerations

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The panel elected to inform their decision based on the RCT [58]. The panel determined the Certainty of evidence to be very low due to concerns with risk of bias (lack of blinding) and imprecision. In the randomized clinical trial conducted by Cao et al, the group that received lopinavir/ritonavir and the group that did not had similar rates of viral decay. This finding suggests that lopinavir/ritonavir is not having a measurable antiviral effect, its purported mechanism of action.

Conclusions and research needs for this recommendation

The guideline panel recommends the use of lopinavir/ritonavir only in the context of a clinical trial. Additional clinical trials or prospective outcome registries are needed to inform research for treatment with lopinavir/ritonavir and other HIV-1 protease inhibitors for patients with COVID-19 (**Table s2**).

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Table 3. GRADE evidence profile, PICO 3

Question: Lopinavir/Ritonavir compared to Placebo for confirmed COVID-19 pneumonia
Setting: Inpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lopinavir/Ritonavir	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1 ¹	randomized trials	serious ^a	not serious	not serious	very serious ^b	none	16/96 (16.7%) ^c	25/100 (25.0%)	RR 0.67 (0.38 to 1.17)	82 fewer per 1,000 (from 155 fewer to 42 more)	⊕○○○ VERY LOW	CRITICAL
Failure of clinical improvement at 14 days (follow up: 14 days)												
1 ¹	randomized trials	serious ^a	not serious	not serious	very serious ^d	none	54/99 (54.5%)	70/100 (70.0%)	RR 0.78 (0.63 to 0.97)	154 fewer per 1,000 (from 259 fewer to 21 fewer)	⊕○○○ VERY LOW	CRITICAL
AEs leading to treatment discontinuation												
1 ¹	randomized trials	serious ^a	not serious	not serious	very serious ^e	none	Nearly 14% of lopinavir–ritonavir recipients were unable to complete the full 14-day course of administration. This was due primarily to gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse events, both acute gastritis. Two recipients had self-limited skin eruptions. Such side effects, including the risks of hepatic injury, pancreatitis, more severe cutaneous eruptions, and QT prolongation, and the potential for multiple drug interactions due to CYP3A inhibition, are well documented with this drug combination. The side-effect profile observed in the current trial arouses concern about the use of higher or more prolonged lopinavir–ritonavir dose regimens in efforts to improve outcomes.			⊕○○○ VERY LOW	IMPORTANT	

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. Unblinded study which can affect outcomes that require judgment, such as how investigators judge clinical improvement or decide to stop the treatment in patients with side effects.
- b. 95% CI includes substantial beneficial effects as well as substantial harms (potentially a relative increase in mortality increase of 17% and a doubling of the likelihood of not clinically improving)
- c. Modified intention to treat analysis data used for this outcome. Some deaths were excluded when drug was not given.
- d. The upper boundary of the 95% confidence interval crosses the threshold of meaningful improvement as the worst-case estimate is a 3% RRR.
- e. Small number of events making estimates highly uncertain

References

1. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, ~~Ruan~~ L, Song B, Cai Y, Wei M, Li X. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*. 2020

Corticosteroids

Section last reviewed 6/22/20; no updates made. Note: Panel is awaiting publication of the RECOVERY trial data and will update this section once available.

Recommendation 4. Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence)

Recommendation 5. Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap)

Summary of the evidence

No studies were found specifically examining the role of steroids for the treatment of the acute COVID-19. Corticosteroids were widely used in China to prevent the development of ARDS in patients with COVID-19 pneumonia. Four retrospective cohort studies [56, 57, 59, 60] examined several interventions during the COVID-19 outbreak in the Wuhan area. Studies show variability in the benefit of corticosteroid use ([Tables 4 and 5](#)). Study limitations include: 1) critical information not reported on baseline risk/severe pneumonia/ARDS; 2) confounding by indication; 3) unadjusted analyses; 4) timing of disease not given; 5) large variability in treatments given. Due to these limitations, a sensible pooling effort to determine possible treatment effect was not deemed possible.

Benefits and Harms

The panel determined that due to the limitation of direct COVID-19 data, indirect evidence from the 2003 SARS-CoV-1 outbreak and from MERS would also be considered. A systematic review [61] reported on 15 studies, 13 of which were inconclusive to any benefits of corticosteroids. One RCT reported that SARS-CoV-1 viral loads showed delayed viral clearance associated with corticosteroid use.

The same review also reported on a subset of ARDS patients (three trials). One small RCT in 24 patients using a lower dose methylprednisolone for two days showed possible improvement of ARDS;

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however, two larger trials showed little or no effect in critically ill patients with pulmonary failure. The authors concluded that despite widespread use of corticosteroids during the SARS-CoV-1 outbreak, conclusive evidence of benefit was lacking and that administering steroids early in the disease process before viral replication is controlled may lead to a delay in viral clearance.

Other considerations

The panel deemed the certainty of the direct evidence as very low owing to concerns with risk of bias, inconsistency, and imprecision. The panel based their decision to conditionally recommend against the use of corticosteroids among patients admitted to the hospital on the indirect findings from the systematic review on SARS-CoV-1.

Conclusions and research need for these recommendations

As COVID-19 is a self-limited viral illness in most cases, a small subset of patients progresses from COVID-19 pneumonia to develop ARDS. Based on limited data from other coronaviruses, there is no clear benefit and potential harm from corticosteroids. Carefully designed RCTs and prospective outcome registries are needed to determine the dose, route, timing, and duration of such treatment on the prevention of clinical deterioration and to better understand the potential harms associated with its use. If a person is on a steroid (inhaled or systemic) for another indication (e.g., asthma), the steroid should be continued.

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Table 4. GRADE evidence profile, PICO 4

PICO 4: Corticosteroids compared to no corticosteroids for hospitalized patients with COVID-19 without ARDS

Setting: Inpatient

№ of studies	Study design	Certainty assessment					Other considerations	№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision			corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Mortality													
4 ^{1,2,3,4}	observational studies	very serious ^a	serious ^b	not serious	not serious ^c	none	No comparative effectiveness studies. 4 retrospective cohorts examining large number of interventions during COVID-19 outbreak in Wuhan area. Studies show variability of corticosteroid use. Study limitations include: 1) critical information not reported on baseline risk/severe pneumonia/ARDS; 2) confounding by indication; 3) unadjusted analyses; 4) timing of disease not given; 5) large variability in treatments given; preventing a sensible pooling effort. Indirect evidence from the 2003 SARS outbreak showed little or no benefits ⁵ and possible harms by increasing viral loads ⁶			⊕○○○ VERY LOW		CRITICAL	
Clinical deterioration													
1 ¹	observational studies	serious ^d	not serious	not serious	serious ^e	none	No comparative effectiveness trial available. Sun 2020 presents odds of deterioration (includes mortality) across 10+ treatments, including glucocorticoids. unadjusted and adjusted analyses estimate OR = 3.0 (95% CI 1.2-7.8). Limitations of note: 1) restricted patients to less severe population; 2) confounding; 3) timing of when given.			⊕○○○ VERY LOW		CRITICAL	
Progression to ARDS - not reported													
-	-	-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; ARDS: Acute respiratory distress syndrome; OR: Odds ratio

Explanations

- Study limitations include: 1) critical information not reported on baseline risk/severe pneumonia/ARDS; 2) confounding by indication; 3) unadjusted analyses; 4) timing of disease not given; 5) variability in treatments given.
- Some studies show benefits, some no effect, and some harms.
- Imprecision likely given the heterogeneity.
- 1) restricted patients to less severe population; 2) confounding; 3) timing of when given.
- Few patients included.

References

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Table 5. GRADE evidence profile, PICO 5

PICO 5: Corticosteroids compared to no corticosteroids for hospitalized patients with COVID-19 with ARDS

Setting: intensive care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4 ^{1,2,3,4}	observational studies	very serious ^a	serious ^b	not serious	not serious ^c	none	No comparative effectiveness studies. 4 retrospective cohorts examining large number of interventions during COVID-19 outbreak in Wuhan area. Studies show variability of corticosteroid use. Study limitations include: 1) critical information not reported on baseline risk/severe pneumonia/ARDS; 2) confounding by indication; 3) unadjusted analyses; 4) timing of disease not given; 5) large variability in treatments given; preventing a sensible pooling effort. A systematic review [31] reported on 15 studies in patients with SARS outbreak of 2002-2003, 13 of which were inconclusive to any benefits of corticosteroids. One RCT reportedly measured SARS-CoV viral loads which showed a delay of viral clearance associated with corticosteroids. The same review also reported on a subset of ARDS patients (3 trials). One small RCT in 24 patients using a lower dose methylprednisolone for 2 days showed possible improvement of ARDS; however, 2 larger trials showed little or no effect in critically ill patients with pulmonary failure. The authors concluded that despite widespread use of corticosteroids in during the SARS outbreak, conclusive evidence of benefit was lacking and that administering steroids early in the disease process before viral replication is controlled may lead to a delay in viral clearance.				⊕○○○ VERY LOW	CRITICAL
Clinical deterioration												
1 ¹	observational studies	serious ^d	not serious	not serious	serious ^e	none	No comparative effectiveness trial available. Sun 2020 presents odds of deterioration (includes mortality) across 10+ treatments, including glucocorticoids. Unadjusted and adjusted analyses estimate OR = 3.0 (95% CI 1.2-7.8) for deterioration associated with steroids across the entire hospitalization. Limitations of note: 1) restricted patients to less severe population; 2) confounding; 3) timing of when given.				⊕○○○ VERY LOW	CRITICAL
Progression to Acute respiratory distress syndrome (ARDS) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; ARDS: Acute respiratory distress syndrome; OR: Odds Ratio

Explanations

- a. Study limitations include: 1) critical information not reported on baseline risk/severe pneumonia/ARDS; 2) confounding by indication; 3) unadjusted analyses; 4) timing of disease not given; 5) variability in treatments given.
- b. Some studies show benefits, some no effect, and some harms.
- c. Imprecision likely given the heterogeneity.
- d. 1) restricted patients to less severe population; 2) confounding; 3) timing of when given.
- e. Few patients included.

References

1. Sun F, Kou H, Wang S, et al. Medication patterns and disease progression among 165 patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a single-centered, retrospective, observational study. **2020**.
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Tocilizumab

Section last reviewed 6/22/20; no updates made

Recommendation 6. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap)

Summary of the evidence

Studies reporting on the pathogenesis of SARS-CoV-1 and MERS-CoV suggest a release of proinflammatory cytokines including interleukins-6 (IL-6) [62] during the clinical illness. Our search identified one study [62] that reported on 21 severe or critical patients with COVID-19 treated with tocilizumab, an IL-6 blocker ([Table 6](#)). This study had no control group. To estimate a control group rate in patients who did not get treatment with tocilizumab, Xu et al. described findings from Yang 2020, which suggested a baseline mortality rate of 60% in critical patients and 11% in severe patients admitted to the ICU [63].

Benefits

We estimate that the patients in Xu 2020 (21 patients, 4 critical and 17 severe) would have a baseline mortality risk of 20% as matched in severity. Therefore, treatment with tocilizumab may have reduced mortality since there were no deaths reported out of 21 patients. However, this conclusion remains highly uncertain given the lack of a contemporaneous control or adjustments for confounding factors. Out of 21 patients, 19 were discharged from the hospital suggesting a 9.5% rate of failure of clinical improvement in the CT scan findings.

Harms

Xu et al. reported no serious adverse events [62]. However, patients receiving tocilizumab are often at an increased risk of serious infections (bacterial, viral, invasive fungal infections, and tuberculosis) and hepatitis B reactivation [64]. Cases of anaphylaxis, severe allergic reactions, severe liver damage and hepatic failure, and intestinal perforation have been reported after tocilizumab administration in patients without COVID-19.

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Tocilizumab is not metabolized by the cytochrome P450 isoenzyme system, however elevated IL-6 levels seen in inflammatory states have been shown to inhibit these enzymes, thereby slowing the metabolism of drugs through these pathways. As the 3A4 pathway is responsible for metabolism of many commonly used medications, administration of IL-6 inhibitors like tocilizumab may result in enhanced metabolism in drugs utilizing the cytochrome P450 system [65, 66].

Other considerations

The panel determined that the overall certainty of the evidence was very low due to concerns of high risk of bias due to confounding, indirectness, and imprecision.

Conclusions and research needs for this recommendation

The guideline panel recommended tocilizumab only in the context of a clinical trial. Additional clinical trials are needed to inform research on the effectiveness of treatment with tocilizumab for patients with COVID-19 (**Table s2**).

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Table 6. GRADE evidence profile, PICO 6

PICO 6: Tocilizumab compared to no treatment for severe COVID-19 pneumonia

Setting: intensive care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tocilizumab	no treatment	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1 ¹	observational studies	serious ^a	not serious	not serious ^b	serious	none	0/21 (0.0%)	20.0% ^c	not estimable		⊕○○○ VERY LOW	CRITICAL
Failure of clinical improvement (as inferred by CT scan findings)												
1 ¹	observational studies	serious ^a	not serious	serious ^{b,d}	serious ^e	none	2/21 (9.5%) ^f	-	-	-	⊕○○○ VERY LOW	CRITICAL
Severe Aes												
1	observational studies	serious ^g	not serious	not serious	serious ^e	none	Xu et al. reported no serious adverse events. Patients receiving tocilizumab are usually at an increased risk of serious infections (bacterial, viral, invasive fungal infections, and tuberculosis). Hepatitis B reactivation may occur after tocilizumab. Cases of anaphylaxis and severe allergic reactions have occurred. Cases of severe liver damage and hepatic failure have been reported with the use of tocilizumab. Cases of intestinal perforation after tocilizumab have been reported. ^{1,2,3}			⊕○○○ VERY LOW	CRITICAL	

CI: Confidence interval

Explanations

- No contemporaneous control group.
- All patients also received lopinavir and methylprednisolone
- The authors reported a 60% mortality rate in critical patients and 11% in severe patients admitted to the ICU. Given the ratio of 4 "critical" and 17 "severe", out of 21 patients the estimated mortality rate would be 20%
- Imaging finding is a surrogate endpoint for worsening clinical status.
- Few case reports
- 19/21 were discharged from the hospital including 2 critical patients; The two patients who remain hospitalized have improved; most received 400 mg x 1 dose, however 3/21 received a second dose 12 hours later; all patients were on corticosteroids and lopinavir/ritonavir
- Causality remains uncertain

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Convalescent Plasma for COVID-19 Treatment

Section last reviewed and updated on 6/22/20

Recommendation 7. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial. (Knowledge gap)

The last literature search was conducted on June 18, 2020 and we identified one RCT, two comparative cohort studies, and two single-arm registry studies in OVID.

Why is convalescent plasma considered for treatment?

Convalescent plasma (CP) has been used as passive immunotherapy for prevention and treatment of infections for over 100 years [67, 68]. The predominant proposed protective mechanism is thought to be pathogen neutralization, although antibody dependent cellular cytotoxicity and phagocytosis may also play a role. With the advent of effective antimicrobial therapy (i.e., “the antibiotic era”) CP fell out of favor. In recent years, interest in this approach has been revived as a means of addressing viral epidemics such as Ebola, SARS -1 and MERS. Studies of CP derived from people who had recovered from those specific infections showed encouraging results, but were typically small, non-randomized and largely descriptive [69-71]. In the current pandemic, CP obtained from individuals who recovered from COVID-19 has been used in over 20,000 patients with moderate to severe infection as part of an expanded access program.

Many questions remain regarding the minimal antibody titer required for the plasma to provide benefit, the type of antibodies that plasma should contain to be most protective and the optimal timing of therapy. When measurement of neutralizing antibody titers is available, the U.S. Food and Drug Administration (FDA) recommends neutralizing antibody titers of at least 1:160. Such assays have not been widely available and titers in plasma used in the expanded access program have often not been assessed prior to infusion. Multiple prospective clinical trials are in progress utilizing plasma with an IgG ELISA titer cutoff of $\geq 1:320$. Titers at that level are seen in about 80% of donors [72]. The

probability of obtaining a neutralizing antibody titer of $\geq 1:160$ is highest (80% or greater) when the ELISA IgG titer is $\geq 1:1,350$ [73]. Regarding timing of treatment: Based on historical experience and emerging data, efficacy is expected to be best when CP is given at earlier stages of the disease and particularly prior to when patients become critically ill [74, 75].

Summary of the evidence

Our search identified one RCT and two comparative cohort studies, as well as one large (n=5000), single-arm registry study among hospitalized patients with COVID-19 receiving COVID-19 CP reporting on the outcomes of mortality, worsening oxygenation, and transfusion-related adverse events [74-77] ([Table 7](#)) ([Table s3f](#)). We identified an additional small (n=25) single-arm study; however, we excluded it because it did not provide the best available evidence and may have been included in the registry study [73].

All studies had concerns with risk of bias due to lack of adjustment for critical confounders or potential for residual confounding. Timing of receipt of COVID-19 CP during the clinical course of the patients' illness varied across studies.

Li 2020 randomized 103 patients to receive a transfusion or not in an open-label trial with more than 90% of patients enrolled 14 days after symptom onset (median 30 days). Subjects were propensity score matched on the administration of HCQ and AZ, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion; however, there may have been some residual confounding. Duan 2020 compared 10 CP treated patients to 10 historical control patients matched on age, gender, and severity of illness; however, the study did not adjust for critical confounders including co-treatments, baseline characteristics, disease severity, and timing of plasma delivery. Joyner et al. 2020 reported on 5,000 patients with severe or life-threatening COVID-19 enrolled in the U.S. FDA Expanded Access Program for COVID-19 CP study and found <1% severe adverse events within the first four hours after administration.

Benefits

Convalescent plasma transfusion failed to show or to exclude a beneficial or detrimental effect on mortality; the evidence from both RCT and non-randomized studies is uncertain (RR: 0.65; 95% CI:

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0.29, 1.47; very low CoE and HR: 0.34; 95% CI: 0.13, 0.89; very low CoE, respectively). Similarly, receipt of COVID-19 CP may reduce the odds of worsening oxygenation (adjusted odds ratio [OR]: 0.86; 95% CI: 0.75, 0.98; very low CoE); however, the evidence is uncertain because of concerns with risk of bias ([Table 7](#)).

Harms

In the largest safety study, there were 15 deaths reported within 4 hours of transfusion in 5,000 patients (0.3%) [77] and four (0.08%) were judged as possibly or probably related to the transfusion of COVID-19 CP. In addition, 21 serious non-fatal adverse events (SAEs) were reported (0.4%): seven cases of transfusion-associated circulatory overload (TACO), 11 cases of transfusion-related acute lung injury (TRALI), and three cases of severe allergic transfusion reactions. Study authors judged all incidences of TACO and TRALI as related to the transfusion of COVID-19 CP. In another smaller study of 52 patients randomized to receive CP transfusions, two subjects developed transfusion-related adverse events (e.g., chills and rash; shortness of breath, cyanosis, and severe dyspnea) within 6 hours of receipt [74].

Other considerations

The panel agreed on the overall certainty of evidence as very low due to concerns with risk of bias and imprecision.

Conclusions and research needs for this recommendation

The guideline panel recommends COVID-19 CP only in the context of a clinical trial. Additional clinical trials are needed to inform benefit of treatment with COVID-19 CP for patients with COVID-19 ([Table s2](#)).

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Table 7. GRADE evidence profile, PICO 7

Question: Convalescent plasma compared to no convalescent plasma for hospitalized patients with COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	convalescent plasma	no convalescent plasma	Relative (95% CI)	Absolute (95% CI)		

Mortality (RCT)

1 ¹	randomized trials	serious ^a	not serious	not serious	very serious ^b	none	8/52 (15.4%)	12/51 (23.5%)	RR 0.65 (0.29 to 1.47)	82 fewer per 1,000 (from 167 fewer to 111 more)	⊕○○○ VERY LOW	CRITICAL
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Mortality (NRS)

1 ^{2,3}	observational studies	serious ^c	not serious ^d	not serious ^e	very serious ^f	none	5/39 (12.8%)	38/156 (24.4%)	HR 0.34 (0.13 to 0.89) ^g	153 fewer per 1,000 (from 208 fewer to 24 fewer)	⊕○○○ VERY LOW	CRITICAL
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Worsening oxygenation (follow up: 14 days)

1 ³	observational studies	serious ^c	not serious	not serious	very serious ^h	none	7/39 (17.9%)	38/156 (24.4%)	OR 0.86 (0.75 to 0.98)	27 fewer per 1,000 (from 49 fewer to 4 fewer)	⊕○○○ VERY LOW	IMPORTANT
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SAEs (transfusion-associated circulatory overload, transfusion-related acute lung injury, severe allergic transfusion reaction) (follow up: 4 hours)

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	convalescent plasma	no convalescent plasma	Relative (95% CI)	Absolute (95% CI)		
1 ⁴	observational studies	serious ⁱ	not serious	not serious	not serious	none	SAEs from 5,000 transfused patients: Within first 4 hours of transfusion, of the SAEs, 15 deaths were reported (0.3% of all transfusions) and four of those deaths were judged as related (possibly, n=3; probably, n=1; definitely, n=0) to the transfusion of COVID-19 convalescent plasma. There were 21 non-death SAEs reported, with seven reports of transfusion-associated circulatory overload (TACO), eleven reports of transfusion-related acute lung injury (TRALI), and three reports of severe allergic transfusion reaction. All incidences of TACO and TRALI were judged as related (possibly, n=9; probably, n=7; definitely, n=2) to the transfusion of COVID-19 convalescent plasma. ^j		⊕○○○ VERY LOW		CRITICAL	

Transfusion-related adverse events

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^f	none	Two patients experienced transfusion-related AEs within 6 hours of transfusion, both recovered fully with supportive treatment: 1 patient developed chills and rashes, 1 patient presented with shortness of breath, cyanosis, and severe dyspnea.		⊕⊕○○ LOW		IMPORTANT
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	convalescent plasma	no convalescent plasma	Relative (95% CI)	Absolute (95% CI)		
GRADE Working Group grades of evidence												
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect												
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different												
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect												
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect												
Risk of bias: Study limitations												
Inconsistency: Unexplained heterogeneity across study findings												
Indirectness: Applicability or generalizability to the research question												
Imprecision: The confidence in the estimate of an effect to support a particular decision												
Publication bias: Selective publication of studies												

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio; OR: Odds ratio

Explanations

- Li 2020 time between symptom onset and randomization was over 14 days for >90% (median 30 days), no adjustment for co-interventions, allocation concealment methods not reported, and participants and healthcare professionals not blinded.
- The 95% CI includes the potential for appreciable benefit; however, cannot exclude the potential for harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
- Liu 2020 propensity score matching was enforced on the administration of hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion; however, there may be some residual confounding.
- Duan 2020 suggests similar protective benefit when comparing 10 transfusion recipients with 10 historical controls; however, was not pooled with Liu 2020 as the potential for bias was critical due to lack of control of confounders and selection bias.
- All patients had ARDS and were receiving mechanical ventilation at time of treatment. Convalescent plasma donors recovered from SARS-CoV-2 infection, had been diagnosed with laboratory-confirmed COVID-19.
- Few events reported do not meet the optimal information size and suggest fragility in the estimate.
- HR received as personal communication with study author.
- The 95% CI includes the potential for appreciable benefit; however, may not include a clinically meaningful benefit. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
- No comparative effects available. Some subjectivity in classification of outcomes as transfusion related.

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j. Duan 2020 reported no AEs in either 10 transfused vs 10 historical controls.

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Remdesivir

New section added 6/22/20

Recommendation 8. Among hospitalized patients with severe* COVID-19, the IDSA panel suggests remdesivir over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence)

Remark: For consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or extracorporeal mechanical oxygenation (ECMO).

Recommendation 9. Among patients with severe COVID-19 on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, low certainty of evidence)

Remark: In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.

*Severe illness is defined as patients with SpO₂ ≤94% on room air, including patients on supplemental oxygen, on mechanical ventilation and ECMO.

The last literature search was conducted on 6/18/2020 and we identified three RCTs and two non-randomized studies (NRS) in OVID.

Why is remdesivir considered for treatment?

Remdesivir (GS-5734) is an antiviral drug with potent *in vitro* activity against a range of RNA viruses including MERS-CoV, SARS-CoV 1 & 2 [78-80]. Remdesivir acts by causing premature termination of viral RNA transcription [80]. Its use improved disease outcomes and reduced viral loads in SARS-CoV-1 infected mice [79]. In rhesus macaques therapeutic treatment with remdesivir showed reduction in SARS-CoV-2 loads, pathologic changes and progression of clinical disease [81]. In this animal model, remdesivir treatment initiated 12 hours post-inoculation reduced clinical signs, virus replication in the lungs, and decreased the presence and severity of lung lesions. A case series of 53

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patients with severe COVID-19 pneumonia who received remdesivir under a compassionate-use protocol reported clinical improvement in 68% after a median follow-up of 18 days, with 13% mortality and a generally acceptable toxicity profile [82]. However, there was no comparison group of similar patients who received standard care at the participating institutions.

Summary of the evidence

Two RCTs comparing treatment with remdesivir (200 mg day one, 100 mg daily days 2-10) against no remdesivir treatment [83, 84], and one RCT comparing 5 days of treatment (200 mg day one, 100 mg daily days 2-5) against 10 days (200 mg day one, 100 mg daily days 2-10) of treatment [85] served as the best available evidence among hospitalized persons with severe COVID-19. The outcomes assessed were mortality, time to clinical improvement at 14 days, serious adverse events, and adverse events leading to treatment discontinuation ([Tables 8 and 9](#)).

The study by Wang et al 2020 was stopped early due to lack of recruitment into the trial due to decreased incidence in China. When comparing treatment with remdesivir to no remdesivir treatment data after 28-days of observation, we did not pool the mortality data from the Wang et al study and 14-day mortality from the Beigel et al study (i.e., Adaptive Covid-19 Treatment Trial [ACTT-1]). This is because the preliminary analysis of the ACTT-1 presented the mortality results appropriately as time-to-event analysis due to possible chance effects at 14 days, as many patients still remained hospitalized, with 28-day mortality data still unavailable at the time of the preliminary analysis.

Randomization performed in Goldman 2020 failed to establish prognostic balance between baseline clinical status among the 397 patients randomized into the treatment arms, with patients in the 10-day arm more severely ill at study entry. Even with the adjusted analysis, residual confounding is possible. In addition, participants, healthcare workers, and outcome assessors were not blinded to the treatment arms.

Benefits

Preliminary evidence in ACTT-1 showed a trend in reduction of mortality by remdesivir over no remdesivir treatment at 14 days (HR: 0.70; 95% CI: 0.47, 1.04; Moderate CoE) [83]. Wang et al. failed to

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show a mortality benefit at 28 days (RR: 1.09; 95% CI: 0.54, 2.18; Low CoE) [84] but, because the trial was stopped early, the study may have been under-powered to detect an effect. Patients receiving treatment with remdesivir may have greater clinical improvement at 28 days than patients not receiving remdesivir (RR: 1.13; 95% CI: 0.91, 1.41; Low CoE) [84]. In addition, patients receiving treatment with remdesivir had a shorter median time to recovery (median 11 vs. 15 days; HR: 1.32; 95% CI: 1.12, 1.55; High certainty of evidence) [83].

In another study by Goldman et al that compared 5 and 10 days of treatment, the shorter course of remdesivir showed a trend toward decreased mortality (RR: 0.75; 95% CI: 0.51, 1.12; Low CoE) and increased clinical improvement at 14 days (RR: 1.19; 95% CI: 1.01, 1.40; Low CoE); however, the evidence is uncertain because the persons in the 10-day group had more severe disease at baseline and there is the possibility of residual confounding despite the adjusted analysis [85].

Harms

Patients treated with remdesivir do not appear to experience greater SAEs (grade 3/4) than those not receiving remdesivir (RR: 0.88; 95% CI: 0.74, 1.06; Moderate CoE) [83, 84].

Patients receiving five days of remdesivir may experience fewer SAEs and AEs leading to treatment discontinuation than patients receiving 10 days of remdesivir (RR: 0.61; 0.44, 0.85; Low CoE and RR: 0.44; 95% CI: 0.21, 0.95; Low CoE, respectively); however, this evidence is uncertain because of the increased severity of disease among patients in the 10 day arm [85].

Other considerations

The panel agreed that the overall certainty of the evidence for treatment with remdesivir compared to no remdesivir treatment was moderate due to concerns with imprecision. The panel decided to not pool the outcome of mortality as dichotomous data until 28-day data would be released from both trials, due to concerns with 14-day mortality showing a spurious effect. Given the limited evidence across baseline severity, the panel recognized a knowledge gap when assessing whether greater benefit could be attained for patients with less severe disease; however, the panel agreed that

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the reported data supported the prioritization of remdesivir among persons with severe but not critical COVID-19.

The panel agreed on the overall certainty of the evidence for treatment with a 5-day course compared to a 10-day course of treatment as low due to concerns with risk of bias and imprecision. The panel recognized the benefit of a shorter course of treatment, if providing similar or greater efficacy, on the availability of remdesivir.

Conclusions and research needs for this recommendation

The guideline panel suggests remdesivir rather than no remdesivir for treatment of severe COVID-19 in hospitalized patients. Additional clinical trials are needed to provide increased certainty about the potential for both benefit and harms of treatment with remdesivir, as well as understand the benefit of treatment based on disease severity.

Beigel 2020 reported that the 28-day follow up of the ACTT-1 will be made available. At that time, the outcomes will be reassessed.

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Table 8. GRADE evidence profile, Recommendation

Question: Remdesivir compared to no antiviral for hospitalized patients with severe COVID-19

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	no remdesivir	Relative (95% CI)	Absolute (95% CI)		

Mortality (follow up: 14 days)

1 ¹	randomized trials	not serious ^a	not serious	serious ^b	serious ^c	none	32/538 (5.9%)	54/521 (10.4%)	HR 0.70 (0.47 to 1.04)	30 fewer per 1,000 (from 54 fewer to 4 more)	⊕⊕○○ LOW	CRITICAL
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Mortality (follow up: 28 days)

1 ²	randomized trials	not serious ^{d,e}	not serious	not serious	very serious ^{c,f}	none	22/158 (13.9%)	10/78 (12.8%)	RR 1.09 (0.54 to 2.18)	12 more per 1,000 (from 59 fewer to 151 more)	⊕⊕○○ LOW	CRITICAL
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Clinical improvement (follow up: 28 days)

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	no remdesivir	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomized trials	not serious ^{d,e}	not serious	not serious	very serious ^c	none	103/158 (65.2%)	45/78 (57.7%)	RR 1.13 (0.91 to 1.41)	75 more per 1,000 (from 52 fewer to 237 more)	⊕⊕○○ LOW	CRITICAL

SAEs (grade 3/4)

2 ^{1,2}	randomized trials	not serious	not serious	not serious	serious ^g	none	159/693 (22.9%)	173/599 (28.9%)	RR 0.88 (0.74 to 1.06)	35 fewer per 1,000 (from 75 fewer to 17 more)	⊕⊕⊕○ MODERATE	CRITICAL
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Time to recovery

1 ¹	randomized trials	not serious ^a	not serious	not serious	not serious	None	334/538 (62.1%)	273/521 (52.4%)	HR 1.32 (1.12 to 1.55)	101 more per 1,000 (from 41 more to 160 more)	⊕⊕⊕⊕ HIGH	CRITICAL
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	no remdesivir	Relative (95% CI)	Absolute (95% CI)		

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

Publication bias: Selective publication of studies

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference

Explanations

- Some changes made to the protocol.
- The mortality outcome was not pooled as dichotomous variable between studies at 14 and 28 days because the ACCT trial presented the mortality results appropriately as time-to-event analysis due to possible chance effect at 14 days, as many patients still remained in the ICU setting. Rated down for indirectness of outcomes (lack of 28-day data in the ACTT trial).
- 95% CI may not include a clinically meaningful effect. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
- Co-interventions received include interferon alpha-2b, lopinavir/ritonavir, vasopressors, antibiotics, corticosteroid therapy and were balanced between arms.
- Trial stopped early due to lack of recruitment. Trial initiated after reduction in new patient presentation (most patients enrolled later in the disease course).
- The 95% CI includes the potential for appreciable harm but cannot exclude the potential for benefit.
- The 95% CI cannot exclude the potential for benefit or harm.

References

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Table 9. GRADE evidence profile, PICO 9

Question: Remdesivir 5 days compared to remdesivir 10 days for hospitalized patients with severe (not critically ill) COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir 5 days	remdesivir 10 days	Relative (95% CI)	Absolute (95% CI)		

Mortality

1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	16/200 (8.0%)	21/197 (10.7%)	HR 0.75 (0.40 to 1.39)	27 fewer per 1,000 (from 64 fewer to 42 more)	⊕⊕○○ LOW	CRITICAL
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Clinical improvement at 14 days

1 ¹	randomized trials	serious ^b	not serious	not serious	serious ^c	none	129/200 (64.5%)	107/197 (54.3%)	RR 1.19 (1.01 to 1.40)	103 more per 1,000 (from 5 more to 217 more)	⊕⊕○○ LOW	CRITICAL
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SAEs

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir 5 days	remdesivir 10 days	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^b	not serious	not serious	serious ^c	none	42/200 (21.0%)	68/197 (34.5%)	RR 0.61 (0.44 to 0.85)	135 fewer per 1,000 (from 193 fewer to 52 fewer)	⊕⊕○○ LOW	CRITICAL

AEs leading to treatment discontinuation

1 ¹	randomized trials	serious ^{b,d}	not serious	not serious	serious ^c	none	9/200 (4.5%)	20/197 (10.2%)	RR 0.44 (0.21 to 0.95)	57 fewer per 1,000 (from 80 fewer to 5 fewer)	⊕⊕○○ LOW	CRITICAL
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CI: Confidence interval; RR: Risk ratio

Explanations

- The 95% CI includes the potential for both appreciable benefit, as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
- Goldman 2020 did not blind participants, healthcare workers or outcome assessors. After randomization, disease severity was greater in the 10-day arm; while the analysis adjusted for baseline characteristics including disease severity, there is still the potential for residual confounding.
- The lower boundary of the 95% CI may not include a clinically meaningful effect. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
- Goldman stratified adverse events by days 1-5, 6-10. AEs leading to treatment discontinuation during days 1-5 were 9 (4%) in the 5-day arm and 14 (7%) in the 10-day arm.

References

- Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020.

Famotidine

New section added 6/22/20

Recommendation 10. Among hospitalized patients with severe COVID-19, the IDSA panel suggests against famotidine use for the sole purpose of treating COVID-19 outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)

The last literature search was conducted on June 18, 2020 and we identified one non-randomized study in OVID. There were no new non-indexed RCTs available.

Why is famotidine considered for treatment?

Anecdotal reports from China suggest that patients infected with coronavirus who were receiving famotidine, a H₂ receptor antagonist to treat conditions such as acid reflux and peptic ulcer disease, had improved survival vs. those receiving proton pump inhibitors (PPIs) [86]. This post hoc finding summarized below has led to interest in the drug, though no predominant theory describing a mechanism for its efficacy yet exists. One theory is that famotidine, like many other compounds, binds and therefore inhibits the coronavirus main protease, 3C-like main protease (3CLpro) [87].

Summary of the evidence

Our search identified one cohort study that compared 84 patients treated with famotidine against 1,536 patients not receiving treatment with famotidine [88]. Fifteen percent of patients in the famotidine group (13/84) started famotidine at home before presenting to the hospital. In addition, a subset of 420 patients not treated with famotidine were matched on baseline characteristics to the treated patients.

Benefits

Famotidine may decrease the composite outcome of death or intubation (HR: 0.42; 95% CI: 0.21, 0.85; Very low CoE); however, the evidence is very uncertain ([Table 10](#)).

Harms

Famotidine is well tolerated. Common adverse events include diarrhea or constipation but occur in less than 5% of people. Severe adverse events occur in less than 1% of persons taking famotidine.

Other considerations

The panel determined that the certainty of evidence to be very low due to concerns with risk of bias, imprecision, and possible publication bias. The panel agreed that critically ill patients (i.e., mechanically ventilated) may have been more likely to receive PPIs than famotidine, thus potentially allocating more prognostically favorable patients to the famotidine group; however, the study did not report a protective effect associated with the use of PPIs.

Conclusions and research needs for this recommendation

The guideline panel suggests against famotidine for the sole purpose of treating COVID-19, unless in the context of a clinical trial. Additional clinical trials are needed to inform research for treatment with famotidine for patients with COVID-19 (**Table s2**).

Table 10. GRADE evidence profile, PICO 10

Question: Famotidine compared to no famotidine for hospitalized patients with severe COVID-19

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	famotidine	no famotidine	Relative (95% CI)	Absolute (95% CI)		

Death or intubation (follow up: 30 days)

1 ¹	observational studies	serious ^a	not serious	not serious	serious ^b	publication bias strongly suspected ^c	8/84 (9.5%)	332/1536 (21.6%)	HR 0.42 (0.21 to 0.85)	119 fewer per 1,000 (from 166 fewer to 29 fewer)	⊕○○○○ VERY LOW	CRITICAL
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SAEs

0	observational studies						Post-marketing and registrational reported common adverse events include constipation (1.2%-1.4%), diarrhea (1.7%), dizziness (1.3%) and headache (1%-4.7%), but overall famotidine is well tolerated. Rare but serious adverse events (<1%) include Stevens-Johnson syndrome, toxic epidermal necrolysis, necrotizing enterocolitis, anaphylaxis, angioedema, rhabdomyolysis, seizure, hospital-acquired pneumonia, interstitial pneumonia. (Micromedex)			-	CRITICAL
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Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	famotidine	no famotidine	Relative (95% CI)	Absolute (95% CI)		

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

Publication bias: Selective publication of studies

CI: Confidence interval; **HR:** Hazard Ratio

Explanations

- Freedberg analysis adjusted for baseline characteristics of age, sex, race/ethnicity, BMI, comorbidities, and initial oxygen requirement (room air, nasal cannula, non-rebreather); however, 27% in the control arm were missing information on BMI. Potential residual confounding due to provision of famotidine being used in less sick/severe cases and PPIs in severe cases. Co-interventions/treatments were not reported (HCQ provided but not disaggregated across arms) and could modify the effect of the intervention. Approximately 15% of patients started famotidine at home, prior to hospitalization, which may lead to earlier co-interventions.
- Number of events is less than the optimal information size, which may suggest fragility in the estimate of effect.
- Concerns about selective reporting due to unavailability of disaggregated data for outcomes of mortality or intubation, missing supplemental files, and raw data for primary outcome from propensity-matched control group.

References

- Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. *Gastroenterology* 2020.

Narrative summaries of treatments undergoing evaluation

Last reviewed 6/22/20; updates to this section pending

In addition to the clinical questions addressed above, the panel identified several treatments currently undergoing evaluation for which additional data are needed to rate recommendations. Narrative summaries for these treatments are provided below.

HIV antivirals

In-vitro antiviral activity of darunavir against SARS-CoV-2 showed no activity at clinically relevant concentrations. Three randomized, open-label clinical trials are currently listed on evaluating darunavir/cobicistat as a potential therapeutic option for COVID-19. Janssen, the manufacturer of darunavir/cobicistat has reported that one of these trials [89] has concluded that darunavir/cobicistat plus conventional treatments was not effective in achieving viral clearance at day seven post randomization, compared to conventional treatments alone. Clinical outcomes of this trial including rate of critical illness and mortality 14 days after randomization, have not been reported to date.

Lopinavir-ritonavir combined with interferon beta or other antivirals

Lopinavir-ritonavir is a combination of protease inhibitors for the treatment of HIV infection. Lopinavir-ritonavir has been shown to have in-vitro antiviral activity against beta-coronaviruses such as SARS-CoV, and MERS-CoV [90-93]. Since lopinavir-ritonavir is not specifically designed for treatment of coronavirus, lopinavir-ritonavir alone may not demonstrate a difference from placebo in reducing viral load when treatment was initiated at a median of 13 days after symptoms onset [92]. In an open label treatment trial, lopinavir-ritonavir with ribavirin reduced the mortality and requirement of intensive care support of hospitalized SARS-CoV-1 patients compared with historical control [92]. Many interferons, especially interferon beta have been shown to have modest in-vitro antiviral activity against SARS-CoV and MERS-CoV [90, 91]. Lopinavir-ritonavir or interferon beta-1b has been shown to

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reduce viral load of MERS-CoV and improve lung pathology in a nonhuman primate model of common marmoset [93]. Lopinavir/ritonavir and interferon- β 1b alone or in combination are being evaluated in clinical trials.

COVID-19 convalescent plasma for prophylaxis

There is a long history of using CP as treatment for infectious diseases, including severe viral lower respiratory tract infections [94]. Individuals who have recovered from SARS-CoV-2 infection may generate neutralizing antibodies [95, 96] that could have application to prevention of infection in certain settings, such as individuals with underlying conditions predisposing to severe disease and those with high-risk exposure. Monoclonal antibodies against other respiratory viruses have been shown to be protective against hospitalization in specific high-risk populations [97, 98] and animal models have suggested utility in prophylaxis against SARS-CoV-1 coronavirus infection [99]. There are some risks associated with the use of CP like transfusion-related acute lung injury or a theoretical risk of antibody-dependent enhancement of infection (ADE). Antibody-dependent enhancement of infection can occur in several viral diseases and involves an enhancement of disease in the presence of certain antibodies [100]. A trial from patients recovered from SARS-CoV-2 infection for use as prophylaxis in adults with a high-risk exposure is expected to begin recruiting shortly [101].

Ribavirin

There are only *in vitro* data available on the activity of ribavirin on SARS-CoV-2 currently. The EC₅₀ (half maximal effective concentrations) was significantly higher than for chloroquine and remdesivir, so it appears less potent *in vitro* compared to these agents [16]. There are limited clinical studies in SARS-CoV-1 and MERS-CoV infections. In a systematic review of ribavirin treatment in patients infected with SARS-CoV-1, 26 studies were classified as inconclusive, and four showed possible harm [61]. In a retrospective observational study in patients with MERS-CoV infection, the combination of ribavirin and interferon, compared to no antiviral treatment, was not associated with improvement in the 90-day mortality or more rapid MERS-CoV RNA clearance [102].

Oseltamivir

Oseltamivir is a neuraminidase inhibitor used for prophylaxis and treatment of influenza. Given its specificity for an enzyme not found on coronaviruses, it is unclear what the mechanism of action would be against COVID-19. However, this has been used in combinations of antiviral therapy in Wuhan [103] and continues to be explored as a therapeutic option as part of combination regimens. Two trials evaluating combination regimens are underway in Wuhan [104, 105] as well as a trial in Thailand proposing different combinations [106]. None of the trials or case reports have examined oseltamivir as monotherapy.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has been used as an adjuvant to treat a variety of pathogens either as a pooled product or in a concentrated more pathogen focused (hyperimmune) form. As the community from which a given batch of IVIg is derived from includes increasing numbers of individuals who have recovered from SARS-CoV-2, the possibility of protective antibodies being present in the pooled product is increased. However, the potential utility of IVIg for the treatment of SARS-CoV-2 is unknown at this time. Its use has been reported in a few patients with COVID-19 [107], but studies are needed to determine if there may be a role for IVIg in the treatment of SARS-CoV-2.

Should NSAIDs be stopped in patients with COVID-19?

The role of Nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of SARS-CoV2 has been discussed widely. Recent anecdotal reports and subsequent warnings from health officials have suggested against the use of NSAIDs in the care of patients with COVID-19; however, neither FDA, European Medicines Agency, or the World Health Organization have identified evidence linking NSAIDs to COVID-related clinical deterioration. Human coronaviruses, including SARS CoV-2, use ACE2 to bind to human targets and gain entry into target cells [108]. It has been theorized that NSAIDs, due to upregulation in ACE2 in human target cells, may lead to a more severe course of COVID-19 in those taking NSAIDs. While no

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causal evidence of adverse outcomes with NSAIDs in the management of COVID-19 have been published, there are well known risks of non-steroidal anti-inflammatory agents including cardiovascular, gastrointestinal and renal adverse events [109, 110]. In the setting of bacterial pneumonia, NSAIDs may impair recruitment of polymorphonuclear cells, resulting in a delayed inflammatory response and resolution of infection, however a causal relationship has not been established [111, 112]. RCTs are needed to better understand the safety of NSAIDs in the management of patients with COVID-19. One RCT is currently underway to evaluate the role of naproxen in those critically ill with COVID-19 [113].

Should ACE inhibitors and ARBs for hypertension be stopped in patients with COVID-19?

Angiotensin converting enzyme 2 (ACE2) is the receptor for SARS CoV-2 on human cells. Because angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may increase ACE2 expression, the possibility has been raised that these drugs may increase the likelihood of acquiring SARS-CoV-2 or may exacerbate the course of COVID-19. To date, however, there are no clinical data to support this hypothetical concern. For this reason, the American Heart Association, the Heart Failure Society of America and the American College of Cardiology all recommend that ACE inhibitors or ARBs be continued in people who have an indication for these medications [114].

Discussion

During epidemics like the current COVID-19 pandemic, when there are no clinically proven treatments, the tendency is to use drugs based on *in vitro* antiviral activity, or on anti-inflammatory effects or based on limited observational studies. It is commendable that observational studies are done during an epidemic, but often they do not have concurrent controls, have a significant risk of bias, and use surrogate outcomes like viral clearance rather than patient-important outcomes. Medications that were thought to be effective based on *in*

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vitro studies and observational studies for other diseases were later proven to be ineffective in clinical trials [115].

Due to the understandable urgency in producing, synthesizing and disseminating data during the current pandemic, there has been a noticeable increase in fast track publication of studies. In addition to well-established concerns that may decrease our certainty in the available evidence, there may be additional issues that will ultimately influence the trustworthiness of that evidence, including: 1) Circumvention of usual research steps (delay of IRB approval [116], inclusion of same patients in several studies); 2) Limited peer-review process (the usual due diligence from editors and reviewers is side-stepped, potentially leading to unnoticed errors in data and calculations, incomplete reporting of methods and results, as well as underestimation of study limitations); 3) Increased potential for publication bias (in the interest of showing promising data and in the race to achieve recognition, there may be added inclination to publish positive results and disregard negative ones). The extent and impact of these considerations remain currently uncertain but were acknowledged in the development of this guideline.

Despite these limitations, the recommendations in this guideline are based on evidence from the best available clinical studies with patient-important endpoints. The panel determined that when an explicit trade-off between the highly uncertain benefits (e.g., the panel was unable to confirm that HCQ increases viral cure or reduces mortality) and the known putative harms (QT prolongation and drug-drug interactions) were considered, a net positive benefit was not reached and could possibly be negative (risk of excess harm). The safety of drugs used for the treatment of COVID-19, especially in patients with cardiovascular disease, immunosuppressive conditions, or those who are critically ill with multi-organ failure has also not been studied. Drugs like AZ and HCQ can cause QT prolongation and potentially life-threatening arrhythmias. Steroids and IL-6 inhibitors can be immunosuppressive and potentially increase risk of secondary infections. Steroids may produce long term side effect such as osteonecrosis [117]. In instances where the panel could not make a determination whether the benefits outweigh harms, it is be ethical and prudent to enroll patients with COVID-19 in clinical

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trials, rather than use clinically unproven therapies [118]. There are multiple ongoing trials, some with adaptive designs, which potentially can quickly answer pressing questions on efficacy and safety of drugs in the treatment of patients with COVID-19.

We acknowledge that enrolling patients in RCTs might not be feasible for many frontline providers due to limited access and infrastructure. Should lack of access to clinical trials exist, we encourage setting up local or collaborative registries to systematically evaluate the efficacy and safety of drugs to contribute to the knowledge base. Without such evaluations we often attribute success to drugs and failure to disease (COVID-19) [115]. During such a pandemic, barriers to conducting studies and enrolling patients in trials for already overburdened front line providers should be minimized while ensuring the rights and safety of patients [119].

For clinical trials and observational studies, it is critical to determine *a priori* standardized and practical definitions of patient populations, clinical syndromes, disease severity and outcomes. Observational and non-experimental studies can sometimes answer questions not addressed by trials, but there is still a need for standardized definitions. For clinical syndromes clearly distinguishing between asymptomatic carrier state, upper respiratory tract infection and lower respiratory tract infection is important. Illness severity should be reasonably defined using readily available clinical criteria of end organ failure, like the degree of respiratory failure using SpO₂ (percentage of oxyhemoglobin saturation) or PaO₂:FiO₂ ratios (partial pressure of oxygen in arterial blood: fractional percentage of inspired oxygen) for lower respiratory tract infection, as opposed to location-based severity determinations such as ICU admission, which can lead to bias based on resource limitations (i.e., bed availability) or regional/institutional practice patterns [120]. For outcomes of prophylaxis trials, the primary endpoint should be prevention of infection and for therapeutic trials patient centered outcomes like reduction of mortality (both short term and long term) [121]. Trials should also study treatments in high risk populations or special populations like immunosuppressed patients, people with HIV, patients with cardiovascular comorbidities and pregnant women. The panel expressed the overarching goal that patients be recruited into ongoing trials, which

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would provide much needed evidence on the efficacy and safety of various therapies for COVID-19.

This is a living guideline that will be frequently updated as new data emerges. Updates and changes to the guideline will be posted to the IDSA website.

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COI Summary:

The following list is a reflection of what has been reported to the IDSA. To provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the Board of Directors liaison to the Standards and Practice Guideline Committee and, if necessary, the Conflicts of Interest (COI) and Ethics Committee. The assessment of disclosed relationships for possible COI is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. **L.B.**

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