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

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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: 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.

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 against hydroxychloroquine. (Strong recommendation, Moderate certainty of evidence)

- **Remark:** Chloroquine is considered to be class equivalent to hydroxychloroquine.

Recommendation 2: Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine plus azithromycin. (Strong recommendation, Low certainty of evidence)

- **Remark:** Chloroquine is considered to be class equivalent to hydroxychloroquine.

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 hospitalized patients with severe* COVID-19, the IDSA guideline panel suggests glucocorticoids rather than no glucocorticoids. (Conditional recommendation, Moderate certainty of evidence)

- **Remark:** Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

*Severe illness is defined as patients with SpO_2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or extracorporeal mechanical oxygenation (ECMO).

Recommendation 5: Among hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)

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: In 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 ECMO.

*Severe illness is defined as patients with SpO_2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.

Recommendation 9: In patients 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.

Recommendation 10: 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.

Recommendation 11: 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.

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 Conflicts 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 August 7, 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 two or fewer 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].

As higher quality direct evidence for clinical outcomes becomes available, outcomes previously deemed critical by the panel became less important for decision-making. For example, at the time of the first guideline, clinical improvement outcomes (e.g. need for mechanical ventilation) were not reported, only the results of radiographic findings. However, with the recent publication of RCTs and non-randomized studies reporting on direct measures of clinical improvement, results of radiographic studies were deemed to be less critical for decision making.

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**).

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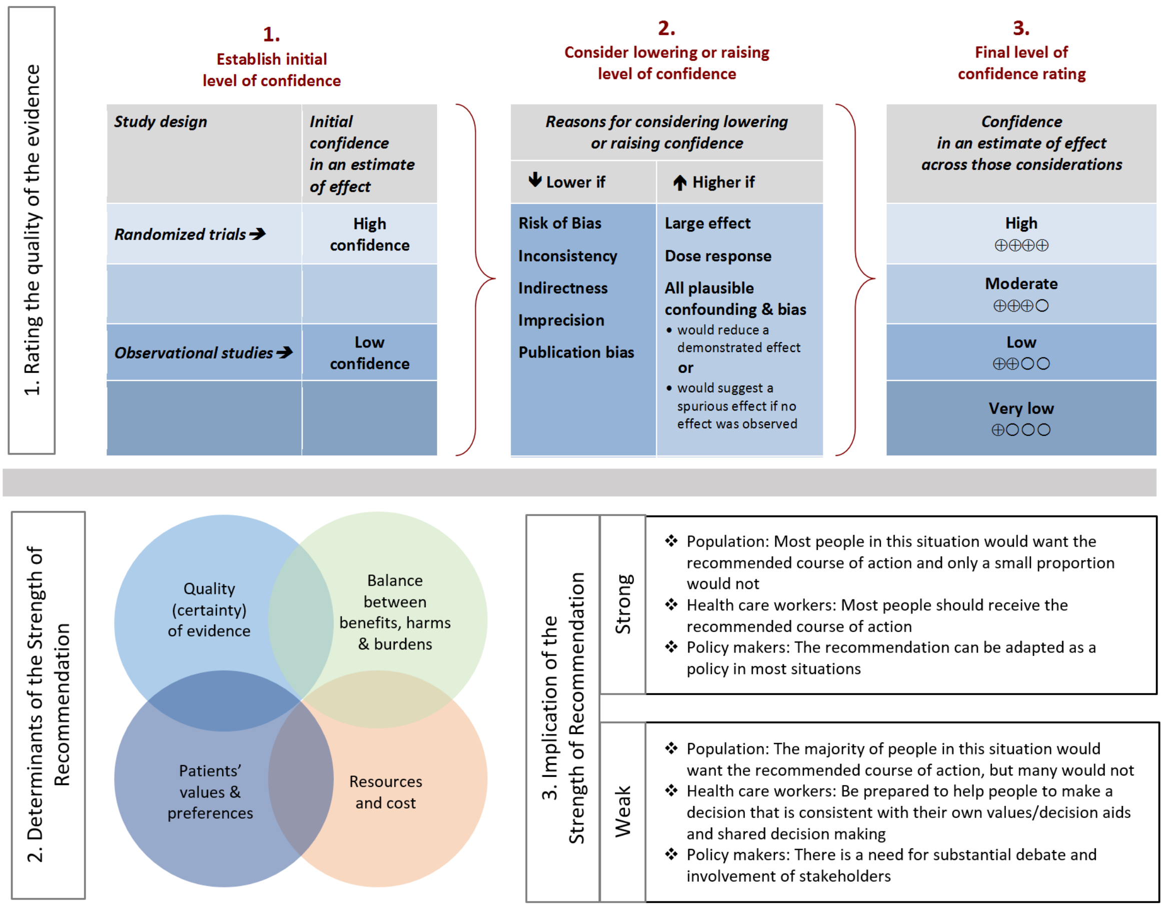
Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network)



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 PICOs, 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 8/20/20

Recommendation 1: Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine*. (Strong recommendation, Moderate certainty of evidence)

- **Remark:** Chloroquine is considered to be class equivalent to hydroxychloroquine.

Recommendation 2: Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine* plus azithromycin. (Strong recommendation, Low certainty of evidence)

- **Remark:** Chloroquine is considered to be class equivalent to hydroxychloroquine.

The last literature search was conducted on August 7, 2020. The summary of evidence is based on five RCTs and eight non-randomized studies.

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]. Both drugs have been used in the treatment of autoimmune diseases because of their immunomodulatory effects on several cytokines, including IL-1 and IL-6 [13]. There is some evidence that these drugs also have antiviral properties against many different viruses, including the coronaviruses [14, 15]. They have demonstrated *in vitro* activity against SARS-CoV-2, which range considerably between studies but are generally within the range of predicted achievable tissue concentrations [14, 16-18]. The *in vitro* activity, the extensive use for other conditions, and widespread availability of generic versions of the drug made it an 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 also been shown to have *in vitro* antiviral activity [20-22]. While the exact mechanism of antiviral activity is unknown, possibilities include inhibiting endocytosis and limiting viral replication [23] and the induction of interferon [22, 24]. Macrolides have also been shown to have anti-inflammatory activity [25, 26].

Summary of the evidence

Our search identified five RCTs and seven comparative cohort studies of hospitalized patients with confirmed COVID-19 treated with HCQ with reported mortality, clinical progression or clinical improvement, and adverse events outcomes [27-38] (**Table s3a**) (**Table 1**).

In addition, we identified one RCT, four comparative cohort studies, and one case-control study reporting adjusted analyses of hospitalized patients with confirmed COVID-19 treated with HCQ plus AZ with reported mortality, failure of virologic clearance (assessed with polymerase chain reaction [PCR] test), clinical improvement, and adverse events (i.e., significant

QT prolongation leading to treatment discontinuation) [27, 28, 34, 36, 38, 39] **(Table s3a**) (**Table 2**).

Benefits

Hydroxychloroquine

Two RCTs failed to show at least a 1% absolute risk reduction assuming a baseline risk of 25% mortality or to exclude mortality among patients with COVID-19 treated with HCQ compared to those who were not (relative risk [RR]: 1.07; 95% confidence interval [CI]: 0.97, 1.19, Moderate certainty in the evidence) (**Table 1**) [28, 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% 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); and Rosenberg 2020 reported an adjusted HR of 1.08 (95% CI: 0.63, 1.85) [33-36, 38]. One non-randomized study reported a decrease in mortality among hospitalized persons treated with HCQ (adjusted HR: 0.36; 95% CI: 0.18, 0.75) [37]. An additional non-randomized study suggested a decrease in mortality among persons treated with HCQ when compared with no treatment (HR: 0.34; 95% CI: 0.25, 0.46); however, it did not adjust for severity of disease in analysis and there were imbalances in steroid use (which may have affected mortality) between the groups [27]. Controlling for the critical confounder of disease severity is especially important during the first 24- to 48-hour period after intake, since high mortality may be observed with no treatment, when in fact patients actually presented at the hospital with advanced disease state. In this study, 78.9% of patients given HCQ also received steroids vs. 35.7% who did not receive HCQ. Given the beneficial effect of steroids on reducing mortality and increasing likelihood of hospital discharge seen in the RECOVERY trial, the disproportionate nature of steroid use in the HCQ arm is a major confounder. Others have raised concerns with the method in which patients were allocated into treatment groups (referred to no treatment arm if a poor prognosis was present at baseline, i.e., palliative intent), as well as how and which variables were adjusted to address residual confounding from known prognostic variables [40-43].

Hydroxychloroquine + Azithromycin

One RCT could not exclude the risk of in-hospital mortality among patients treated with HCQ+AZ compared to those not receiving HCQ or HCQ+AZ (HR: 0.64; 95% CI: 0.18, 2.21; Low certainty of evidence [CoE]) [28]. 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) [34, 36, 38]. As stated in the HCQ section, one non-randomized study reported a reduction in mortality among patients receiving HCQ+AZ (HR: 0.29; 95% CI: 0.22, 0.40); however, it failed to adjust for the critical confounder of disease severity and imbalances in steroid use [27]. As described in the HCQ section, similar methodologic concerns exist among patients allocated to HCQ+AZ in the Arshad study, leading to several sources of bias in interpreting their favorable results.

Harms

Hydroxychloroquine

One RCT reported that persons treated with HCQ experienced a longer time until hospital discharge (median 16 days compared with 13 days) and lower probability of being discharged alive within the 28-day study period (rate ratio: 0.92; 95% CI: 0.85, 0.99) [29]. In addition, persons treated with HCQ who were not on mechanical ventilation at baseline were more likely to be placed on mechanical ventilation during follow up (rate ratio: 1.11; 95% CI: 0.89, 1.37; Low CoE). Across the body of evidence from four RCTs, treatment with HCQ may increase the risk of experiencing adverse events (RR: 2.36; 95% CI: 1.49, 3.75; Low CoE) [28, 30-32]. One RCT and two non-randomized studies suggest increased risk of QT prolongation among patients treated with HCQ compared to those not receiving HCQ (RR: 8.47; 95% CI: 1.14, 63.03; Low CoE and RR: 2.89; 95% CI: 1.62, 5.16; Very low CoE, respectively) [28, 35, 36]. 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; Very low CoE).

Gastrointestinal side effects occurred in 7% of patients in a prospective cohort study in 224 COVID-19 uninfected patients with systemic lupus erythematosus (SLE) who received either chloroquine or hydroxychloroquine for routine care [44].

While the 4-aminoquinolines, chloroquine and HCQ, have not been demonstrated to cause hemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency [45, 46], case reports of hemolysis have emerged when these agents have been used for the treatment of COVID-19 [47-49]. It is possible that infection with SARS-CoV-2 may trigger hemolysis in G6PD deficient individuals in the absence of a 4-aminoquinolone. Caution should be exercised 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. Chloroquine and HCQ are metabolized by cytochrome P450 isoenzymes 2C8, 2D6, and 3A4 [50]. Therefore, inhibitors and inducers of these enzymes may result in altered pharmacokinetics of these agents.

Hydroxychloroquine + Azithromycin

One RCT suggests increased risk of QT prolongation among patients treated with HCQ+AZ compared to those not receiving HCQ (RR: 8.50; 95% CI: 1.16, 62.31; Low CoE) [28, 30-38]Two studies described significant QT prolongation in 10 of 95 patients treated with HCQ+AZ, illustrating the high risk for clinically relevant arrhythmias with this treatment [51, 52]. In addition, several case reports of QT prolongation related to HCQ have also been published [53-56]. 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) compared to controls (n=34) [39].

Additional case reports have cited 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 either no antibiotic or amoxicillin, respectively [57]. Given the cumulative effect on cardiac conduction seen with HCQ and AZ, if this combination was used, 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.

Azithromycin has a low risk for cytochrome P450 interactions [58]; 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.

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

Other considerations

The panel agreed that the overall certainty of evidence against treatment with HCQ was moderate due to concerns with imprecision around the risk for a trend towards harms from increased mortality. When considering the addition of AZ, the overall certainty of the evidence was low; however, the panel recognized even greater concern with the toxicity. In addition, based on the moderate certainty of increased QT prolongation, the panel determined that this demonstrated certain harm with uncertain benefit; therefore, the panel made a strong recommendation against HCQ+AZ.

Conclusions and research needs for this recommendation

The guideline panel recommends against the use of either HCQ alone or in combination with AZ in the hospital setting as higher certainty benefits (e.g., mortality reduction) are now highly unlikely even if additional high quality RCTs would become available.

This recommendation does not address the use of azithromycin for secondary bacterial pneumonia in 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: range 22 days to 49 days)												
2 [1,2]	randomized trials	not serious [a]	not serious	not serious [b]	serious [c]	none	425/1720 (24.7%)	794/3328 (23.9%)	**RR 1.07** (0.97 to 1.19)	**17 more per 1,000** (from 7 fewer to 45 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical status (assessed with: 7-point scale, higher values represent worse clinical outcomes)												
1 [2]	randomized trials	serious [d]	not serious	not serious	serious [e]	none	159	173	-	median **1.21 higher** (0.69 higher to 2.11 higher)	⨁⨁◯◯ LOW	CRITICAL
Progression to invasive mechanical ventilation												
1 [1]	randomized trials	serious [f]	not serious	not serious	serious [e]	none	118/1300 (9.1%)	215/2623 (8.2%)	**RR 1.11** (0.89 to 1.37)	**9 more per 1,000** (from 9 fewer to 30 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events, any												
4 [2,3,4,5]	randomized trials	serious [g]	not serious	not serious	serious [e]	none	94/315 (29.8%) [h]	18/176 (10.2%) [i]	**RR 2.36** (1.49 to 3.75)	**139 more per 1,000** (from 50 more to 281 more)	⨁⨁◯◯ LOW	IMPORTANT
QT prolongation (RCTs)												
1 [2]	randomized trials	not serious	not serious	not serious	very serious [j]	none	13/89 (14.6%)	1/58 (1.7%)	**RR 8.47** (1.14 to 63.03)	**129 more per 1,000** (from 2 more to 1,000 more)	⨁⨁◯◯ LOW	IMPORTANT

QT prolongation (NRS)												
2 [6,7]	observational studies	very serious [k,l]	not serious	not serious	serious [j]	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
Arrhythmias												
1 [6]	observational studies	very serious [k]	not serious	not serious	very serious [e,j]	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
Severe AEs												
0	observational studies	serious [m]	not serious	not serious	serious [m]	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]				⨁◯◯◯ VERY LOW	CRITICAL

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. Co-interventions were provided to patients in both studies but balanced across arms.
b. Cavalcanti 2020 excludes persons receiving supplemental oxygen at a rate of more than 4 liters per minute.
c. The 95% CI cannot exclude the potential for no benefit or harm.
d. Cavalcanti was an open-label trial.
e. The 95% CI includes the potential for both benefit and harm.
f. Horby 2020 was an open-label trial.
g. 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.
h. 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%).
i. 3 AEs reported in 2 patients include: AST elevation, creatinine elevation and anemia

j. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
k. Concerns with unmeasured and residual confounding. Multiple co-interventions received across arms.
l. Mahevas 2020 does not report on AEs in the comparator arm.
m. Case reports

References

1. Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. medRxiv **2020**.
2. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med **2020**.
3. Chen J, LIU D, LIU L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Journal of Zhejiang University (Medical Sciences) **2020**; 49(1): 0-.
4. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv **2020**.
5. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. bmj **2020**; 369.
6. 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**.
7. 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.**
8. Wang C, Fortin PR, Li Y, Panaritis T, Gans M, Esdaile JM. Discontinuation of antimalarial drugs in systemic lupus erythematosus. J Rheumatol **1999**; 26(4): 808-15.

Table 2. GRADE evidence profile, PICO 2

Question: Hydroxychloroquine and azithromycin compared to no hydroxychloroquine/azithromycin 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 and azithromycin	no HCQ/azithromycin	Relative (95% CI)	Absolute (95% CI)		
Mortality (RCTs) (follow up: range 22 days to 49 days)												
1 [1]	randomized trials	not serious [a]	not serious	not serious [b]	very serious [c,d]	none	5/172 (2.9%)	6/173 (3.5%)	**HR 0.64** (0.18 to 2.21)	**12 fewer per 1,000** (from 28 fewer to 40 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality (NRS)												
3 [2,3,4]	observational studies	very serious [e]	not serious	not serious	serious [d]	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)(Ip, Magagnoli 2020, Rosenberg 2020).				⨁◯◯◯ VERY LOW	CRITICAL
Clinical status (assessed with: 7-point scale, higher values represent worse clinical outcomes)												
1 [1]	randomized trials	serious [f]	not serious	not serious [b]	serious [d,g]	none	172	173	-	MD **0.99 higher** (0.57 higher to 1.73 higher)	⨁⨁◯◯ LOW	CRITICAL

Virologic Failure (follow up: range 5 days to 6 days; assessed with: PCR Test)												
2 [5,6,7]	observational studies	very serious [h]	serious [i]	serious [j]	serious [c]	none	29/71 (40.8%) [k]	12/12 (100.0%) [l]	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
QT prolongation (RCTs)												
1 [1]	randomized trials	not serious	not serious	serious [m,n]	serious [c]	none	17/116 (14.7%)	1/58 (1.7%)	**RR 8.50** (1.16 to 62.31)	**129 more per 1,000** (from 3 more to 1,000 more)	⨁⨁◯◯ LOW	IMPORTANT
QT prolongation (NRS)												
2 [7,8]	observational studies	very serious [h]	not serious	serious [n]	serious [c]	none	10/95 (10.5%) [n]	-	-	-	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events												
1 [1]	randomized trials	serious [f]	not serious	not serious [o]	serious [c,d]	none	5/239 (2.1%)	0/50 (0.0%)	**RR 2.34** (0.13 to 41.61)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Co-interventions were provided to patients but balanced across arms. Cavalcanti 2020 was open label; however, likely did not influence the outcome of mortality.
b. Cavalcanti 2020 excludes persons receiving supplemental oxygen at a rate of more than 4 liters per minute.
c. A very small number of events. Optimal information size not met.
d. The 95% CI includes the potential for both benefit and harm.
e. Concerns with unmeasured and residual confounding. Multiple co-interventions received across arms.
f. Cavalcanti was an open-label trial.
g. Optimal information size not met.
h. No contemporaneous control groups; no adjustment for baseline severity, resulting in high risk for residual confounding
i. 2 case series from France showed divergent results
j. Surrogate marker for mortality or resolution of COVID-19.
k. Goutret 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%)
l. Gautret reported on a historical viral clearance rate in symptomatic patients from a separate hospital. Criteria for selection of patients remains unclear, as presumably a sizable number of untreated patients could have been available with data on viral clearance.
m. Indirect measure of arrhythmia-specific mortality.
n. 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.
o. Molina 2020: 1/11 leading to treatment discontinuation; Chorin 2020: 9/84 with significant QTc prolongation of more than 500 ms.
p. Cavalcanti 2020 serious adverse events included pulmonary embolism, Qtc prolongation, myocardial infarction, abdominal-wall hemorrhage.

References

1. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med **2020**.
2. 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**.
3. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Med **2020**.
4. Ip A, Berry DA, Hansen E, et al. Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients-An Observational Study. medRxiv **2020**.
5. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents **2020**: 105949.
6. 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**.
7. Molina JM, Delaugerre C, Goff J, et al. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Médecine et Maladies Infectieuses **2020**.
8. Chorin E, Dai M, Shulman E, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. medRxiv **2020**.

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 [59-61] (**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 seven-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

The panel elected to inform their decision based on the RCT [61]. 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**).

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 a 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

Glucocorticoids

Section last reviewed and updated 6/25/20

Recommendation 4: Among hospitalized patients with severe* COVID-19, the IDSA guideline panel suggests glucocorticoids rather than no glucocorticoids. (Conditional recommendation, Moderate certainty of evidence)

- **Remark:** Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendation 5: Among hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)

*Severe illness is defined as patients with SpO_2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.

The last literature search was conducted on June 18, 2020 and we identified one RCT pre-print and seven comparative non-randomized studies.

Why are corticosteroids considered for treatment?

In the early days of the SARS-CoV-2 pandemic, based on experience in both SARS and MERS, recommendations [62] cautioned against the use of systemic corticosteroids due to risk of worsening clinical status, delayed viral clearance, and adverse events [63-65]. Given the hyper-inflammatory state in COVID-19, immunomodulatory approaches, including steroids, continue to be evaluated to address both ARDS and systemic inflammation. ARDS stemming from dysregulated systemic inflammation may translate into prolonged ventilatory requirements and in-hospital mortality. In non-viral ARDS settings there is increasing support for the role of steroids in the management of ARDS [66]. A recent multicenter RCT in patients with moderate-severe ARDS demonstrated a reduced number of ventilatory days and reduction in mortality with use of a 10-day regimen of dexamethasone [67].

Summary of the evidence

Our search identified one RCT, one "partially" randomized trial, one prospective cohort, and five retrospective cohort studies [59, 68-74]. The RCT provided the best available evidence on treatment with corticosteroids for persons with COVID-19 [68] (**Tables 4 and 5**). Corral-Gudino et al. reported on a study that randomized patients to receive methylprednisolone or standard of care; however, patients expressing a preference for methylprednisolone were assigned to the same treatment arm [69]. Corral-Gudino et al. did not report the disaggregated results from the randomized trial; therefore, succumbing to the same potential for bias as reported subsequently for the non-randomized studies. The non-randomized studies had significant limitations with controlling for multiple co-interventions and disease severity at baseline [59, 70-74]. All non-randomized studies had concerns with risk of bias due to lack of adjustment for critical confounders or potential for residual confounding. Timing of receipt, dose and duration of corticosteroids varied across studies.

The RECOVERY trial is a randomized trial among hospitalized patients in the United Kingdom [68]. In that study, 2104 participants were randomized to receive dexamethasone (6 mg daily for up to 10 days) and 4321 were randomized to usual care. The RECOVERY trial reported on the outcomes of mortality and hospital discharge. Participants and study staff were not blinded to the treatment arms.

Benefits

Among hospitalized patients, 28-day mortality was 17% lower in the group that received dexamethasone than in the group that did not receive dexamethasone (RR 0.83; 0.74-0.92; Moderate certainty of evidence). In addition, at 28 days, patients receiving dexamethasone are more likely to be discharged from the hospital (RR: 1.11; 95% CI: 1.04, 1.19; Moderate certainty of evidence).

In sub-group analyses of patients without hypoxia not receiving supplemental oxygen, there was no evidence for benefit and a trend toward harm with dexamethasone in participants who were not on supplemental oxygen (RR 1.22; 0.86, 1.75; Low certainty of evidence).

Harms

Patients receiving a short course of steroids may experience hyperglycemia, neurological side effects (e.g., agitation/confusion), adrenal suppression, and risk of bacterial and fungal infection [70, 75, 76].

Other considerations

The panel agreed the overall certainty of evidence for treatment with glucocorticoids for patients with severe COVID-19 as moderate due to concerns with indirectness since the evidence was from dexamethasone. The panel agreed that the overall certainty of evidence for patients without hypoxemia requiring supplemental oxygen as low due to concerns with risk of bias (post hoc analysis) and imprecision.

Conclusions and research needs for this recommendation

The guideline panel suggests glucocorticoids for patients with severe COVID-19. The guideline panel suggests against glucocorticoids for patients with COVID-19 without hypoxemia requiring supplemental oxygen.

Additional research is needed to inform the generalizability of treatment with different glucocorticoids for patients with COVID-19 (**Table s2**).

Table 4. GRADE evidence profile, PICO 4

Question: Glucocorticoids compared to no glucocorticoids for hospitalized patients with severe COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucocorticoids	no glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1 [1]	randomized trials	not serious [a]	not serious	serious [b]	not serious	none	454/2104 (21.6%)	1065/4321 (24.6%)	**RR 0.83** (0.74 to 0.92)	**42 fewer per 1,000** (from 64 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospital discharge (follow up: 28 days)												
1 [1]	randomized trials	not serious [a]	not serious	serious [b]	not serious	none	1360/2104 (64.6%)	2639/4321 (61.1%)	**RR 1.11** (1.04 to 1.19)	**67 more per 1,000** (from 24 more to 116 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse events												
							Patients receiving a short course of steroids may experience hyperglycemia, neurological side effects (e.g., agitation/confusion), adrenal suppression, and risk of infection (Salton 2020; Henzen 2000; Siemieniuk 2015).				-	CRITICAL

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. Analysis adjusted for baseline age.
b. Indirectness due to different health care system (allocation of intensive care resources in an unblinded study). Indirectness to other corticosteroids.

References

1. Horby P, Lim WS, Emberson J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv 2020: 2020.06.22.20137273. **2020**.

Table 5. GRADE evidence profile, PICO 5

Question: Glucocorticoids compared to no glucocorticoids for hospitalized patients with COVID-19 not receiving supplemental oxygen

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucocorticoids	no glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	85/501 (17.0%)	137/1034 (13.2%)	**RR 1.22** (0.93 to 1.61)	**29 more per 1,000** (from 9 fewer to 81 more)	⨁⨁◯◯ LOW	CRITICAL
Hospital discharge (follow up: 28 days)												
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [c]	none	366/501 (73.1%)	791/1034 (76.5%)	**RR 0.99** (0.87 to 1.12)	**8 fewer per 1,000** (from 99 fewer to 92 more)	⨁⨁◯◯ LOW	IMPORTANT
Adverse events												
							Patients receiving a short course of steroids may experience: hyperglycemia, neurological side effects (e.g., agitation/confusion), adrenal suppression, and risk of infection (Salton 2020; Henzen 2000; Siemieniuk 2015).				-	CRITICAL

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

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. RoB due to post-hoc subgroup effect among persons not receiving supplemental oxygen.
b. The 95% CI includes the potential for appreciable harm and cannot exclude the potential for benefit. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
c. The 95% CI cannot exclude the potential for either appreciable harm or benefit.

References

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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) [77] during the clinical illness. Our search identified one study [77] 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 [78].

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 [77]. However, patients receiving tocilizumab are often at an increased risk of serious infections (bacterial, viral, invasive fungal infections, and tuberculosis) and hepatitis B reactivation [79]. 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.

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 [80, 81].

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**).

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

a. No contemporaneous control group.
b. All patients also received lopinavir and methylprednisolone
c. 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%
d. Imaging finding is a surrogate endpoint for worsening clinical status.
e. Few case reports
f. 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
g. Causality remains uncertain

References

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Convalescent Plasma for COVID-19 Treatment

Section last reviewed 9/2/20; updated 9/4/20

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 August 21, 2020 and we identified two RCTs and nine non-randomized 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 [82, 83]. 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 [84-86]. In the current pandemic, CP obtained from individuals who recovered from COVID-19 has been used in over 75,000 patients with moderate to severe infection as part of an expanded access program [87]. When measurement of neutralizing antibody titers is available, the United States 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 ≥1:320. Titers at that level are seen in about 80% of donors [88]. The probability of obtaining a neutralizing antibody titer of ≥1:160 is highest (80% or greater) when the ELISA IgG titer is ≥1:1,350 [89]. In an analysis of a convalescent plasma expanded access program, higher levels of antibodies were associated with significant improvements in mortality compared to those receiving CP with lower concentrations of neutralizing antibodies [87]. 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 [90, 91]. The analysis of the convalescent plasma expanded access program suggests the most benefit is seen when CP is given in the first three days from diagnosis [87]. On August 23, 2020, the Food and Drug Administration issued an emergency use authorization for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients [92].

Summary of the evidence

Our search identified two RCTs, four comparative cohort studies, and three publications from a large (n=35,322), single-arm registry study among hospitalized patients with COVID-19 receiving COVID-19 convalescent plasma reporting on the outcomes of mortality, worsening oxygenation, and transfusion-related adverse events [87, 89-91, 93-97] (**Table 7**) (**Table s3f**). This recommendation was informed by evidence from the two RCTs and the most recent registry study [87, 90, 94, 96], as they provided the best available evidence.

Two open-label trials randomized 189 patients to receive a transfusion with COVID-19 convalescent plasma [90, 94]. Both trials 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 convalescent plasma during the clinical course of the patients' illness varied across studies [90, 94]. Joyner 2020b provided comparative analyses examining early (≤3 days) vs later (>4 days) receipt of convalescent plasma among 1,076 patients with severe or life-threatening COVID-19 enrolled in the US FDA Expanded Access Program for COVID-19 convalescent plasma study for whom relevant data was available. In addition, Joyner 2020c reported on safety outcomes of over 20,000 patients enrolled in the same US FDA Expanded Access Program for COVID-19 convalescent plasma study.

Benefits

Convalescent plasma transfusion failed to show or to exclude a beneficial or detrimental effect on mortality based on the body of evidence from RCTs (relative risk [RR]: 0.60; 95% CI: 0.33, 1.10; very low CoE); however, non-randomized studies suggest a decrease in mortality at 7- and 30-days (RR: 0.75; 95% CI: 0.61, 0.93; moderate CoE and RR: 0.65; 95% CI: 0.46, 0.92; moderate CoE, respectively).

Similarly, receipt of COVID-19 convalescent plasma may reduce the odds of worsening oxygenation (adjusted 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 [96] (n=20,000), within four hours of completion of convalescent plasma transfusion authors reported 146 serious adverse events classified as transfusion reactions (<1% of all transfusions) [96]. Of these, 63 deaths were reported (0.3%), 13 judged as possibly or probably related to the transfusion. The non-mortality serious adverse events include 37 reports of transfusion-associated circulatory overload (TACO), 20 cases of transfusion-related acute lung injury (TRALI), and 26 cases of severe allergic transfusion reactions.

Within seven days of transfusion, 1,711 deaths were reported (mortality rate: 8.56%; 95% CI: 8.18, 8.95). In addition, 1,136 serious adverse events were reported: 643 cardiac events (569 judged as unrelated to the transfusion); 406 sustained hypotensive events requiring intravenous pressor support; and 87 thromboembolic or thrombotic events (55 judged as unrelated to the transfusion).

In another smaller study of 52 patients randomized to receive convalescent plasma 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 [90]. No adverse events were reported among patients in either Gharbharan 2020 or Duan 2020.

Other considerations

The panel agreed on the overall certainty of evidence as very low due to concerns with risk of bias, mostly driven by the uncertainty of trade-offs between desirable and undesirable consequences as an untreated comparison group was unavailable for the largest body of evidence [96].

Conclusions and research needs for this recommendation

The guideline panel continues to recommend COVID-19 convalescent plasma only in the context of a clinical trial. Additional clinical trials are needed to determine whether there is a benefit of treatment with COVID-19 convalescent plasma for patients with COVID-19 (**Table s2**). Existing data suggests that if a benefit exists, CP is most useful when given early and with a high titer of neutralizing antibodies; future trials should attempt to compare outcomes of CP given in this optimal setting to the standard of care.

With the end of the expanded access program, clinicians may not have access to clinical trials to enroll patients for CP but may do so through the EUA. Clinicians who choose to give CP outside of a trial should have a detailed discussion with patients about the lack of certainty of benefits, and potential risks before administering this therapy. Clinicians are also encouraged to utilize available registries or other methods for capturing data on patient experience and outcomes, as well as to report any adverse events.

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) (follow up: range 15 days to 60 days)												
2 [1,2]	randomized trials	serious [a,b]	not serious	not serious	very serious [c]	none	14/95 (14.7%)	23/94 (24.5%)	**RR 0.60** (0.33 to 1.10)	**98 fewer per 1,000** (from 164 fewer to 24 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality at 30 days (NRS)												
1 [3]	observational studies	serious [d,e]	not serious	not serious [e]	not serious	none [f]	115/515 (22.3%) [g]	166/561 (29.6%)	**RR 0.75** (0.61 to 0.93) [e,h]	**74 fewer per 1,000** (from 115 fewer to 21 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Mortality at 7 days (NRS)												
1 [3]	observational studies	serious [d,e]	not serious	not serious [e]	not serious	none [f]	46/515 (8.9%) [g]	77/561 (13.7%)	**RR 0.65** (0.46 to 0.92) [e,i]	**48 fewer per 1,000** (from 74 fewer to11 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Worsening oxygenation (follow up: 14 days)												
1 [4]	observational studies	very serious [j]	not serious	not serious	very serious [k]	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
SAEs (transfusion-associated circulatory overload, transfusion-related acute lung injury, severe allergic transfusion reaction) (follow up: 4 hours)												
1 [5]	observational studies	extremely serious [l]	not serious	not serious	not serious	none	SAEs from 20,000 transfused patients: Within first 4 hours, of the SAEs, 63 deaths were reported (0.3% of all transfusions) and 13 of those deaths were judged as possibly or probably related to the transfusion of COVID-19 convalescent plasma. There were 83 non-death SAEs reported, with 37 reports of transfusion-associated circulatory overload (TACO), 20 reports of transfusion-related acute lung injury (TRALI), and 26 reports of severe allergic transfusion reaction.				⨁◯◯◯ VERY LOW	CRITICAL

SAEs (mortality, cardiac, thrombotic, sustained hypotensive events requiring intervention) (follow up: 7 days)

1 [5]	observational studies	extremely serious [l]	not serious	not serious	not serious	none	SAEs from 20,000 transfused patients: Within 7 days of transfusion, 1,711 deaths (8.56%) and 1,136 serious adverse events (5.68%) were reported. Non-mortality SAEs included: 643 cardiac events (569 judged as unrelated to the transfusion); 406 sustained hypotensive events requiring intravenous pressor support; and 87 thromboembolic or thrombotic events (55 judged as unrelated to the transfusion).	⊕◯◯◯ VERY LOW	CRITICAL

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

a. 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.
b. Gharbharan 2020 was an open-label trial, allocation concealment not reported, and no adjustments for co-interventions.
c. 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.
d. Joyner 2020 adjusted for time epoch, gender, race, age at enrollment (as categories), and indicator variables having already developed one or more severe COVID-19 conditions, being on a ventilator, use of hydroxychloroquine, use of remdesivir, and use of steroids prior to transfusion.
e. Comparator arm received low titer convalescent plasma, not no convalescent plasma, which was postulated to be less effective than the high titer. The directionality, since the comparator group did not receive placebo, may have underestimated the effectiveness of convalescent plasma (biased toward the null).
f. Mortality analyses suggests a decreasing trend of mortality between low, moderate, and high IgG groups.
g. Additional analysis included a timing comparison between transfusing at </= to 3 days from diagnosis (not symptoms) and 4+ days: 7 day mortality: 1,340/15,407 (8.7%) vs. 2,366/19,915 (11.9%) - RR 0.73 (95% CI 0.69 - 0.78); 30 day mortality: 3,329/15,407 (21.6%) vs. 5,323/19,915 (26.7%) - RR 0.81 (95% CI 0.78 - 0.84). Low certainty evidence. Overall, the adjusted 30-day mortality in patients treated within 3 days of diagnosis with high antibody levels (20%) compared favorably to those treated beyond 3 days with low antibody level plasma (30%) - RR 0.77.
h. Crude relative risk. Adjusted inverse relative risk = 1.18 (95% CI: 0.99, 1.41).
i. Crude relative risk. Adjusted inverse relative risk = 1.45 (95% CI: 1.00, 2.03).
j. 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.

k. 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.
l. No comparative effects available. Some subjectivity in classification of outcomes as transfusion related.

References

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Remdesivir

Section last reviewed 9/10/20; updated 9/15/20

Recommendation 8: In hospitalized patients with severe* COVID-19 (SpO_2 ≤94% on room air; on supplemental oxygen, mechanical ventilation, or ECMO, 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 ECMO.

*Severe illness is defined as patients with SpO_2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.

Recommendation 9: In patients 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.

Recommendation 10: In patients with COVID-19 admitted to the hospital without the need for supplemental oxygen and oxygen saturation >94% on room air, IDSA suggests against the routine use of remdesivir. (Conditional recommendation, Very low certainty of evidence)

The last literature search was conducted on September 4, 2020 and we identified three RCTs and two non-randomized studies 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 [98-100]. Remdesivir acts by causing premature termination of viral RNA transcription [100]. Its use improved disease outcomes and reduced viral loads in SARS-CoV-1 infected mice [99]. In rhesus macaques therapeutic treatment with remdesivir showed reduction in SARS-CoV-2 loads, pathologic changes and progression of clinical disease [101]. 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 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 [102]. However, there was no comparison group of similar patients who received standard care at the participating institutions.

Summary of the evidence

<u>Hospitalized patients with oxygen saturation >94% without supplemental oxygen</u>

One RCT compared treatment with five days of remdesivir (200 mg day one, 100 mg daily days 2-5), 10 days of remdesivir (200 mg day one, 100 mg daily days 2-10), or no remdesivir for patients hospitalized with oxygen saturation >94% on room air [103]. The outcomes assessed were mortality, clinical improvement, and serious adverse events. Randomization and lack of blinding failed to control for or balance receipt of co-interventions (e.g., treatment with HCQ, lopinavir/ritonavir, dexamethasone, and tocilizumab) equally across arms. In addition, the study did not adjust for severity of disease.

<u>Hospitalized patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen, on mechanical ventilation, and ECMO</u>

Two RCTs comparing treatment with remdesivir (200 mg day one, 100 mg daily days 2-10) against no remdesivir treatment [104, 105] and one RCT comparing five 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 [106] 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 8-10**).

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

Hospitalized patients with oxygen saturation >94% without supplemental oxygen

Treatment with a five-day course of remdesivir failed to show or to exclude a reduction in mortality when compared with no remdesivir (RR: 0.12; 95% CI: 0.01, 2.15; Very low CoE). A five-day course of remdesivir may increase clinical improvement over no remdesivir (RR: 1.16; 95% CI: 1.00, 1.34; Very low CoE) but a 10-day course of remdesivir was not associated with improved clinical status as compared with no remdesivir.

Hospitalized patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen, on mechanical ventilation and ECMO

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) [104]. Wang et al. failed to show a mortality benefit at 28 days (RR: 1.09; 95% CI: 0.54, 2.18; Low CoE) [105] 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) [105]. 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) [104].

In another study by Goldman et al that compared five 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 [106].

Harms

Hospitalized patients with oxygen saturation >94% without supplemental oxygen

Patients treated with five days of remdesivir do not appear to experience greater serious adverse events than those not receiving remdesivir (RR: 0.52; 95% CI: 0.24, 1.14; Very low CoE).

Hospitalized patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen, on mechanical ventilation and ECMO

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) [104, 105].

Patients receiving five days of remdesivir may experience fewer SAEs and adverse events 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 [106].

Other considerations

Hospitalized patients with oxygen saturation >94% without supplemental oxygen

The panel agreed that the overall certainty of the evidence for treatment of patients with an oxygen saturation >94% with remdesivir compared to no remdesivir was very low due to concerns with study limitations and imprecision. The panel decided to compare five days of remdesivir against no remdesivir treatment, as additional analyses suggested no benefit of a 10-day over a five-day treatment course. Because of the study limitations and the relatively small effect of remdesivir in patients with moderate COVID-19, the panel suggests remdesivir not be used routinely in these patients. There is a need for more rigorous trials to assess the benefits and harms of remdesivir in patients with moderate COVID-19.

Hospitalized patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen, on mechanical ventilation and ECMO

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 oxygen saturation >94% and no supplemental oxygen; however, agreed that 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 five-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 against remdesivir for routine treatment of patients with oxygen saturation >94% and no supplemental oxygen; however, strongly urges continued study through recruitment into RCTs.

The guideline panel suggests remdesivir rather than no remdesivir for treatment of severe COVID-19 in hospitalized patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen, on mechanical ventilation and ECMO. 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.

Table 8. GRADE evidence profile, PICO 8

Question: Remdesivir compared to no antiviral treatment for hospitalized patients with COVID-19 and oxygen saturation >94% without supplemental oxygen

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-day treatment with remdesivir	no remdesivir	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1 [1]	randomized trials	very serious [a,b]	not serious	not serious	serious [c]	none	0/191 (0.0%)	4/200 (2.0%)	**RR 0.12** (0.01 to 2.15)	**18 fewer per 1,000** (from 20 fewer to 23 more)	⊕◯◯◯ VERY LOW	CRITICAL
Clinical improvement at day 11 (assessed with: >=2-pt improvement on 7-pt scale; higher = better)												
1 [1]	randomized trials	very serious [a,b]	not serious	not serious	serious [d]	none	134/191 (70.2%)	121/200 (60.5%)	**RR 1.16** (1.00 to 1.34) [e]	**97 more per 1,000** (from 0 fewer to 206 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse events												
1 [1]	randomized trials	very serious [a,b]	not serious	not serious	serious [c]	none	9/191 (4.7%)	18/200 (9.0%)	**RR 0.52** (0.24 to 1.14)	**43 fewer per 1,000** (from 68 fewer to 13 more)	⊕◯◯◯ VERY LOW	CRITICAL

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. Co-treatments were not balanced between arms: 45% of patients randomized to control arm received HCQ or CQ compared to 11% in 10-day arm or 8% in five-day arm; lopinavir/ritonavir was 22% in control arm, 6% in 10-day arm, and 5% in five-day arm.
b. Open-label trial design may have led to different clinical practices (co-interventions and time of hospital discharge).
c. The 95% CI includes the potential for both appreciable benefit as well as the potential for harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
d. The 95% CI may not include a clinically meaningful benefit.
e. Spinner 2020 reported an odds ratio of 1.65 (95% CI: 1.09, 2.48); however, compared to relative risks, odds ratios tend to overestimate the effect with baseline risk is high.

References

1. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA **2020**.

Table 9. GRADE evidence profile, PICO 9

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

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)		
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
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
Clinical improvement (follow up: 28 days)												
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
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

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

f. Some changes made to the protocol.
g. 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).
h. 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.
i. Co-interventions received include interferon alpha-2b, lopinavir/ritonavir, vasopressors, antibiotics, corticosteroid therapy and were balanced between arms.
j. Trial stopped early due to lack of recruitment. Trial initiated after reduction in new patient presentation (most patients enrolled later in the disease course).
k. The 95% CI includes the potential for appreciable harm but cannot exclude the potential for benefit.
l. The 95% CI cannot exclude the potential for benefit or harm.

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med **2020**.
2. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet **2020**; 395(10236): 1569-78.

Table 10. GRADE evidence profile, PICO 10

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
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
SAEs												
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

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

Explanations

a. 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.
b. 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.

c. 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.
d. 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

1. 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 11: 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) [107]. 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) [108].

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 [109]. 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 11**).

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 11. GRADE evidence profile, PICO 10

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ 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
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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ 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

a. 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.
b. Number of events is less than the optimal information size, which may suggest fragility in the estimate of effect.
c. 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

1. 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

Select sections updated 9/4/20

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/cobcistat has reported that one of these trials [110] 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

Updated 9/4/20

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 [111-114]. 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 [113]. In an open-label treatment trial, lopinavir-ritonavir with ribavirin reduced the mortality and requirement of intensive care support of hospitalized SARS patients compared with historical control [113]. Many interferons, especially interferon beta have been shown to have modest in-vitro antiviral activity against SARS-CoV and MERS-CoV [111, 112]. Lopinavir-ritonavir or interferon beta-1b has been shown to reduce viral load of MERS-CoV and improve lung pathology in a nonhuman primate model of common marmoset [114].

An RCT on the triple combination of lopinavir-ritonavir, ribavirin, and interferon beta-1b, compared with single agent lopinavir-ritonavir for 14 days was conducted in the treatment of 127 adult patients admitted to hospital with COVID-19 [115]. Patients who had NEWS2 of least one, and with symptom duration of 14 days or less were recruited and randomly assigned to either triple combination or control group in a ratio of 2:1. Treatment with triple combination was well tolerated, and had a significantly shorter median time to suppress the viral load in nasopharyngeal specimen, and a significantly shorter time to alleviate symptoms, and resulted in shorter hospital stay. Since the median number of days from symptom onset to the start of study treatment was five days, only one patient in the control group received ventilator support and no patient died during the study. It is not possible to generalize the effectiveness of triple therapy in critically ill patients.

Lopinavir-ritonavir was further investigated in two retrospective cohort studies using HCQ [116] and arbidol [117], an indole-derivative licensed for decades in Russia and China against influenza, for comparison. Lopinavir-ritonavir was associated with more rapid viral clearance (median, 21 days vs. 28 days) than HCQ in 65 mild to moderate COVID-19 patients in South Korea, but there was no difference in time to clinical improvement [116]. Lopinavir-ritonavir was found to be inferior to arbidol in terms of viral clearance on day 14 after admission. But the number of patients was small (n=50) and all patients received atomized inhalation of recombinant human interferon-α2b injection. The efficacy of arbidol monotherapy remains uncertain [117].

Subcutaneous injection of interferon β-1a was used for the treatment of 42 severe COVID-19 adult patients in an open-label randomized clinical trial in Iran. Although there was no significant improvement in time to clinical response in the interferon-treated group, the overall mortality at 28 days was reduced in the interferon-treated then the control group (19% vs. 43.6%, p= 0.015) [118].

COVID-19 convalescent plasma for prophylaxis

Last searched 08/06/20; updated 9/4/20

Studies of CP for treatment of hospitalized patients with COVID-19 were discussed in a previous section. Use of CP as prophylaxis in individuals with high-risk exposure to SARS-CoV-2 is under study, with at least five clinical trials in clinicaltrials.gov as of August 6, 2020 that include arms in which individuals exposed to SARS-CoV-2 but without disease may receive CP [119-123]. Issues associated with regulatory concerns, safety, workflow, and trial design were recently reviewed [124]. Distinct from the polyclonal antibodies present in CP, monoclonal antibodies specific for respiratory viruses have also been used in certain populations for protection against disease in specific high-risk populations [125, 126], and animal models have suggested utility in prophylaxis against SARS coronavirus infection [127]. There are multiple trials listed in clinicaltrials.gov of different SARS-CoV-2 monoclonal antibodies for treatment or prophylaxis, with other potential monoclonal antibodies in earlier stages of development. No data on safety or efficacy are yet reported.

Ribavirin

There are only *in vitro* data available on the activity of ribavirin on SARS-CoV-2 currently. The EC_{50} (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 [128]. 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 [129].

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 [130] and continues to be explored as a therapeutic option as part of combination regimens. Two trials evaluating combination regimens are underway in Wuhan [131, 132] as well as a trial in Thailand proposing different combinations [133]. None of the trials or case reports have examined oseltamivir as monotherapy.

Intravenous immunoglobulin

Last searched 8/6/20; updated 9/4/20

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 [134], but studies are needed to determine if there may be a role for IVIg in the treatment of SARS-CoV-2.

One open-label trial randomized patients with COVID-19 (SPO_2 ≤96% on ≥4 liters O_2 by nasal cannula but not on mechanical ventilation) to either three days of IVIg (n=16) or no IVIg (n=17) [135]. During the study period (30 days or hospital discharge), two patients in the IVIg arm and seven in the standard of care arm required mechanical ventilation, one patient in the IVIg arm and three patients in the standard of care arm died. No adverse events were reported in the IVIg arm. Co-treatments with remdesivir, convalescent plasma, and corticosteroids were balanced across arms at baseline; however, methylprednisolone was provided with each IVIg dose in the treatment arm, and co-interventions provided during the treatment period were unbalanced. One retrospective cohort reported on 58 patients who received IVIg; however, the study did not identify a standard of care group and multiple co-treatments were provided [136]. Two case series reported on eight patients [134, 137] with severe COVID-19 who received IVIg for five consecutive days. All patients were discharged from the hospital.

Should NSAIDS be stopped in patients with COVID-19?

Updated 9/4/20

The role of nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of SARS-CoV-2 was debated widely in the first few months of the COVID-19 pandemic. The discussion was prompted by warnings from European health officials regarding the possibility of increased risk of infection or severity of disease in those taking NSAIDS. These concerns were based on early unconfirmed reports in four patients and supported by theoretical mechanistic concerns about the role NSAIDs play in SARS-CoV-2 pathogenesis. Human coronaviruses, including SARS-CoV-2, use ACE2 to bind to human targets and gain entry into target cells [138]. It has been theorized that NSAIDs, due to upregulation in ACE2 in human target cells, may lead to an increased risk of infection or a more severe course of COVID-19 in those taking NSAIDs. In addition, there are well known risks of non-steroidal anti-inflammatory agents including cardiovascular, gastrointestinal and renal adverse events [139, 140]. 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 [141, 142].

A case-control study from Italy published in May 2020 did not demonstrate an increased risk of SARS-CoV-2 infection in those taking NSAIDs chronically (adjusted OR: 1.06; 95% CI 0.98, 1.15) [143]. In April 2020, the WHO produced a scientific brief detailing a systematic review that included 73 studies in patients with acute respiratory infections. While no direct studies for patients with MERS, SARS or SARS-CoV-2 were available for analysis, there was no evidence of adverse events [144]. In a large registry trial that included data from five hospitals in Massachusetts, there was a lower risk of hospitalization in those with SARS-CoV-2 prescribed naproxen or ibuprofen, however it is difficult to determine if these patients were actively taking these medications at the time of COVID-19 diagnosis [145]. Randomized controlled trials are currently underway to better understand the safety of NSAIDs in the management of patients with COVID-19 [146, 147].

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

Last searched 8/3/20; updated 9/4/20

Angiotensin converting enzyme 2 (ACE2) is the entry receptor for SARS-CoV-2 on human cells. Animal experiments have shown mixed findings on the effect of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) on ACE2 levels and activity, leading to two contrasting hypotheses in COVID-19 [148-150]. The harmful hypothesis is that ACEIs and ARBs may increase the risk of infection and severity of COVID-19 via increased ACE2 expression. On the contrary, infection with other coronaviruses have been shown to decrease ACE2 levels *in vitro* [151], which may lead to increased angiotensin II activity resulting in pulmonary, cardiovascular and other end organ damage in patients with COVID-19 [148, 152]. This has led to speculation about a beneficial hypothesis that ACEI and ARBs may have a therapeutic role in COVID-19, by inhibiting the renin-angiotensin-aldosterone axis.

There have been several recent observational studies on the effects of ACEIs and ARBs in patients tested for and diagnosed with COVID1-19. A multi-center retrospective study [153] evaluated 1,128 patents admitted to 9 hospitals in Hubei province, China with COVID-19 including 188 (17%), who were on an ACEI or ARB. The risk of 28-day all-cause mortality was lower in ACEI/ARB group vs non-ACEI/ARB group (IRD: -0.24; 95% CI: -0.43, -0.05). After adjusting the all-cause mortality was still lower in the ACEI/ARB group compared to the non-ACEI/ARB group (HR: 0.42; 95% CI 0.15, 0.89). Another single center retrospective study [154] among 1178 hospitalized patients with COVID-19, had 362 patients with hypertension and 115 were on ACEI/ARBs. There was no difference between those with severe vs non-severe illness in use of ACEIs (9.2% vs 10.1%; P = .80), and ARBs (24.9% vs 21.2%; P = 0.40). There was also no difference between non-survivors and survivors in use of ACEIs (9.1% vs 9.8%; P = 0.85) and ARBs (19.5% vs 23.9%; P = 0.42).

Another study [155] among 1200 COVID-19 patients hospitalized in two hospitals in London, UK observed that chronic ACEI/ARB use was not associated with an increase in severity of COVID-19. Within their cohort of 1200 patients, 399 (33.3%) were on an ACEI/ARB and while unadjusted odds of critical care admission or death within 21 days were not significantly different between patients on ACEI/ARB vs not (OR 0.83; 95% CI 0.64, 1.07), adjustment for age, sex and co-morbidities presented an OR of 0.63 (95% CI 0.47, 0.84, p<0.01) for the composite outcomes in patients on ACEI/ARB. An observational study from Italy [156] evaluated multiple predictors of in-hospital mortality in 311 patients with hypertension and COVID-19. The patients in this study were significantly older, with a higher BMI, comorbidities, and severity of disease. In a multivariate Cox regression analysis chronic use of ACEI and ARBs (aHR, 0.97; 95% CI: 0.68, 1.39; *P* = .88) were not associated with an increase in in-hospital mortality.
A population-based case-control study [143] from Lombardy, Italy compared 6272 COVID-19 patients with 30,759 controls matched on sex, age, and municipality of residence. In a logistic-regression multivariate analysis, use of ARBs or ACEI did not show an association with COVID-19 among cases (aOR, 0.95, 95% CI 0.86 to 1.05 for ARBs and 0.96, 95% CI, 0.87 to 1.07 for ACEI). It also did not show an association with severe or fatal disease (for ARBs, aOR 0.83; 95% CI 0.63, 1.10; for ACEI, aOR 0.91; 95% CI 0.69, 1.21). Reynolds et al [157] analyzed data available for patients tested for COVID-19, available in the electronic medical records for New York University Langone Health system. In the study, 12,594 patients were tested, 5,894 (46.8%) were positive and 1,002 of these patients (17.0%) had severe illness. They performed propensity score matching and a Bayesian analysis to assess the relationship between various classes of antihypertensives including ACEI and ARBs and the likelihood of a positive COVID-19 test and severe disease. The study did not show a positive association for ACEI and ARBs with having a positive test for SARS-CoV-2 or developing severe infection. A retrospective cohort study using data from Danish national administrative registries, had an unadjusted 30-day mortality of 18.1% in the group with ACEI/ARB use compared to the 7.3% in the nonuser group, but the association was not significant after adjustment for age, sex and medical history (aHR 0.83; 95% CI: 0.67, 1.03). In that study, ACEI/ARB use compared with other antihypertensive agents was not significantly associated with higher incidence of COVID-19 (a HR 1.05 95% CI

0.80–1.36) [158]. One retrospective cohort study done in severe COVID-19 patient's showed ACEI/ARB use, after adjusting for other variables, to be independently associated with elevated creatinine >10.1 mg/L (OR 3.22; 95% CI: 2.28, 4.54). Consistent ACEI/ARB use was independently associated with AKI stage $\geq$1 (ALT ratio 3.28; 95% CI: 2.17, 4.94) [159].

Data from these observational studies suggest that ACEI and ARBs do not increase the risk of acquiring COVID-19, developing severe disease or death. One study showed possible increase risk of renal dysfunction in severe COVID-19. There are limitations though inherent to retrospective observational studies, especially differences in unmeasured prognostic factors between the compared groups that might be responsible for the difference in outcomes and not treatment with ACEI or ARBs. Most professional scientific and medical societies have recommended that ACEI or ARBs be continued in people who have an indication for these medications [160-162].

Antibacterials and antifungals

New section added 9/4/20; last searched 6/22/20

Patients with COVID-19 often present to hospitals with viral pneumonia with accompanying febrile illness and respiratory symptoms. Differential diagnoses may include bacterial pneumonia, for which antibiotics are prescribed. Concerns for bacterial superinfections also exist. Studies performed early in the COVID-19 pandemic reported high percentages of antibiotic use in China (58-95%) [1, 130, 163], Spain (74%) [164], and New York (65%) [165]. These studies are not granular and do not report if they describe co-infection at presentation or the development of superinfection, limiting the ability to ascertain the reasons for antibiotic use.

Data reporting co-infection in patients presenting with COVID-19 for care is sparse. Rawson and colleagues reviewed 18 studies of human coronavirus infections reporting co-infections, of which nine were COVID-19 [166]. These cumulatively reported a bacterial and fungal co-infection rate of 8% (62/806). The studies evaluated were heterogeneous. One brief report of 393 patients in New York reported a bacteremia rate of 5.6%, which varied significantly between patients receiving invasive mechanical ventilation (15/126 [11.9%]) and those who were not (4/222 [1.8%]) [167]. Another study looked at 88,201 blood cultures performed during March 2020 in New York, comparing order volume, positivity, and etiologies between patients with COVID-19 and others during the time period [168]. The study found a significantly lower rate of bacteremia in COVID-19 patients (3.8%) than either COVID-19 negative (8%) or untested (7.1%) ($p<0.001$). When commensal skin organisms were excluded, the positivity rate in COVID-19 patients was 1.6% [168]. A study in Texas reviewed the use of antibiotics and incidence of coinfections in 147 PCR-positive COVID-19 patients [169]. Eighty-seven (59%) patients received empiric antibiotics, though none of the 47 (32%) patients with respiratory cultures had positive results. 112 patients (76%) had blood cultures collected also, and while nine were positive, eight of those were considered contaminants [169].

The apparent discordance between bacterial and fungal co-infection in patients with COVID-19 at presentation and the use of antibacterial therapy has potential negative effects, namely in antimicrobial resistance. Publications report on patients with severe and critical COVID-19 patients treated with immunomodulatory therapies, including corticosteroids, IL-6 antagonists, IL-1 antagonists, and others [170]. In one preprint examining outcomes of in a cohort of 154 patients receiving invasive mechanically ventilation, mortality was reduced in patients treated with tocilizumab (IPTW-adjusted model, HR 0.55; 95% CI 0.33, 0.90); however, superinfections were more commonly reported (54% vs 26%, $p<0.001$), primarily due to ventilator-associated pneumonia [171]. Initiating and continuing empiric antibiotics at the time of admission may lead to superinfections that are antibiotic resistant [172].

Favipiravir

New section added 9/4/20; last searched 6/18/20

Favipiravir is a purine analogue that inhibits the RNA dependent RNA polymerase of influenza and other RNA viruses [173]. The drug is approved in Japan for treatment of influenza. However, because of its teratogenicity risk, favipiravir should not be given during pregnancy and there are substantial concerns about its use in women in child-bearing potential.

In terms of its potential role in COVID-19, favipiravir has *in vitro* activity against SARS-CoV-2 [16]. However, it is uncertain whether adequate drug levels can be achieved in vivo to inhibit SARS-CoV-2. There have been small clinical trials with this drug in people with COVID-19. In a non-randomized, open-label study in China [174], oral favipiravir was associated with shorter time to viral clearance and greater improvement in chest imaging than lopinavir/ritonavir (in both groups, the oral antiviral was given with aerosolized alpha-interferon). However, because the study was small and not randomized, it was not possible to conclude that favipiravir is effective in treating COVID-19. A randomized, open-label trial compared favipiravir to umifenovir, an antiviral approved in Russia and China, in people with COVID-19 [175]. The clinical recovery rate at day seven was not significantly different between the two groups. There appeared to be an impact of favipiravir in the sub-group of people who did not have critical illness, but more data are needed. An exploratory clinical trial, also conducted in China, randomized 30 hospitalized adults with COVID-19 into a baloxavir marboxil, favipiravir or control group. There was no apparent effect of favipiravir (or baloxivir) on viral clearance [176]. There are ongoing clinical trials assessing favipiravir for treatment of COVID-19.

Immunomodulatory agents

New section added 9/4/20

Some patients with COVID-19 develop a hyperinflammatory state that may incorporate elements of cytokine release syndrome seen in conditions such as secondary hemophagocytic lymphohistiocytosis (sHLH). The etiology is unclear, but patients who develop significantly elevated CRP, ferritin, and D-dimer levels with the syndrome have an increased risk of mortality, associated with respiratory failure, multiorgan dysfunction, and hypercoagulability. Numerous immunomodulatory agents are under investigation to address this immunologic complication.

IL-1 inhibitors: Anakinra is an FDA approved IL-1-beta inhibitor that is currently FDA approved for rheumatoid arthritis and Neonatal-Onset Multisystem Inflammatory Disease. High- and low-dose anakinra was investigated in a recent retrospective cohort study in Italian patients with

COVID-19, moderate to severe ARDS, and hyperinflammation. Patients receiving anakinra were compared to a historical control group with COVID-19 who fulfilled eligibility criteria for anakinra. The low-dose anakinra group was stopped early due to lack of effect. In the high-dose anakinra group, 3/29 (10%) patients died vs. 7/16 (44%) in the historical control group, however there was no difference in the rates of mechanical ventilation-free survival [177]. Anakinra is being investigated in numerous trials including this randomized placebo-controlled trial [178]. Canakinumab is another IL-1-beta antagonist with limited human data for COVID-19 that is being studied in a phase III clinical trial [179, 180].

Janus kinase inhibitors: Baricitinib, a Janus kinase inhibitor (anti-JAK) currently FDA approved for the treatment of rheumatoid arthritis, is being investigated in multiple studies for COVID-19. The proposed benefits of baricitinib in the management of COVID-19 are two-fold as it has both anti-inflammatory and likely antiviral activity. Janus kinase mediates cytokine signaling which contributes to inflammation, which may reduce risk of the associated hyperinflammatory syndrome and ARDS. Baricitinib inhibits AP2-associated protein kinase 1 (AAK1) and also binds G-associated kinase (GAK), both thought to play a role in receptor mediated endocytosis of many viruses including SARS-CoV-2 [181]. In an open-label non-randomized study from Italy, baricitinib with lopinavir/ritonavir (n=12) were compared to lopinavir/ritonavir (n=12) alone at one institution over two consecutive time periods. After two weeks in the baricitinib group, no patients required ICU transfer and 7/12 (58%) were discharged. In the lopinavir/ritonavir group, 4/12 (33%) required ICU transfer and only 1/12 patients were discharged by day 14. No serious adverse events or infections occurred in the baricitinib group [182]. In the ACTT-2 trial, baricitinib is being compared to remdesivir and numerous other RCTs are currently underway to better understand the role of baricitinib in the management of COVID-19 [183-187].

GM-CSF inhibitors: Monoclonal antibodies that bind to GM-CSF are under investigation for the treatment of hyperinflammation associated with COVID-19. GM-CSF inhibitors are postulated to disrupt the downstream signaling of pro-inflammatory cytokines. One agent, mavrilimumab was studied in a single center non-randomized cohort study in non-ventilated patients in Italy. Trial participants had SARS-CoV-2 infection with a PaO_2: FiO_2 ratio < 300 mm Hg, pulmonary infiltrates, and evidence of hyperinflammation (CRP > 100 mg/L or ferritin > 900 µg/L and any increase in LDH). Patients in the treatment group received a single dose of mavrilimumab 6 mg/kg (n=13). A similar cohort managed by the same medical team received no mavrilimumab due to lack of consent and lack of access to mavrilimumab (n=26). Mortality rates were 0/13 in the mavrilimumab group and 7/26 (27%) died in the control group. Median days to clinical improvement (defined as a reduction of two or more points on the seven-point ordinal scale) was 8 (IQR: 5-11) vs. 19 (IQR: 11- > 28), in the mavrilimumab vs. control groups, respectively. Mavrilimumab was well tolerated in all patients [188]. Randomized controlled trials are underway to investigate the role of GM-CSF inhibitors in the management of COVID-19 [189-191].

Complement inhibitors: In mouse models of both SARS-CoV and MERS-CoV, complement activation has been shown to play a role in the pathogenesis of ARDS. Eculizumab, is a complement inhibitor that is already approved by the FDA for other conditions including myasthenia gravis and paroxysmal nocturnal hemoglobinuria, is currently being studied for the treatment of COVID-19 [192]. Ravulizumab, another complement inhibitor, is also being investigated in randomized trials for COVID-19 [184].

SARS-CoV-2 in children and treatment of multisystem inflammatory syndrome in children (MIS-C)

New section added 9/4/20

Treatment

Compared with adults, children generally have milder illness from SARS-CoV-2 infection [193, 194]. However, severe illness does occur in children, even those with no predisposing factors [194, 195]. Among children admitted to the hospital for COVID-19, one-third are admitted to intensive care [194]. Despite this, clinical trials of therapeutic interventions for COVID-19 have almost exclusively focused on adult patients. For example, in the first of two recent studies of the antiviral remdesivir [196, 197], patients younger than 18 years were excluded [104], and the number of children between 12 and 18 years included in the analysis for the second paper was not reported [106]. These studies led to FDA Emergency Use Authorization of remdesivir for both adults and children [198], with no published data available on either safety or efficacy in children under 12 years. A phase II/III open label study in this population has started (the "CARAVAN" trial [199]). Future studies of both therapeutics and vaccines will need to include children to assure their safety and efficacy in this population.

Multisystem inflammatory syndrome in children

Multisystem inflammatory syndrome in children (MIS-C) or Pediatric Multisystem Inflammatory Syndrome (PMIS) is a rare acute inflammatory syndrome with some similarities to Kawasaki disease that has recently been reported in children. Reports from Europe and the United States generally describe critically ill children with fever, rash, conjunctivitis, abdominal complaints, shock, and significant cardiac dysfunction [200-212]. Case definitions have been developed to better characterize these patients (**Table 12**) [213, 214].

Patients with Kawasaki disease also present with fever and symptoms including rash, conjunctivitis, peripheral extremity changes, lymphadenopathy, and oral mucosal changes such as red, cracked lips and "strawberry tongue." However, while Kawasaki disease and MIS-C share some similarities, there are also key differences [215]. Both are hyperinflammatory syndromes, both have findings of medium vessel vasculitis and both can present with the signs/symptoms described for Kawasaki disease. MIS-C is more likely to affect older children (average age 8-11 years vs. younger than five years in Kawasaki disease), cause more severe disease (more patients presenting with shock), present frequently with gastrointestinal symptoms, includes some neurologic involvement, and more commonly causes cardiac myocarditis and ventricular dysfunction leading to hypotension or arrhythmias. In contrast, Kawasaki disease more commonly causes coronary artery dilatation. A small study of cytokine profiles in children distinguished MIS-C from severe COVID-19 based on a higher level of the combination of TNF-α and IL-10 in MIS-C patients [216].

Empiric treatment of MIS-C has generally involved immunomodulatory agents such as high-dose intravenous immunoglobulin (2 g/kg), corticosteroids, aspirin and rarely more targeted anti-inflammatory medications such as anakinra [200-203, 209, 210, 212]. Most of the children with MIS-C have had a history of prior SARS-CoV-2 infection several weeks earlier confirmed by viral detection of antibody testing or have had documented prior exposure to COVID-19, suggesting that this condition is a post-infectious immunologic phenomenon.

Future research should focus on how and why the immune system responds to SARS-CoV-2 causing a spectrum of illness in children, identifying genetic or environmental risk factors for MIS-C, and discovering optimum treatment for children with MIS-C. Multidisciplinary, collaborative approaches to data registries and clinical trials that promote evidence-based care for these children are needed.

Table 12. Case definitions for Multisystem Inflammatory Syndrome in Children (MIS-C) and Paediatric multisystem inflammatory syndrome (PMIS)

	MIS-C (CDC 2020)[1]	**PMIS (Royal College of Paediatrics and Child Health 2020)[2]**
Includes	Age <21 years presenting with: • Fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours) • Laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin), • Evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)	A child presenting with: • Persistent fever >38.5°C • Laboratory evidence of inflammation (neutrophilia, elevated CRP and lymphopenia) • Evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (listed in Appendix of reference)

Excludes	Patients with alternative plausible diagnoses	Patients with any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus
Other criteria	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR COVID-19 exposure within the 4 weeks prior to the onset of symptoms	SARS-CoV-2 PCR testing may be positive or negative

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2. Royal College of Paediatrics and Child Health. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19, 2020.

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 vitro* studies and observational studies for other diseases were later proven to be ineffective in clinical trials [217].

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 [218], 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 [219]. 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 trials, rather than use clinically unproven therapies [220]. 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) [217]. 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 [221].

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 SpO_2 (percentage of oxyhemoglobin saturation) or PaO2:FiO_2 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 [222]. 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) [223]. 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 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.** receives research funding from the National Institutes of Health/National Institute of Allergy and Infectious Diseases, Bill and Melinda Gates Foundation, and Wellcome Trust, and serves as chair of the Antimicrobial Drug Advisory Committee of the Food and Drug Administration. **V.C.**

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