

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 COVID-19. There is a need for frequently updated practice guidelines on their use, based on critical evaluation of rapidly emerging literature.

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

Methods: IDSA formed a multidisciplinary guideline panel of infectious disease clinicians, pharmacists, and methodologists with varied areas of expertise. 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: The IDSA guideline panel agreed on 7 treatment recommendations and provided narrative summaries of other treatments undergoing evaluations.

Conclusions: 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, given that we could not make a determination whether the benefits outweigh harms for most treatments.

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Executive Summary

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, 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 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. The guideline panel used the word “only” in recommendations about therapeutic agents with higher uncertainty and/or more potential for harm. These recommendations acknowledge the current “knowledge gap” and aim at avoiding premature favorable recommendations for potentially ineffective or harmful interventions.

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

Recommendation 2. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin only in the context of a clinical trial. (Knowledge gap)

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

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

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

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

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

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. The panel determined that when an explicit trade-off between the highly uncertain benefits and the 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 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 coronavirus disease 2019 (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 used a methodologically rigorous process for evaluating the best available evidence and providing treatment recommendations. Two additional guidelines on diagnostic testing and infection prevention are also under development. These guidelines will be frequently updated as substantive literature becomes available and will be accessible on an easy to navigate web and device interface at <http://www.idsociety.org/covid19guidelines>.

The guideline panel considered making a recommendation for therapeutic agents that were currently available for use. The panel chose not to give a recommendation for remdesivir as it is mostly available in the context of ongoing trials with limited availability for compassionate use and expanded access use. We anticipate data from RCTs for remdesivir will be soon available; at that point, we will update the guidelines to provide formal recommendations on its use.

There are 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 GIN/McMaster checklist for the development of rapid recommendations [4].

Panel composition

The panel was composed of nine members including front line clinicians, infectious diseases specialists who are members of the IDSA, the HIV Medical Association (HIVMA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS). They represented the disciplines of public health, pharmacology, pediatrics, medical microbiology, preventive care, critical care, as well as hepatology, nephrology and gastroenterology. The Evidence Foundation provided technical support and guideline methodologists for the development of this guideline.

Disclosure and Management of Potential Conflict of Interest (COI)

The conflict of interest (COI) review group included two representatives from IDSA who were responsible for reviewing, evaluating and approving all disclosures. All members of the expert panel complied with the COI process for reviewing and managing conflicts of interest, which required 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 was 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 ensured that the majority of the panel and chair was without potential relevant (related to the topic) conflicts. The chair and all members of the technical team were determined to be unconflicted.

Question generation

Clinical questions were developed into a PICO format (Population, Intervention, Comparison, Outcomes) [5] prior to the first panel meeting. Panel members prioritized questions with 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 leading to treatment discontinuation. Additional drug specific harms were evaluated when clinically relevant, including possible drug-drug reactions, if applicable.

Search strategy

The NICE highly-sensitive search was reviewed by the methodologist in consultation with the technical team information specialist and was determined to have high sensitivity [6]. An additional term, COVID, was added to the search strategy used in addition to the treatment terms identified in the PICO questions (Supplementary Table s1). Ovid Medline and Embase were searched from 2019 through April 4, 2020. Horizon scans were performed daily 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 randomized controlled trials of effectiveness were found, no additional non-randomized studies or non-comparative evidence (i.e., single arm case series) were sought. Evidence from single arm studies reporting on non-comparative rates of outcomes of interest were included if a historical control event rate could be estimated from the literature. Reviewers extracted relevant information into a standardized data extraction form.

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

Data collection and analysis

Data extracted from the available evidence included: mortality, clinical progression or improvement as reported in the studies, virologic clearance, and adverse events. Where applicable, data were pooled using random effects model (fixed effects model for 2 or less trials or pooling of rates) using RevMan or OpenMeta [7].

Risk of bias and certainty of evidence

Cochrane risk of bias tools for randomized clinical trials (RCTs) and Observational Studies and modified domains were used in assessing confounding bias, selection bias, and misclassification bias [8]. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [9]. 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 [10].

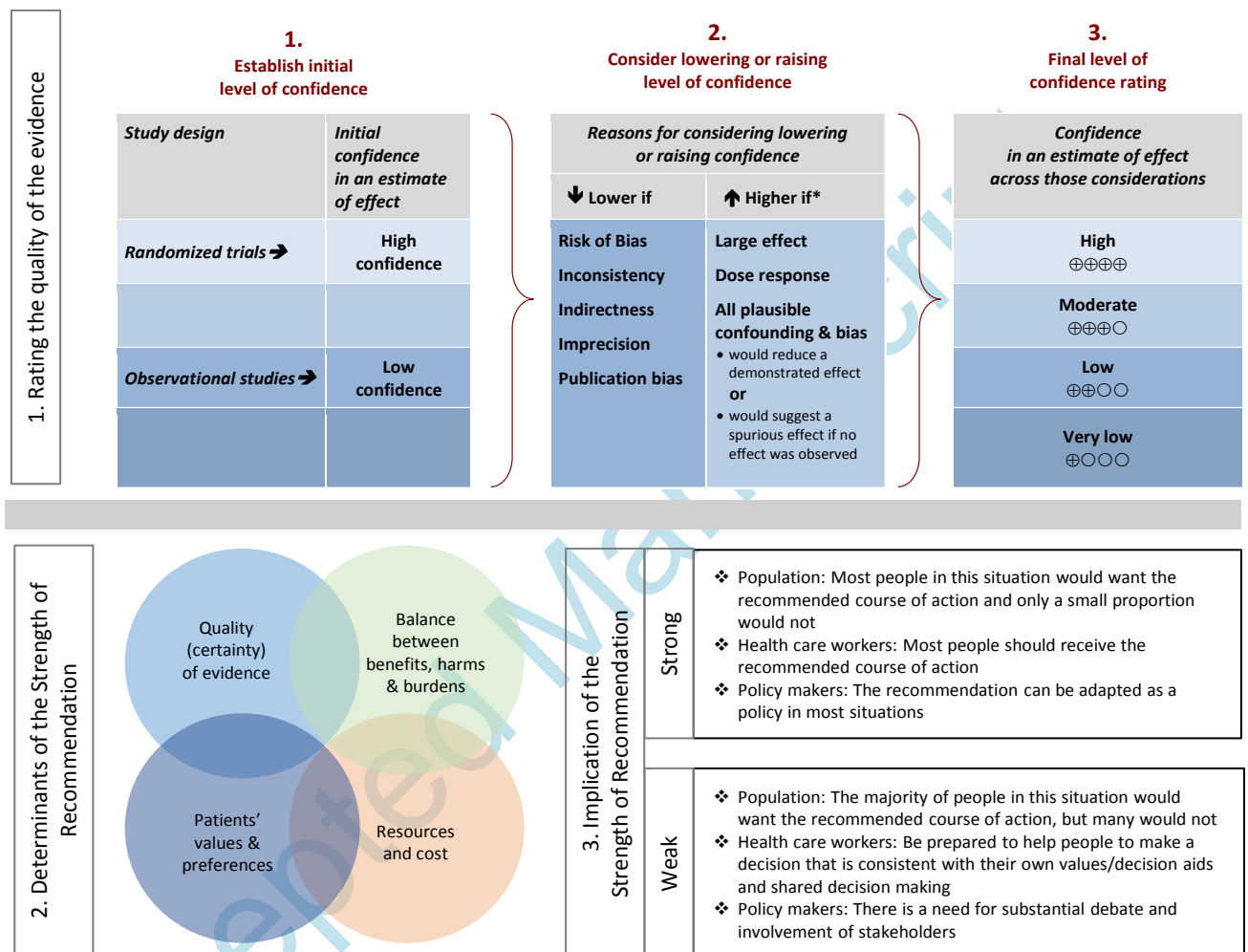
Evidence to recommendations

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". The guideline panel used the word "only" in recommendations about therapeutic agents with higher uncertainty and/or more potential for harm. For example, the toxicity of hydroxychloroquine/chloroquine plus azithromycin (Recommendation 2) carries particular risk for patients in the outpatient setting who may not be enrolled in a trial and therefore may have inadequate monitoring; or, for Recommendation 6, there is concern related to tocilizumab shortages for other indications and potential toxicity of worsening infection/drug interactions. 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 Supplementary Table s2).

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



Review process

The draft guideline underwent a rapid review for approval by IDSA Board of Directors Executive Committee external to the guideline development panel. The guideline was reviewed and endorsed by SHEA and PIDS. The IDSA Board of Directors Executive Committee reviewed and approved the guideline prior to dissemination

Updating process

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. If necessary, the entire expert panel will be reconvened to discuss potential changes.

Results

Systematic review and horizon scan of the literature identified 435 references of which 13 informed the evidence base for these recommendations (Supplementary Figure s1). Characteristics of the included studies can be found in Supplementary Tables s2a-2f.

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

Recommendation 2. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin only in the context of a clinical trial. (Knowledge gap)

Summary of the evidence

Two RCTs of patients with confirmed COVID-19 with mild pneumonia (e.g., positive CT scan without oxygen requirement) or non-severe infection admitted to the hospital treated with hydroxychloroquine (HCQ) reported on mortality at 14 days, clinical progression (radiological progression on CT scan), clinical improvement, failure of virologic clearance (PCR), and adverse events (both) [11, 12] ([Table 1](#)).

In addition, we identified four publications describing three trials of combination treatment with HCQ plus azithromycin (AZ) among hospitalized patients with COVID-19 reporting on the outcomes of mortality, failure of virologic clearance (assessed with PCR test), and adverse events (i.e., significant QT prolongation leading to treatment discontinuation) [13-16] ([Table 2](#)).

Benefits

The currently available best evidence failed to demonstrate or to exclude a beneficial effect of HCQ on clinical progression of COVID-19 (as inferred by radiological findings; RR: 0.61; 95% CI: 0.26, 1.43; see Figure s2), or on viral clearance by PCR tests (RR: 2.00; 95% CI: 0.02, 20.00; see Figure s3), although a somewhat higher proportion in the HCQ group experienced clinical improvement (RR: 1.47; 95% CI 1.02, 2.11). However, the certainty in the evidence was rated as very low mainly due to small sample sizes (sparse data), co-interventions, and risk of bias due to methodological limitations. In addition, the selected outcomes should be considered indirect, as important patient outcomes (e.g., mortality, rate of progression to ARDS and need for mechanical ventilation) were unavailable.

Studies evaluating the addition of azithromycin to HCQ provided indirect comparisons of failure of virologic clearance to historical controls. The observed risk of mortality among patients receiving HCQ+AZ during hospital stay was 3.4% (6/175 patients). However, an estimated mortality rate in an untreated cohort was not provided in the manuscript. When compared to a lack of viral clearance in historical controls (100% virologic failure), 12 symptomatic patients were compared at day 5 or 6 from a separate hospital in France. Patients receiving treatment with HCQ+AZ experienced numerically fewer cases of virologic failure (43% pooled virologic failure; 29/71 patients) (Figure s3). There is very low certainty in this comparison of treatment effect mainly due to very high-risk selection bias, making any claims of effectiveness highly uncertain. In addition, relying on intermediary outcomes, such as viral clearance to determine patient-important outcomes (including a reduction in development of pneumonia, hospital or ICU admission, or need for intubation) add another layer of imprecision.

Harms

Two studies described significant QT prolongation in 10 of 95 treated patients, either resulting in an QT increase to over 500 ms or discontinuation of the HCQ/AZ treatment, illustrating the high risk for clinically relevant arrhythmias for this treatment [15, 16]. In addition, several case reports of QT prolongation related to hydroxychloroquine have also been published [17-20].

In another prospective cohort study in 224 COVID-19 uninfected patients with SLE who received either chloroquine or hydroxychloroquine for routine care, gastrointestinal side effects occurred in 7% of patients [21].

Several case reports have been published citing the risk of a prolonged QT prolongation, torsades de pointes, and ventricular tachycardia in patients receiving azithromycin alone. In a large cohort study, patients taking a five-day course of azithromycin had an increased risk of sudden cardiac death with a hazard ratio of 2.71 (1.58-4.64) vs. 0.85 (0.45-1.60), compared to patients receiving no antibiotic or amoxicillin, respectively [22]. Given the cumulative effect on cardiac conduction seen with hydroxychloroquine and azithromycin, if this combination was to be used in the context of a clinical trial, baseline and follow-up ECG monitoring would be indicated, as well as careful surveillance for other concomitant medications known to prolong the QT interval.

Renal clearance accounts for 15-25% of total clearance of hydroxychloroquine, however dose adjustments are not recommended according to package labeling. Chloroquine and hydroxychloroquine are metabolized by cytochrome P450 isoenzymes 2C8, 2D6, and 3A4 [23], therefore inhibitors and inducers of these enzymes may result in altered pharmacokinetics of these agents.

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

Azithromycin is low risk for cytochrome P450 interactions [24]; however additional pharmacologic adverse events including gastrointestinal effects and QT prolongation need to be carefully considered particularly in the outpatient setting where frequent ECG monitoring is not feasible.

Other considerations

The panel agreed that the overall certainty of evidence was very low due to concerns with risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Conclusions and research needs for this recommendation

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

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Table 1. GRADE evidence profile, PICO 1

Question: Hydroxychloroquine compared to no HCQ for hospitalized patients with COVID-19 (combined)

Setting: Hospitalized patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ	no HCQ	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 14 days)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	very serious ^c	none	0/15 (0.0%)	0/15 (0.0%)	not estimable		⊕○○○ VERY LOW	CRITICAL
Clinical progression (as inferred by radiological/CT scan progression) (follow up: range 3 days to 6 days; assessed with: CT Scan)												
2 ^{1,2}	randomised trials	serious ^b	not serious	serious ^d	serious ^e	none	5/46 (10.9%)	11/46 (23.9%)	RR 0.61 (0.26 to 1.43)	93 fewer per 1,000 (from 177 fewer to 103 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement (as inferred by CT scan findings) (follow up: 6 days)												
1 ²	randomised trials	serious ^b	not serious	serious ^d	serious ^f	none	25/31 (80.6%)	17/31 (54.8%)	RR 1.47 (1.02 to 2.11)	258 more per 1,000 (from 11 more to 609 more)	⊕○○○ VERY LOW	CRITICAL
Failure of virologic clearance (follow up: 7; assessed with: PCR)												
1 ¹	randomised trials	serious ^b	not serious	serious ^g	very serious ^e	none	2/15 (13.3%)	1/15 (6.7%)	RR 2.0 (0.2 to 20.0)	67 more per 1,000 (from 53 fewer to 1,000 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse events, any												
2 ^{1,2}	randomised trials	serious ^b	not serious	not serious	very serious ^e	none	6/46 (13.0%) ^h	2/46 (4.3%) ⁱ	RR 2.60 (0.67 to 10.00)	70 more per 1,000 (from 14 fewer to 391 more)	⊕○○○ VERY LOW	IMPORTANT
Severe Adverse Events												
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ	no HCQ	Relative (95% CI)	Absolute (95% CI)		
	observational studies	serious ^j	not serious	not serious	serious ^j	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. ³			⊕○○○ VERY LOW	CRITICAL	

CI: Confidence interval; RR: Risk ratio; SLE: Systemic Lupus Erythematosus

Explanations

- Chen Z 2020 did not explicitly report on deaths
- 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 Abidol in the hydroxychloroquine vs. placebo arm, respectively. Two subjects in the control arm received lopinavir/ritonavir;
- Zero events
- Radiological progression is an intermediary for worsening to ARDS, need for intubation, and death
- 95% CI includes substantial beneficial effect as well as substantial harms
- Small sample size, optimal information size not met
- Viral clearance is a surrogate for clinical improvement, such as worsening to ARDS, intubation, and death
- Chen J 2020: 4 AEs include diarrhea, fatigue and transient AST elevation. Chen Z 2020: 1 rash, 1 headache. 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. (Wang, et al J Rheumatol. 1999 Apr;26(4):808-15.)
- 2 AEs include: AST elevation, creatinine elevation and anemia
- Case reports

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Table 2. GRADE evidence profile, PICO 2

PICO 2: Hydroxychloroquine and azithromycin compared to no HCQ/azithromycin for hospitalized patients with COVID-19

Setting: Inpatients

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine and azithromycin	no HCQ/azithromycin	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3 ^{1,2,3}	observational studies	very serious ^a	not serious	not serious	serious ^b	none	6/175 (3.4%) ^c	-	-	-	⊕○○○ VERY LOW	CRITICAL
Virologic Failure (follow up: range 5 days to 6 days; assessed with: PCR Test)												
2 ^{1,2,4}	observational studies	very serious ^a	serious ^d	serious ^e	serious ^b	none	29/71 (40.8%) ^f	12/12 (100.0%) ^g	not estimable		⊕○○○ VERY LOW	CRITICAL
Significant QT prolongation												
2 ^{1,3}	observational studies	very serious ^a	not serious	serious ^h	serious ^b	none	10/95 (10.5%) ⁱ	-	-	-	⊕○○○ VERY LOW	CRITICAL
Adverse events												
	observational studies	serious ^j	not serious	not serious	serious ^j	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 ⁵ . Several case reports have been published citing the risk of a prolonged QT prolongation, torsades de pointes, and ventricular tachycardia in patients receiving azithromycin. In a large cohort study, patients taking a 5-day course of azithromycin had an increased risk of sudden cardiac death with a hazard ratio of 2.71 (1.58-4.64) vs. 0.85 (0.45-1.60), compared to no antibiotic or amoxicillin, respectively ⁶ . Given that both medications have QT prolonging effects, any combination is likely to substantially increase the risk of clinically relevant harmful effects. ^{5,6}			⊕○○○ VERY LOW	IMPORTANT	

CI: Confidence interval; RR: Risk ratio; SLE: Systemic Lupus Erythematosus

Explanations

- a. No contemporaneous control groups; no adjustment for baseline severity, resulting in high risk for residual confounding
- b. A very small number of events. Optimal information size not met.
- c. One study reported 1/11 at day 5; one study reported 1/80; one study reported 4/84.
- d. 2 case series from France showed divergent results
- e. Surrogate marker for mortality or resolution of COVID19
- f. Gautret reported 21/61 patients as positive at day 6 (estimate from supplied graph); Molina reported 8/10 patients positive at day 5 or 6. Pooled rates of virologic failure using fixed effects inverse variance method resulted in a 43% failure rate (95% CI, 32% to 54%)
- g. Gautret reported on a historical viral clearance rate in symptomatic patients from a separate hospital. Criteria for selection of patient remains unclear, as presumably a sizable number of untreated patient could have been available with data on viral clearance.
- h. 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.
- i. Molina 2020: 1/11 leading to treatment discontinuation; Chorin 2020: 9/84 with significant QTc prolongation of more than 500 ms
- j. Case reports

References

1. 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.
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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 [25-27] (Table 3). Cao et al. randomized 199 hospitalized patients with severe COVID-19 to receive treatment with lopinavir/ritonavir in addition to standard of care (n=99) or standard of care alone (n=100) for 14 days. The trial reported on the following outcomes: mortality, failure of clinical improvement (measured using a 7-point scale or hospital discharge), and adverse events leading to treatment discontinuation.

Benefits

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

Harms

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

Other considerations

The panel elected to inform their decision based on the RCT [27]. 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 (Supplementary Table s2).

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Table 3. GRADE evidence profile, PICO 3

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

Setting: Inpatients

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

CI: Confidence interval; RR: Risk ratio

Explanations

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

References

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ACCEPT

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

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

Summary of the evidence

No studies were found specifically examining the role of steroids for the treatment of the acute COVID-19. Corticosteroids were widely used in China to prevent the development of ARDS in patients with COVID-19 pneumonia. Four retrospective cohort studies [25, 26, 28, 29] examined several interventions during the COVID-19 outbreak in the Wuhan area. Studies show variability in the benefit of corticosteroid use (Tables 4 and 5). Study limitations include: 1) critical information not reported on baseline risk/severe pneumonia/ARDS; 2) confounding by indication; 3) unadjusted analyses; 4) timing of disease not given; 5) large variability in treatments given. Due to these limitations, a sensible pooling effort to determine possible treatment effect was not deemed possible.

Benefits and Harms

The panel determined that due to the limitation of direct COVID-19 data, indirect evidence from the 2003 SARS outbreak and from MERS would also be considered. A systematic review [30] reported on 15 studies, 13 of which were inconclusive to any benefits of corticosteroids. One RCT reported that SARS-CoV-1 viral loads showed delayed viral clearance associated with corticosteroid use.

The same review also reported on a subset of ARDS patients (three trials). One small RCT in 24 patients using a lower dose methylprednisolone for two days showed possible improvement of ARDS; however, two larger trials showed little or no effect in critically ill patients with pulmonary failure. The authors concluded that despite widespread use of corticosteroids during the SARS outbreak, conclusive evidence of benefit was lacking and that administering steroids early in the disease process before viral replication is controlled may lead to a delay in viral clearance.

Other considerations

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

Conclusions and research need for these recommendations

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

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Table 4. GRADE evidence profile, PICO 4

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

Setting: Inpatient

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

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

Explanations

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

References

- Sun F, Kou H, Wang S, et al. Medication patterns and disease progression among 165 patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a single-centered, retrospective, observational study. *2020*.
- Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. *medRxiv 2020*.
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- Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med 2006*; 3(9): e343.
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Table 5. GRADE evidence profile, PICO 5

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

Setting: intensive care

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

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

Explanations

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

References

1. Sun F, Kou H, Wang S, et al. Medication patterns and disease progression among 165 patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a single-centered, retrospective, observational study. 2020.
2. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv 2020.
3. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020.
4. Liu Y, Sun W, Li J, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv 2020.

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 and MERS-CoV suggest a release of proinflammatory cytokines including interleukins-6 (IL-6) [31] during the clinical illness. Our search identified one study [31] 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 [32].

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 [31]. However, patients receiving tocilizumab are often at an increased risk of serious infections (bacterial, viral, invasive fungal infections, and tuberculosis) and hepatitis B reactivation [33]. 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 [34, 35].

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 (Supplementary Table s2).

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Table 6. GRADE evidence profile, PICO 6

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

Setting: intensive care

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

CI: Confidence interval

Explanations

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

References

- Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with Tocilizumab. *ChinaXiv* 2020; 202003(00026): v1.
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Recommendation 7. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. (Knowledge gap)

Summary of the evidence

Our search identified two case series of a total of 15 patients reporting on the outcomes of mortality, failure of clinical improvement (as inferred by need for continued mechanical ventilation), and treatment related adverse events among hospitalized patients with COVID-19 (Table 7) [36, 37]. All five patients in Shen 2020 were mechanically ventilated at time of treatment compared with three out of 10 patients in the Duan et al study. Duan 2020 included a comparison of the 10 treated patients to 10 historical control patients matched on age, gender, and severity of illness. Both studies lacked adjustments for critical confounders including co-treatments, baseline characteristics, disease severity, and timing of plasma delivery.

Benefits

Compared with a 30% mortality rate in the historical control (3/10), no deaths were reported among patients receiving COVID-19 convalescent plasma. Out of eight patients across both studies on mechanical ventilation at time of treatment, 50% (n=4) were extubated at time of data collection.

Harms

Among 10 patients, no serious adverse reactions or safety events were recorded following COVID-19 convalescent transfusion.

Other considerations

The panel agreed on the overall certainty of evidence as very low due to concerns with risk of bias and imprecision. Continuation of mechanical ventilation was used as a surrogate for failure of clinical improvement; however, the panel recognized the importance of the timeframe for extubation when associating it to plasma transfusion. Given the limited information provided about time of extubation, the panel recognized an additional knowledge gap with the assessment of this outcome.

Conclusions and research needs for this recommendation

The guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. Additional clinical trials are needed to inform research for treatment with COVID-19 convalescent plasma for patients with COVID-19 (Supplementary Table s2).

Table 7. GRADE evidence profile, PICO 7

PICO 7: Convalescent plasma compared to no convalescent plasma for hospitalized patients with COVID-19

Setting: Inpatient

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												
2 ^{1,2}	observational studies	serious ^{a,b}	not serious	not serious ^c	very serious ^d	none	0/15 (0.0%) ^e	3/10 (30.0%) ^f	not estimable		⊕○○○ VERY LOW	CRITICAL
Failure of clinical improvement (as inferred by need for continued mechanical ventilation)												
2 ^{1,2}	observational studies	serious ^{a,g}	not serious	not serious ^{c,h}	very serious ⁱ	none	4/8 (50.0%)	-	-	-	⊕○○○ VERY LOW	CRITICAL
Adverse events												
1 ²	observational studies	serious ^f	not serious	not serious	serious ^d	none	No serious adverse reactions or safety events were recorded after CP transfusion.			⊕○○○ VERY LOW	CRITICAL	

CI: Confidence interval

Explanations

- Studies lacked adjustment for critical confounders (co-treatments, baseline characteristics, disease severity, timing of plasma delivery). Shen 2020 patients received concurrent treatment with methylprednisolone and antivirals. Duan 2020: 9 patients received arbidol monotherapy or combination therapy with remdesivir, ribavirin, or peramivir; 1 patient ribavirin monotherapy, 6 IV methylprednisolone. Antibacterial or antifungal treatment was used when patients had co-infection.
- Mortality is naively pooled from one study of 5 mechanically ventilated patients and one study with 10 patients (3 mechanically ventilated, 3 on high-flow nasal cannula).
- All patients had ARDS and were receiving mechanical ventilation at time of treatment. Convalescent plasma donors recovered from SARS-CoV-2 infection, had been diagnosed with laboratory-confirmed COVID-19.
- Concerns with no events reported out of a small sample.
- 5 patients from Shen 2020 and 10 patients from Duan 2020.
- Historical control provided by Duan 2020 for 10 patients matched by age, gender, and severity.
- Continued mechanical ventilation is naively pooled from one study of 5 mechanically ventilated patients and one study of 3 patients (out of 10) mechanically ventilated before convalescent plasma therapy.
- Need for continued mechanical ventilation serves as a surrogate for clinical improvement. The time frame is important when considering extubation posttransfusion, less likely associated with the CP is less than 24 hours.
- Concerns with few events reported out of a small sample

References

- Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020.
- Duan K, Liu B, Li C, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. *medRxiv* 2020.

Narrative summaries of treatments undergoing evaluation

In addition to the clinical questions addressed above, the panel identified several treatments currently undergoing evaluation for which additional data are needed to formulate 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 clinicaltrials.gov evaluating darunavir/cobicistat as a potential therapeutic option for COVID-19. Janssen, the manufacturer of darunavir/cobicistat has reported that one of these trials [38] has concluded that darunavir/cobicistat plus conventional treatments was not effective in achieving viral clearance at day seven post randomization,

compared to conventional treatments alone. Clinical outcomes of this trial including rate of critical illness and mortality 14 days after randomization, have not been reported to date.

Lopinavir-ritonavir combined with interferon beta or other antivirals

Lopinavir-ritonavir is a combination of protease inhibitors for the treatment of HIV infection. Lopinavir-ritonavir has been shown to have in-vitro antiviral activity against beta-coronaviruses such as SARS-CoV, and MERS-CoV [39-42]. 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 [41]. 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 [41]. Many interferons, especially interferon beta have been shown to have modest in-vitro antiviral activity against SARS-CoV and MERS-CoV [39, 40]. 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 [42]. Lopinavir/ritonavir and interferon- β 1b alone or in combination are being evaluated in clinical trials.

COVID-19 convalescent plasma for prophylaxis

There is a long history of using convalescent plasma as treatment for infectious diseases, including severe viral lower respiratory tract infections [43]. Individuals who have recovered from SARS-CoV-2 infection may generate neutralizing antibodies [44, 45] that could have application to prevention of infection in certain settings, such as individuals with underlying conditions predisposing to severe disease and those with high-risk exposure. Monoclonal antibodies against other respiratory viruses have been shown to be protective against hospitalization in specific high-risk populations [46, 47] and animal models have suggested utility in prophylaxis against SARS coronavirus infection [48]. There are some risks associated with the use of convalescent plasma like transfusion-related acute lung injury or a theoretical risk of antibody-dependent enhancement of infection (ADE). ADE can occur in several viral diseases and involves an enhancement of disease in the presence of certain antibodies [49]. A trial from patients recovered from SARS-CoV-2 infection for use as prophylaxis in adults with a high -risk exposure is expected to begin recruiting shortly [50].

Ribavirin

There are only *in vitro* data available on the activity of ribavirin on SARS-CoV-2 currently. The EC₅₀ (half maximal effective concentrations) was significantly higher than for chloroquine and remdesivir, so it appears less potent *in vitro* compared to these agents [51]. 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 [30]. 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 [52].

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 [53] and continues to be explored as a therapeutic option as part of combination regimens. Two trials evaluating combination regimens are underway in Wuhan [54, 55] as well as a trial in Thailand proposing different combinations [56]. None of the trials or case reports have examined oseltamivir as monotherapy.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has been used as an adjuvant to treat a variety of pathogens either as a pooled product or in a concentrated more pathogen focused (hyperimmune) form. As the community from which a given batch of IVIg is derived from includes increasing numbers of individuals who have recovered from SARS-CoV-2, the possibility of protective antibodies being present in the pooled product is increased. However, the potential utility of IVIg for the treatment of SARS-CoV-2 is unknown at this time. Its use has been reported in a few patients with COVID-19 [57], but studies are needed to determine if there may be a role for IVIg in the treatment of SARS-CoV-2.

Remdesivir

Remdesivir (GS-5734) is a broad-spectrum antiviral nucleotide prodrug with potent in vitro activity against a range of RNA viruses including Ebola virus, Marburg, MERS-CoV, SARS-CoV, respiratory syncytial virus, Nipah virus, and Hendra virus [58-60]. The mechanism of action of remdesivir is premature termination of viral RNA transcription [60]. Its use improved disease outcomes and reduced viral loads in SARS-CoV-infected mice [59]. The efficacy of prophylactic and therapeutic remdesivir was tested in a rhesus macaque model of MERS-CoV infection [61]. Prophylactic remdesivir treatment initiated 24 hours prior to inoculation completely prevented MERS-CoV-induced clinical disease, strongly inhibited MERS-CoV replication in respiratory tissues, and prevented the formation of lung lesions [61]. Therapeutic 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 recent 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 [62]. However, there was no comparison group of similar patients who received standard care at the participating institutions. Because RCTs for remdesivir have not been completed, formalized recommendations will be made once the entire body of evidence for remdesivir is available.

Should NSAIDs be stopped in patients infected with COVID-19?

The role of NSAIDs in the management of SARS-CoV2 has been discussed widely. Recent anecdotal reports and subsequent warnings from health officials have suggested against the use of NSAIDs in the care of patients with COVID-19; however, neither FDA, EMA, or WHO have identified evidence linking NSAIDs to COVID-related clinical deterioration. Human coronaviruses, including SARS CoV-2, use ACE2 to bind to human targets and gain entry into target cells [63]. It has been theorized that NSAIDs, due to upregulation in ACE2 in human target cells, may lead to a more severe course of COVID-19 in those taking NSAIDs. While no causal evidence of adverse outcomes with NSAIDs in the management of COVID-19 have been published, there are well known risks of non-steroidal anti-inflammatory agents including cardiovascular, gastrointestinal and renal adverse events [64, 65]. 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 [66, 67]. RCTs are needed to better understand the safety of NSAIDs in the management of patients with COVID-19. One RCT is currently underway to evaluate the role of naproxen in those critically ill with COVID-19 [68].

Should ACE and ARB's for hypertension be stopped in patients infected with COVID19?

Angiotensin converting enzyme 2 (ACE2) is the receptor for SARS CoV-2 on human cells. Because angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may increase ACE2 expression, the possibility has been raised that these drugs may increase the likelihood of acquiring SARS-CoV-2 or may exacerbate the course of COVID-19. To date, however, there are no clinical data to support this hypothetical concern. For this reason, the American Heart Association, the Heart Failure Society of America and the American College of Cardiology all recommend that ACE inhibitors or ARBs be continued in people who have an indication for these medications [69].

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 [70].

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 [71], 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 were 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 azithromycin and hydroxychloroquine 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 [72]. Given that the panel could not make a determination whether the benefits outweigh harms for these treatments it would be ethical and prudent to enroll patients with COVID-19 in clinical trials, rather than use clinically unproven therapies [73]. 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) [70]. 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 [74].

For clinical trials and observational studies, it is critical to determine *a priori* standardized & 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 SaO₂ or FiO₂:PaO₂ ratios 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 [75]. 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) [76]. 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.

Accepted Manuscript

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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.** receives research funding from the Health and Medical Research Fund (HMRF); **K. E.** serves as a scientific advisor for Merck, Bionet, IBM, Sanofi, X4 Pharmaceuticals, Inc., Seqirus, Inc., Moderna, Inc. and Pfizer, and receives research funding from the Centers for Disease Control and Prevention and the National Institutes of Health; **R. G.** has served on a scientific advisory board for Gilead Sciences, Inc., serves on a scientific advisory board for Merck, receives research funding from the NIH; **M.H.M** receives research funding from the Agency for Healthcare Research and Quality, the Endocrine Society, the Society for Vascular Surgery and The American Society of Hematology, is a Board member for the Evidence Foundation; **W.J.M.** serves in an advisory role for Seqirus, Inc. and receives research funding Ansun BioPharma, Astellas Pharma, Inc, AstraZeneca, Janssen Pharmaceutica, Karius, Melinta, Merck, Roche and Tetrphase; **S.S.** serves as an advisory board member for Amplyx Pharmaceuticals, Inc., as an advisor/consultant to ReViral Ltd., receives research funding from Ansun BioPharma, F2G, Shire (now Takeda), University of Nebraska, Cidara Therapeutics, and has served as an advisor for Janssen Pharmaceutica and Acidophil; **A.H.S.** receives research grant funding from the U.S. Department of Veterans Affairs; and **Y.F.Y.** receives honoraria for evidence reviews and teaching from the Evidence Foundation, honoraria for evidence reviews for the American Gastroenterological Association, and serves as a Director for the Evidence Foundation and for the U.S. GRADE Network. All other authors: no disclosures reported. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed. All other authors: no disclosures reported.

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