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

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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 infection.

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 infection.

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. 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, 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.

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]. GRADE summary of findings tables were developed in GRADEpro Guideline Development Tool [10].

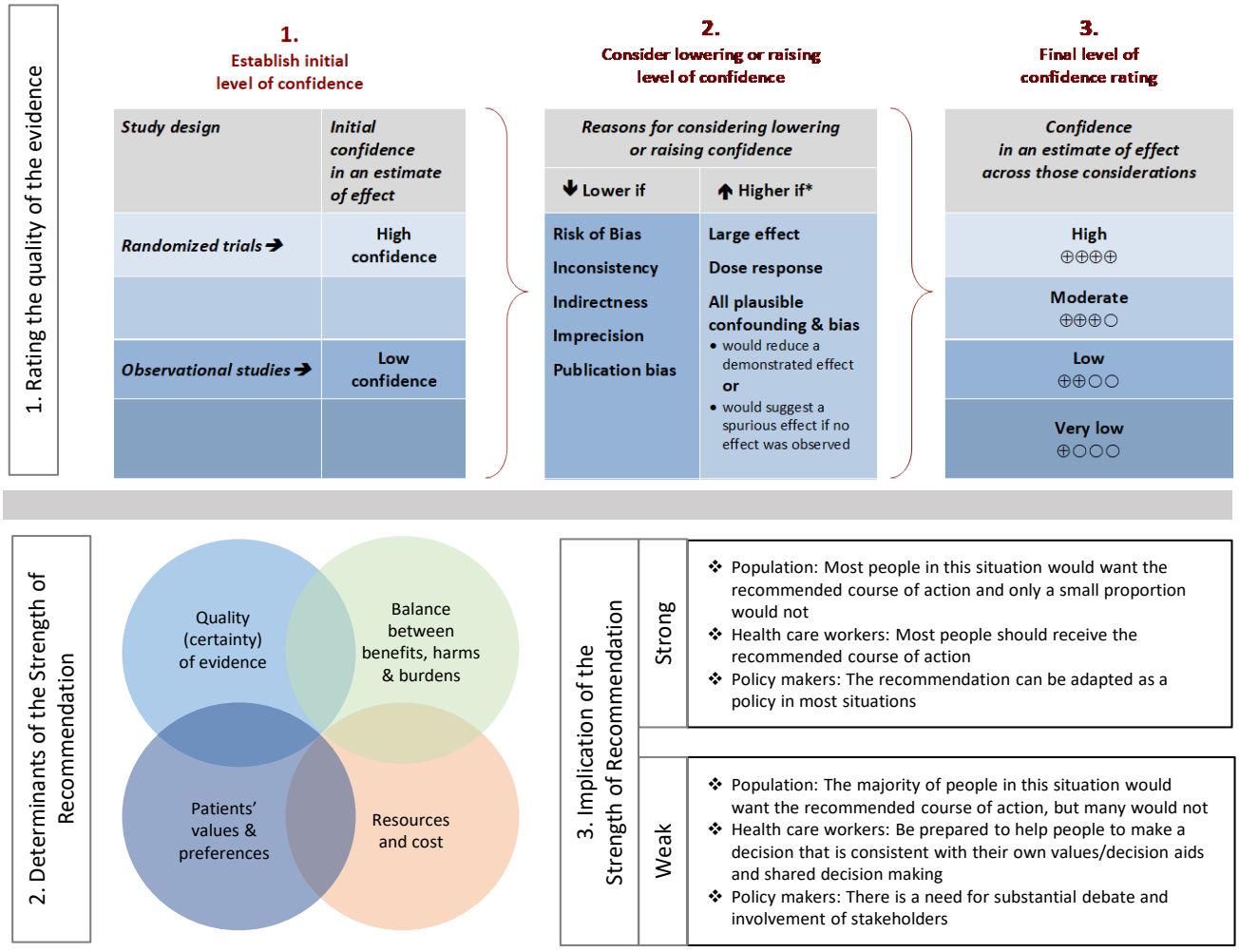
Evidence to recommendations

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".

In situations where promising interventions were judged with 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 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 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 s3a-3f.

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 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 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 the use of HCQ or 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 infection. 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).

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												
	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

a. Chen Z 2020 did not explicitly report on deaths
b. Did not report on blinding (including outcome adjudication committee), sequence generation or allocation concealment; Chen J 2020: all patients received nebulized alpha-interferon, 80% vs. 67.7% of subjects received Abidiol in the hydroxychloroquine vs. placebo arm, respectively. Two subjects in the control arm received lopinavir/ritonavir;
c. Zero events
d. Radiological progression is an intermediary for worsening to ARDS, need for intubation, and death
e. 95% CI includes substantial beneficial effect as well as substantial harms
f. Small sample size, optimal information size not met
g. Viral clearance is a surrogate for clinical improvement, such as worsening to ARDS, intubation, and death
h. 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.)
i. 2 AEs include: AST elevation, creatinine elevation and anemia
j. Case reports

References

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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							№ 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												
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. 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%)
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 availble 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

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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) or on clinical improvement (RR: 0.78; 95% CI: 0.63, 2.20).

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).

Table 3. GRADE evidence profile, PICO 3
PICO 3: 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]	randomised 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]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	54/99 (54.5%)	70/100 (70.0%)	**RR 0.78** (0.63 to 2.20)	**154 fewer per 1,000** (from 259 fewer to 840 more)	⨁◯◯◯ VERY LOW	CRITICAL
AEs leading to treatment discontinuation												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [d]	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. Small number of events making estimates highly uncertain

References

1. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med **2020**.

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 infection. 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 infection 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.

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

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**.
5. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med **2006**; 3(9): e343.
6. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol **2004**; 31(4): 304-9.

Table 5. GRADE evidence profile, PICO 5
PICO 5: Corticosteroids compared to no corticosteroids for hospitalized patients with COVID-19 with ARDS
Setting: intensive care

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

CI: Confidence interval; **ARDS:** Acute respiratory distress syndrome; **OR**: Odds Ratio
Explanations
a. Study limitations include: 1) critical information not reported on baseline risk/severe pneumonia/ARDS; 2) confounding by indication; 3) unadjusted analyses; 4) timing of disease not given; 5) variability in treatments given.
b. Some studies show benefits, some no effect, and some harms.
c. Imprecision likely given the heterogeneity.
d. 1) restricted patients to less severe population; 2) confounding; 3) timing of when given.
e. Few patients included.
References
1. Sun F, Kou H, Wang S, et al. Medication patterns and disease progression among 165 patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a single-centered, retrospective, observational study. **2020**.
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 infection 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 infections.

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).

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
1. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with Tocilizumab. ChinaXiv **2020**; 202003(00026): v1.
2. Jacobs B, Jawad A, Fattah Z. Pneumatosis Intestinalis and Intestinal Perforation in a Patient Receiving Tocilizumab. Arch Rheumatol **2018**; 33(3): 372-5.
3. Genovese MC, Kremer JM, van Vollenhoven RF, et al. Transaminase Levels and Hepatic Events During Tocilizumab Treatment: Pooled Analysis of Long-Term Clinical Trial Safety Data in Rheumatoid Arthritis. Arthritis Rheumatol **2017**; 69(9): 1751-61.

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 infection (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
a. 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.
b. 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).
c. 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 COVD-19.
d. Concerns with no events reported out of a small sample.
e. 5 patients from Shen 2020 and 10 patients from Duan 2020.
f. Historical control provided by Duan 2020 for 10 patients matched by age, gender, and severity.
g. 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.
h. 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.
i. Concerns with few events reported out of a small sample
References
1. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA **2020**.
2. 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/cobcistat has reported that one of these trials [38] has concluded that darunavir/cobicstat 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-β1b alone or in combination are being evaluated in clinical trials.

COVID 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 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 [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 Sa02 or Fi02:Pa02 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 guidance 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.** 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

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Supplementary Information

Table s1. Search strategy

Embase 1974 to 2020 April 03, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2016 to April 03, 2020

1	exp coronavirus/	14237
2	((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.	897
3	(coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw.	30015
4	(((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.	783
5	((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw.	176
6	"severe acute respiratory syndrome*".ti,ab,kw.	6173
7	exp Coronavirus Infections/	13790
8	1 or 2 or 3 or 4 or 5 or 6 or 7	42105
9	limit 8 to yr="2019 -Current"	9709
10	exp Chloroquine/	36522
11	exp hydroxychloroquine/	24156
12	(Hydroxychloroquine or chloroquine or chlorochin or hydroxychlorochin or Aralen or Plaquenil or Resochin or Dawaquin or Lariago or Hydroquin or Axemal or Dolquine or Quensyl or Quinori).ti,ab,kw.	32249
13	exp Azithromycin/	35854
14	(Azithromycin or Sumamed or Zithromax or Zmax or Z-Pak).ti,ab,kw.	15897
15	exp Lopinavir/	7061
16	lopinavir.ti,ab,kw.	4228
17	exp Receptors, Interleukin-6/ai [Antagonists & Inhibitors]	152
18	exp interleukin 6 antibody/ use oemezd	1427
19	(anti-IL-6 or (IL-6 adj2 inhibitor*) or (Anti-IL6 adj2 antibod*)).ti,ab,kw.	3836
20	exp Plasma/ use ppmc	4390
21	exp plasma transfusion/ use oemezd	4637
22	convalescent plasma.ti,ab,kw.	241

23	exp Adrenal Cortex Hormones/ use ppmc	33572
24	exp Pregnenediones/ use ppmc	13224
25	exp corticosteroid/ use oemezd	909723
26	corticosteroid*.ti,ab,kw.	176255
27	glucocorticoid*.ti,ab,kw.	104945
28	methylprednisolone*.ti,ab,kw.	28613
29	exp Anti-Inflammatory Agents, Non-Steroidal/ use ppmc	21970
30	exp nonsteroid antiinflammatory agent/ use oemezd	726190
31	(nsaid* or (anti-inflammator* adj2 non-steroid*) or (antiinflammator* adj2 nonsteroid*)).ti,ab,kw.	70642
32	exp Ribavirin/	39517
33	(Ribavirin or Copegus or Ribasphere or Rebetol).ti,ab,kw.	29178
34	exp Oseltamivir/	11029
35	(Oseltamivir or Tamiflu).ti,ab,kw.	6464
36	exp Immunoglobulins, Intravenous/ use ppmc	2087
37	exp immunoglobulin/iv [Intravenous Drug Administration]	35005
38	(ivig or (intravenous* adj2 immunoglobulin*) or Flebogamma or Gamunex or Privigen or Octagam or Gammagard).ti,ab,kw.	33436
39	exp Interferon-beta/ use ppmc	1375
40	exp beta interferon/ use oemezd	24723
41	(interferon adj2 beta).ti,ab,kw.	17228
42	exp remdesivir/ use oemezd	92
43	(GS-5734 or remdesivir).ti,ab,kw.	89
44	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43	1824148
45	8 and 44	2551
46	limit 45 to yr="2019 -Current"	458

Table s2. Best practices and suggestions for research of treatments for patients with COVID-19

Protocol	Favor study designs that may optimize rapid accrual (e.g., multicentric)
Registration/ IRB-IEC	All RCTs must still be registered at clinicaltrials.gov. All studies must follow Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki, including IRB approval. IRBs should increase resources to facilitate and accelerate study protocol review.
Critical elements to define *a priori*	
Study design	Although RCTs are the favored study designs to evaluate new interventions, other study designs have value especially when data needs to be evaluated quickly: -non-randomized controlled studies (especially cohort studies) -single-arm studies (prospective outcome registries), especially to identify harm
Participants	Depending on the aim of the study, different populations may be included: Aiming to evaluate efficacy: strict inclusion/exclusion criteria (excluding patients with comorbidities and comedications), smaller sample size. This design decreases variability but can increase the risk of slow accrual rate and results can be less generalizable. Aiming to evaluate impact in real-life scenarios: broader population (including special populations such as patients with immunosuppression, HIV, cardiovascular comorbidities and pregnancy). This design increases variability but makes results more generalizable to the general population with better evaluation of drug-drug interactions and harms.
Laboratory-confirmed	Standardized laboratory-confirmation should be based on NAT (nucleic acid testing) for SARS-CoV-2 on respiratory specimen rather than relying on radiological suspicion on imaging studies which are much less specific.
Clinical syndrome	Distinguish between asymptomatic carrier state, upper respiratory tract infection and lower respiratory tract infection
Disease severity	Use standardized definitions, for example as per WHO-China Joint Mission[1]: -mild-to-moderate: non-pneumonia and mild pneumonia -severe defined as tachypnoea[2], oxygen saturation ≤93% at rest, or PaO_2/FiO_2 ratio <300 mm Hg -critical respiratory failure requiring mechanical ventilation, septic shock, or other organ dysfunction or failure that requires intensive care Despite these standardized criteria, disease severity should focus on objective readily available clinical criteria, like the degree of respiratory failure using Sa02 or FiO2:PaO2 ratios, 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.
Interventions	Studied interventions should be detailed in terms of dose, interval, duration and timing of administration according to clinical status.
Outcomes	Efficacy as well as harms should be reported. Outcomes should focus on patient-important outcomes (clinical improvement rather than improvement in inflammatory markers such as CRP or procalcitonin). Outcomes should be objectively measured especially if the study is not blinded. Preferably, avoid outcomes that are participant-or observer-reported involving judgement that reflect decision made by the intervention providers which can be influenced by the clinical context (for example, mortality and clinical improvement based on Sa02 or Fi02:Pa02 ratios should be selected as important outcomes rather than duration of mechanical ventilation or ICU stay). Also, the timing at which the outcomes will be measured should be decided *a priori*. In absence of directly measurable outcomes (especially if events are rare), surrogates can be used. If surrogates are used, select those which are the most closely associated with the outcome of

	interest (e.g. select the oxygen requirement in L/min rather than radiological improvement or reduction in viral load as a surrogate for clinical improvement).
Avoid biases	
Selection bias	Define early stoppage criteria before the onset of the study
Information bias	Blinding the participants and the clinicians will not always be possible due to the urgency of the situation, in which case, at minimum and in order to reduce information bias, outcome assessors should be blinded.
Confounders	Multiple cointerventions (such as antivirals, corticosteroids, immunomodulators) are used. Protocolize their use to ensure that studied groups received the same cointerventions and timing of administrations. If not possible, adjust the analysis for potential confounders (including time-varying confounding) and explore for interactions.
Avoid imprecision	
Sample size	Because the a priori estimation of efficacy may be unknown, it is important to readjust sample sizes prior to stopping recruitment as new evidence emerges.
Submission	
Peer-review	Peer-review remains crucial in the process. Journals should add resources to expedite reviews by increasing the number of editors and reviewers, shorten the review process, favor statistical review and adhere to reporting guidelines (i.e., CONSORT for RCTs or STROBE for non-randomized studies at equator-network.org)[3,4,5]

1. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), 2020 28 February.
2. 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.
3. Equator Network. Reporting guidelines for main study types. Available at: http://www.equator-network.org.
4. Hopewell S, Collins GS, Boutron I, et al. Impact of peer review on reports of randomised trials published in open peer review journals: retrospective before and after study. BMJ 2014; 349: g4145.
5. Keserlioglu K, Kilicoglu H, Ter Riet G. Impact of peer review on discussion of study limitations and strength of claims in randomized trial reports: a before and after study. Res Integr Peer Rev 2019; 4: 19.

Figure s1. PRISMA Flow Diagram

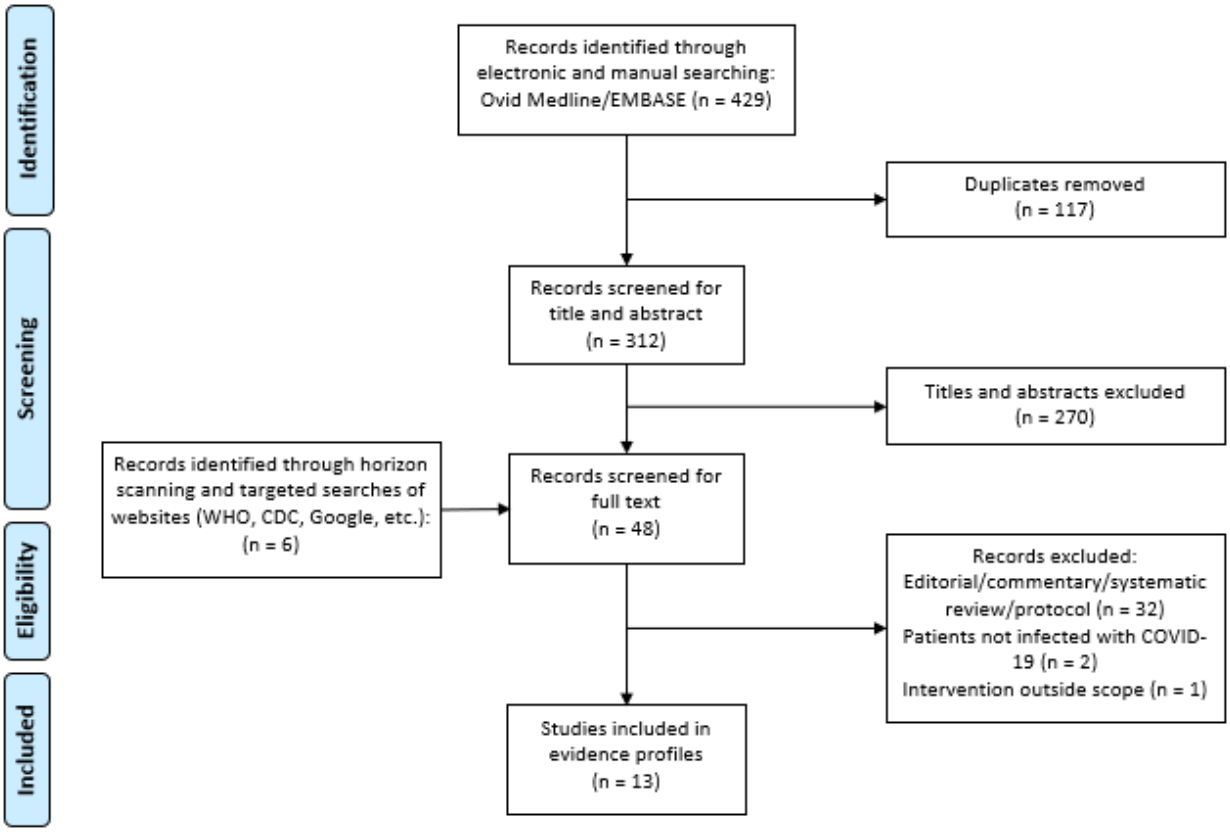
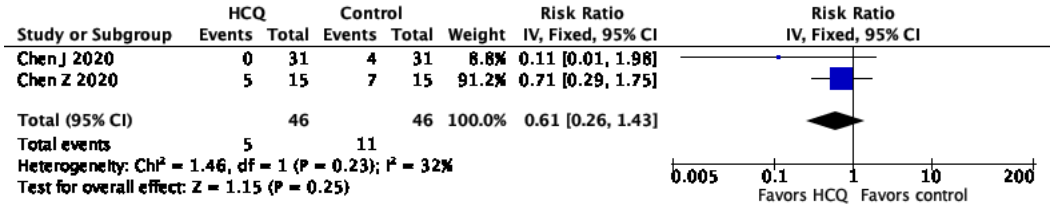


Figure s2: HCQ vs control: pooled estimates

Clinical progression



Any adverse events

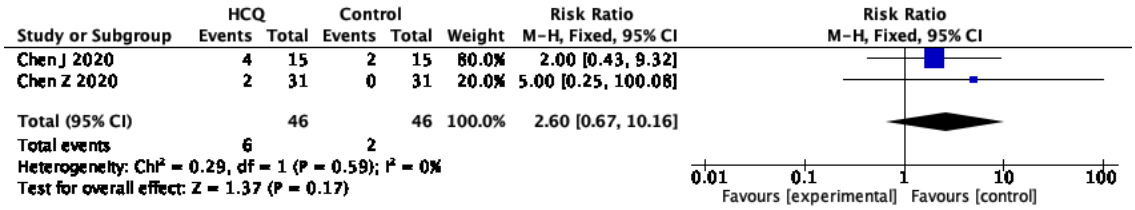
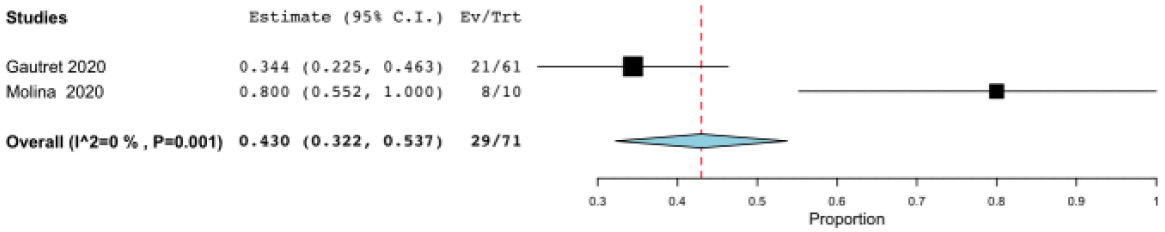


Figure s3: Pooled rates of virological failure using fixed effect model (inverse variance)



Tables s3a – s3f. Characteristics of Included Studies

Table s3a. Intervention/comparator: Hydroxychloroquine vs no HQC
Population: hospitalized patients with COVID-19

Study / year	Country/ Hospital	Study design	# patients / severity of disease	Intervention	Comparator	Outcomes reported	Risk of bias considerations	Funding source
Chen Z/ 2020	China /Renmin Hospital of Wuhan University	RCT	N= 62 hospitalized patients with chest CT with pneumonia Sa02 > 93% Pa02:Fi02 > 300 mmHg	Hydroxychloroquine 400 mg/day x 5 days and standard of care	Standard of care	Radiological changes from day 0-6 Progression to severe disease Adverse events	Allocation concealment unclear Researchers and patients blinded to treatment assignment; however, did not mention placebo Unclear if outcome assessments were blinded Method of assessment for progression to severe disease and adverse events not described	Epidemiologic study of COVID-19 Pneumonia to Science and Technology Department of Hubei Province
Chen J/ 2020	China/ Shanghai Public Health Clinical Center	RCT	30 hospitalized patients	Hydroxychloroquine 400 mg daily x 5 days and standard of care	Standard of care	Mortality Radiological progression at day 3 Adverse events	Did not report allocation concealment or blinding Standard of care included supportive care in additional antiviral agents	Shanghai Science and Technology Commission Fudan First-Class University and First-Class Discipline Construction Project

							No mortality events reported in either arm	Emergency Research Project of New Coronavirus Pneumonia of Zhejiang University Shanghai Public Health Clinical Center Shanghai Key Specialty Infectious Diseases Project

Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv **2020**.
Chen J, LIU D, LIU L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). Journal of Zhejiang University (Medical Science) **2020**; 49(1): 0-.

Table s3b. Intervention/comparator: Hydroxychloroquine + azithromycin vs no HQC/azithromycin
Population: hospitalized patients with COVID-19

Study / year	**Country/ Hospital**	**Study design**	**# patients / severity of disease**	**Intervention**	**Comparator**	**Outcomes reported**	**Risk of bias considerations**	**Funding source**
Gautret P/ 2020a*	France/ Méditerranée Infection University Hospital Institute, Marseille Centre (recruited from various centers in France)	Nonrandomized, Case control	42 symptomatic adult patients Upper and/or lower tract infection	Hydroxychloroquine 200 mg three times a day x 10 days and azithromycin 500 mg x 1 day, then 250 mg x 4 days (n=6) Hydroxychloroquine 200 mg three times a day x 10 days (n=14, excluded from data extraction)	No treatment group total (n=12) (4 asymptomatic pediatric patients excluded from data extraction)	Viral clearance at day 6	No adjustment for critical confounders (such as cotreatments and their timing of administration) Attrition of 6/42 patients due to cessation of treatment No description of subject inclusion/	French Government-Investments for Future Program

							selection for treatment arms Co-author is Editor in Chief of journal	
Gautret P/2020 b*	France/ Méditerranée Infection University Hospital Institute, Marseille Centre (recruited from various centers in France)	Single arm, Case-series	80 patients: 4 asymptomatic / 76 symptomatic	Hydroxychloroquine 200 mg three times a day x 10 days and azithromycin 500 mg x 1 day, then 250 mg x 4 days	No control group	Mortality Viral clearance at day 6 QT prolongation	Uncontrolled study Unclear timing of the intervention Virologic assessment at day 6 included 61/80 patients due to early discharge 14/80 patients remained hospitalized at time of publication	French Government-Investments for Future Program
Molina JM/ 2020	France/Saint Louis Hospital	Single arm, Case-series	11 hospitalized patients	Hydroxychloroquine 600 mg daily x 10 days and azithromycin 500 mg x 1 day, then 250 mg x 4 days	No control group	Mortality Nasopharyngeal viral clearance at days 5-6 Treatment discontinuation due to QT prolongation	Uncontrolled study Unclear timing of the intervention Cointerventions not reported	Not stated
Chorin E/ 2020	United States/ NYU Langone Health	Single arm, Case-series	84 consecutive, hospitalized patients	Hydroxychloroquine and azithromycin	No control group	Mortality Significant QTc prolongation (> 500)	Uncontrolled study Unclear timing of the intervention	Not stated

							Cointerventions not reported	

*Overlapping study populations

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.

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**.

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**.

Chorin E, Dai M, Shulman E, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. medRxiv **2020**.

Table s3c. Intervention/comparator: lopinavir/ritonavir vs no lopinavir/ritonavir
Population: confirmed COVID-19 pneumonia

Study / year	**Country/ Hospital**	**Study design**	**# patients / severity of disease**	**Intervention**	**Comparator**	**Outcomes reported**	**Risk of bias considerations**	**Funding source**
Cao B/ 2020	China/ Jin Yin-Tan Hospital	RCT	199 hospitalized patients Sa02 < 94% on RA or Pa02:Fi02 < 300 mmHg	Lopinavir/ritonavir 400/100 mg twice daily x 14 days and standard of care	Standard of care	Clinical status at day 14 Mortality at day 28 Adverse events leading to discontinuation of treatment	Lack of blinding for patients, providers, clinical outcome assessments Time of illness onset to randomization: median 13 days Fourteen percent of lopinavir/ritonavir treated patient were not able to complete the 14-day treatment due to adverse events	Major Projects of National Science and Technology on New Drug Creation and Development Chinese Academy of Medical Sciences Emergency Project of COVID-19 National Science Grant for Distinguished Young Scholars

Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med **2020**.

Table s3d. Intervention/comparator: corticosteroids vs no corticosteroids
Population: hospitalized patients with COVID-19 without ARDS

Study / year	Country/ Hospital	Study design	# patients / severity of disease	Intervention	Comparator	Outcomes reported	Risk of bias considerations	Funding source
Wu C, 2020	China, Jinyintan Hospital in Wuhan	Retrospective cohort study	201 hospitalized patients with confirmed COVID-19 pneumonia, from which 84 patients with ARDS were analyzed	Methylprednisolone (dose and interval not reported) (n=50)	No methylprednisolone (n=34)	Mortality in patients with ARDS	Critical information not reported on baseline patients' characteristics and severity illness between the groups of interest Confounding-by-indication regarding administration of intervention of interest Variability in cointerventions (antivirals, antioxidants, immunomodulators) Unadjusted analysis	Prevention and Treatment of Infection in Novel Coronavirus Pneumonia Patients from the Shanghai Science and Technology Committee, the Special Fund of Shanghai Jiaotong University for Coronavirus Disease 2019 Control and Prevention, and Academic Leader of Shanghai Qingpu District Healthcare Commission

Wang Y, 2020	China, Wuhan Union Hospital of Huazhong University of Science and Technology	Retrospective cohort study	46 hospitalized patients with severe confirmed COVID-19 pneumonia Severe was defined as: 1) RR ≥30 breath/min; 2) SaO2 ≤93%; 3) PaO2/FiO2 ≤300 mmHg, 4) older than 60 years or with hypertension, diabetes, coronary disease, cancer, pulmonary heart disease, structural lung disease and immunosuppression	Methylprednisolone 1-2mg/kg/d IV for 5-7 days (n=26)	No methylprednisolone (n=20)	Mortality	Critical information not reported on baseline risk and severity pneumonia/ARDS between the groups of interest Confounding-by-indication very likely Variability in timing, dosage and duration of methylprednisolone administered Multiple cointerventions (all received lopinavir-ritonavir, interferon-alpha, thymosin) Unadjusted analysis	Natural Science Foundation of China
Liu Y, 2020	Central Hospital of Wuhan	Retrospective cohort study	109 hospitalized patients with confirmed COVID-19, from which 53 patients with ARDS were analyzed Patients were excluded if: malignant tumors, previous	Glucocorticoid therapy (dose and interval not reported) (n=37)	No Glucocorticoid therapy (n=16)	Mortality in patients with ARDS	Critical information not reported on patients 'characteristics and baseline risk between the groups of interest Confounding-by-indication	Health and Family Planning Commission of Wuhan Municipality

			craniocerebral operation, or died on admission patients who had been transferred to other hospitals for advanced life support and patients with mild symptoms who had been transferred to mobile cabin hospitals.				Variability in cointerventions (antivirals such as ribavirin, oseltamivir and arbidol, and IV immunoglobulins) Unadjusted analysis	
Sun F, 2020	Zhongnan Hospital of Wuhan University	Retrospective cohort study	165 consecutive hospitalized patients with confirmed COVID-19, from which 139 non-severe were analyzed	Systemic glucocorticoid therapy for 4-11 days (dose and interval not reported) (n=90)	No systemic glucocorticoid therapy (n=49)	Clinical deterioration and mortality	Variability in timing, possibly dosage and duration of glucocorticoid administered Confounding-by-indication Variability in cointerventions (antivirals such as lopinavir-ritonavir, arbidol, oseltamivir and interferon-alpha, immunoglobulins and traditional medicines) Unadjusted and partially adjusted analyses (for age and comorbidities)	National Natural Science Foundation of China

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**.**

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**.

Liu Y, Sun W, Li J, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv **2020**.

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**.

Table s3e. Intervention/comparator: Tocilizumab vs no Tocilizumab
Population: severe COVID-19 pneumonia

Study / year	Country/ Hospital	Study design	# patients / severity of disease	Intervention	Comparator	Outcomes reported	Risk of bias considerations	Funding source
Xu X, 2020	China, First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital) and Anhui Fuyang Second People's Hospital	Case series	21 patients, 17 with severe and 4 with critical disease. Severe case: 1) RR ≥ 30 breaths/min; 2) SpO2 ≤ 93%; or 3) PaO2/FiO2 ≤ 300 mmHg. Critical case: 1) respiratory failure requiring mechanical ventilation; 2) shock; or 3) combined with other organ failure, admitted to ICU.	Tocilizumab 400 mg IV X 1 dose (except for 3 patients who received a second dose 12 hours later)	No control group	Clinical and radiological improvement on CT scan, adverse drug reactions, and mortality	Uncontrolled study Unclear if recruitment was consecutive Unclear timing of the intervention Variability in cointerventions (including lopinavir and methylprednisolone)	Department of Science and Technology of Anhui Province and Health Commission of Anhui Province and the China National Center for Biotechnology Development 175

Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with Tocilizumab. ChinaXiv **2020**; 202003(00026): v1.

Table s3f. Intervention/comparator: convalescent plasma vs no convalescent plasma
Population: hospitalized patients with COVID-19

Study / year	Country/ Hospital	Study design	# patients / severity of disease	Intervention	Comparator	Outcomes reported	Risk of bias considerations	Funding source
Duan K, 2020	China/ Wuhan Jinyintan Hospital, Jiangxia District Hospital of Integrative Traditional Chinese and Western Medicine, and First People's Hospital of Jiangxia District, Wuhan	Observational study (case series with comparison to historical controls)	10 patients with severe infection receiving convalescent plasma and 10 historical controls For the intervention group: -Aged ≥18 years with: 1) RR ≥30 beats/min, 2) SpO2 ≤ 93%, or 3) PaO2/FiO2 ≤300 mmHg -Excluded if: 1) previous allergic history to plasma or ingredients, or 2) serious general conditions not suitable for CP transfusion For the historical controls: random selection of 10 patients from the cohort treated in the same hospitals and matched by age, gender and severity of the	Transfusion with 200 mL of convalescent plasma between 10 and 20 days from onset of symptoms (within 4 hours of collection) Convalescent plasma consisted of inactivated CP with neutralization activity >1:640	Historical control group not receiving convalescent plasma	For the intervention group: Clinical improvement (need for mechanical ventilation), adverse events and mortality For the historical controls: Clinical improvement and mortality	No adjustment for critical confounders (such as cotreatments and their timing of administration) Unclear if the outcomes were measured within the same timeframe in both groups Unclear if recruitment was consecutive in the intervention group Variability in cointerventions (all received antivirals such as arbidol, ribavirin, remdesivir, oseltamivir and/or interferon-alpha; some received methylprednisolone)	Shanghai Guangci Translational Medicine Development Foundation

			diseases to the 10 cases					
Shen C, 2020	China / Shenzhen Third People's Hospital	Case series	5 patients, critically ill with ARDS Critical was defined as: 1) respiratory failure requiring mechanical ventilation, 2) shock, or 3) failure of other organs requiring admission to the ICU Patients included if: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; PaO2/FIO2 <300; and mechanical ventilation	Transfusion with 400 mL of convalescent plasma between 10 and 22 days after admission (on the same day as it was obtained from the donors) Convalescent plasma was obtained by apheresis from 5 donors who recovered from COVID-19. Convalescent plasma consisted of SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer by ELISA) and	No control group	Clinical improvement (need for mechanical ventilation), adverse events and mortality	Uncontrolled study Unclear if recruitment was consecutive Variability in cointerventions (all received lopinavir-ritonavir, methylprednisolone, interferon alfa-b1; some also received favipiravir, arbidol and/or darunavir)	National Science and Technology Major Project, Sanming Project of Medicine in Shenzhen, China Postdoctoral Science Foundation, Shenzhen Science and Technology Research and Development Project, National Natural Science Foundation of China, Shenzhen Science and Technology Research and Development Project, and The Key Technology R&D Program of Tianjin

				a neutralization titer greater than 40 (end point dilution titer)				

Duan K, Liu B, Li C, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. medRxiv **2020**.

Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA **2020**