審査結果通知書

高　倫　第１０号
令和２年４月１７日

申請者
高島市民病院
　副院長　土居　健太郎　様

高島市病院事業
人権推進・倫理委員会
　委員長　　鈴木　聡

令和２年４月１５日付けで申請のありました下記の案件について審査の結果、下記のとおり判定しましたので通知します。

記

１．審査対象
　ファビピラビル等の抗ウイルス薬が投与された COVID－19 患者の背景因子と治療効果の検討（観察研究）についての追加審査案件
（ファビピラビルやシクレソニド等、抗ウイルス効果が示された薬剤の COVID－19 に対する適応外使用／Compassionate use に関する倫理的妥当性）

２．判　定　　（承認）・　不承認

３．条件または付記事項　　特になし

令和２年４月１５日

審査申請書

高島市民病院
人権推進・倫理委員会委員長　様

申　請　者
所　属　　高島市民病院

職　名　　副院長
氏　名　　土居健太郎 ㊞

審査対象	ファビピラビルやシクレソニド等、抗ウィルス効果が示された薬剤の COVID-19 に対する適応外使用/Compassionate use に関する倫理的妥当性
課 題 名	ファビピラビル等の抗ウィルス薬が投与された COVID-19 患者の背景因子と治療効果の検討（観察研究）
研究責任者	藤田医科大学　医学部 微生物学講座・感染症科 教授　土井洋平
分担研究者	高島市民病院　内科・総合診療科・循環器科　医師
備　　考	高倫第８号の審査課題に追加

令和 2 年 4 月 15 日

高島市民病院
人権推進・倫理委員会　委員各位

申請者
所属　高島市民病院
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医療行為の概要

新型コロナウィルス感染症(COVID-19)に対する薬物療法や予防療法はまだ確立されていませんが、同じコロナウィルスの SARS（重症急性呼吸器症候群）や MERS（中東呼吸器症候群）などの臨床試験および国内の in vitro の研究成果や海外での使用経験や、すでに中国等で COVID-19 に対して使用された治療経験や臨床研究から、有望視されている医薬品の候補があります。

当院は第二種感染症指定医療機関であり、COVID-19 患者を受け入れる役割を担っています。呼吸器専門医、感染症専門医が常勤していないため、重症症例は、第一種感染症指定医療機関である市立大津市民病院等への転送を想定していましたが、入院した COVID-19 軽症例が一夜にして重症化する症例報告も見受けられ、当院で受け入れた軽症例がそのように重症化した際､滋賀県に設置された COVID-19 災害コントロールセンターの考えでは、基本的には当院で治療継続することが望ましいとしています。現在、滋賀県における感染拡大状況はフェーズ 2 でありますが、今後 7 月～8 月にかけて訪れるフェーズ 4 においては、当院は新型コロナウィルス感染症 100 症例の受け入れを滋賀県から要請されています。集中治療室や ECMO を持ち合わせない当院においては死亡例を減らすためにも重症に陥らないように、軽症から中等症に対して集学的な薬物療法が可能であるか否かが、患者救命において分水嶺になると思われます。

このため、すでに国内で承認されている医薬品および未承認の医薬品の中から、COVID-19 に治療効果が期待される以下の薬剤等について、対象となる患者や候補者が発生した場合、当該患者や家族の同意を得た上で遅滞なく投与できるようにあらかじめ適応外使用、未承認新規医薬品等医療提供の手続きを前回審議いただいた課題に追加で取りたいと考えています。また、COVID-19 症例に対応する医療従事者等の感染予防のため、予防効果が期待できる薬剤もあらかじめ適応外使用および未承認新規医薬品等医療提供の手続きを取りたいと考えています。なお、予防投与に関しては、英国オックスフォード大学で、COPCOV という大規模試験を始めるところですので、現段階ではエビデンスはないことを申し添え

ます。
　そこでこれら抗ウィルス効果が示された下記薬剤や今後新たに治療効果が期待される薬剤の COVID-19 に対する適応外使用/Compassionate use/予防投与/未承認新規医薬品等医療提供に関して包括的に倫理的妥当性を迅速に審議いただきたい。

１）オルベスコ吸入薬（シクレソニド）
２）アビガン（ファビピラビル）
３）カレトラ配合錠（ロピナビル・リトナビル）
４）プラケニル（ヒドロキシクロロキン）
５）フサン注射薬（ナファモスタット）
６）フォイパン（カモスタット）

追加薬
７）アクテムラ（トシリズマブ）：サイトカインストームの治療薬として
８）プラケニル（ヒドロキシクロロキン）：予防薬として
　　https://clinicaltrials.gov/ct2/show/NCT04303507
９）ジスロマック（アジスロマイシン）：予防薬、治療薬として
10）アビガン（ファビピラビル）：予防薬として
10）フォイパン（カモスタット）：予防薬として
11）レムデシビル：治験薬・未承認新規医薬品等医療提供として
　　https://clinicaltrials.gov/ct2/show/study/NCT04280705

参考資料
資料 A：IDSA ガイドライン ver.1.0.3
→　p.13　治療薬として、プラケニル、ジスロマックの有効性
資料 B: ロシュ社、重症 COVID-19 肺炎による入院患者を対象に Actemra/RoActemra の第 III 相臨床試験　→　サイトカインストームの治療薬としてアクテムラの有用性の可能性
資料 C: レムデシビルの有用性
資料 D：COVID-19 の薬物療法の総論
資料 E：COPCOV などの臨床試験

Last updated April 13, 2020 at 4:39 PM EDT and posted online at www.idsociety.org/COVID19guidelines.
Please check website for most updated version of these guidelines.

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

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

Abstract

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

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

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

Results: The IDSA guideline panel agreed on 7 treatment recommendations and provided narrative summaries of other treatments undergoing evaluations.

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

IDSA Disclaimer

It is important to realize that guidelines cannot always account for individual variation among patients. They are assessments of current scientific and clinical information provided as an educational service; are not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); should not be considered inclusive of all proper treatments methods of care, or as a statement of the standard of care; do not mandate any particular course of medical care; and are not intended to supplant physician judgment with respect to particular patients or special clinical situations. Whether and the extent to which to follow guidelines is voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances. While IDSA makes every effort to present accurate, complete, and reliable information, these guidelines are presented "as is" without any warranty, either express or implied. IDSA (and its officers, directors, members, employees, and agents) assume no responsibility for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with these guidelines or reliance on the information presented.

Executive Summary

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

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

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

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

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

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

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

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

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

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

Background

The first cases of coronavirus disease 2019 (COVID-19) were reported from Wuhan, China in early December 2019 [1], now known to be caused by a novel beta-coronavirus, named as Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Within a span of months COVID 19 has become pandemic due to its transmissibility, spreading across continents with the number of cases and deaths rising daily [2]. Although most infected individuals exhibit a mild illness (80%+), 14% have serious and 5% have critical illness. Approximately 10% will require hospital admission due to COVID-19 pneumonia, of which approximately 10% will require ICU care, including invasive ventilation due to acute respiratory distress syndrome (ARDS) [3]. While mortality appears to be more common in older individuals and those with comorbidities, such as chronic lung disease, cardiovascular disease, 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

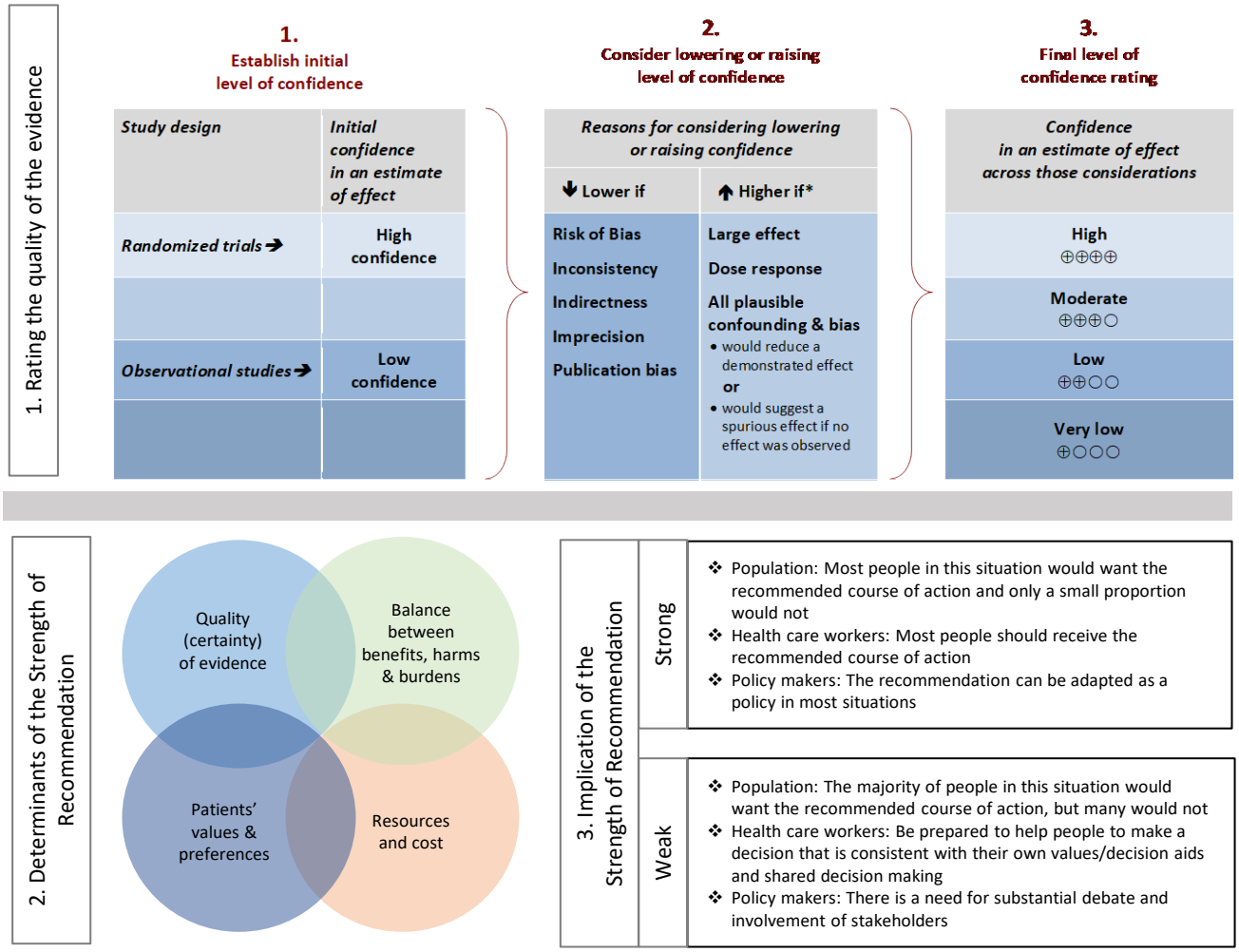
Cochrane risk of bias tools for randomized clinical trials (RCTs) and Observational Studies and modified domains were used in assessing confounding bias, selection bias, and misclassification bias [8]. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development 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". The guideline panel used the word "only" in recommendations about therapeutic agents with higher uncertainty and/or more potential for harm. For example, the toxicity of hydroxychloroquine/chloroquine plus azithromycin (Recommendation 2) carries particular risk for patients in the outpatient setting who may not be enrolled in a trial and therefore may have inadequate monitoring; or, for Recommendation 6, there is concern related to tocilizumab shortages for other indications and potential toxicity of worsening infection/drug interactions. These recommendations acknowledge the current "knowledge gap" and aim at avoiding premature favorable recommendations for their use and to avoid encouraging the rapid diffusion of potentially ineffective or harmful interventions. Detailed suggestions about the specific research questions that should be addressed are found in the table (see Supplementary Table s2).

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



Review process

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

Updating process

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

Results

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

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

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

Summary of the evidence

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

In addition, we identified four publications describing three trials of combination treatment with HCQ plus azithromycin (AZ) among hospitalized patients with COVID-19 reporting on the

outcomes of mortality, failure of virologic clearance (assessed with PCR test), and adverse events (i.e., significant QT prolongation leading to treatment discontinuation) [13-16] (Table 2).

Benefits

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

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

Harms

Two studies described significant QT prolongation in 10 of 95 treated patients, either resulting in an QT increase to over 500 ms or discontinuation of the HCQ/AZ treatment, illustrating the

high risk for clinically relevant arrhythmias for this treatment [15, 16]. In addition, several case reports of QT prolongation related to hydroxychloroquine have also been published [17-20].

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

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

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

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

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

Other considerations

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

Conclusions and research needs for this recommendation

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

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

1. 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-.
2. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv **2020**.
3. Wang C, Fortin PR, Li Y, Panaritis T, Gans M, Esdaile JM. Discontinuation of antimalarial drugs in systemic lupus erythematosus. J Rheumatol **1999**; 26(4): 808-15.

Table 2. GRADE evidence profile, PICO 2
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

References

1. Molina JM, Delaugerre C, Goff J, et al. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Médecine et Maladies Infectieuses **2020**.
2. 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**.
3. Chorin E, Dai M, Shulman E, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. medRxiv **2020**.
4. 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.
5. Wang C, Fortin PR, Li Y, Panaritis T, Gans M, Esdaile JM. Discontinuation of antimalarial drugs in systemic lupus erythematosus. J Rheumatol **1999**; 26(4): 808-15.
6. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med **2012**; 366(20): 1881-90.

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

Summary of the evidence

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

Benefits

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

Harms

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

Other considerations

The panel elected to inform their decision based on the RCT [27]. The panel determined the Certainty of evidence to be very low due to concerns with risk of bias (lack of blinding) and imprecision. In the randomized clinical trial conducted by Cao et al, the group that received lopinavir/ritonavir and the

group that did not had similar rates of viral decay. This finding suggests that lopinavir/ritonavir is not having a measurable antiviral effect, its purported mechanism of action.

Conclusions and research needs for this recommendation

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

Table 3. GRADE evidence profile, PICO 3
Question: Lopinavir/Ritonavir compared to Placebo for confirmed COVID-19 pneumonia
Setting: Inpatients

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

CI: Confidence interval; **RR:** Risk ratio
Explanations
a. Unblinded study which can affect outcomes that require judgment, such a how investigators judge clinical improvement or decide to stop the treatment in patients with side effects.
b. 95% CI includes substantial beneficial effects as well as substantial harms (potentially a relative increase in mortality increase of 17% and a doubling of the likelihood of not clinically improving)
c. Modified intention to treat analysis data used for this outcome. Some deaths were excluded when drug was not given.
d. The upper boundary of the 95% confidence interval crosses the threshold of meaningful improvement as the worst-case estimate is a 3% RRR.
e. Small number of events making estimates highly uncertain
References
1. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine. 2020

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

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

Summary of the evidence

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

Benefits and Harms

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

The same review also reported on a subset of ARDS patients (three trials). One small RCT in 24 patients using a lower dose methylprednisolone for two days showed possible improvement of ARDS; however, two larger trials showed little or no effect in critically ill patients with pulmonary failure. The authors concluded that despite widespread use of corticosteroids during the SARS outbreak, conclusive

evidence of benefit was lacking and that administering steroids early in the disease process before viral replication is controlled may lead to a delay in viral clearance.

Other considerations

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

Conclusions and research need for these recommendations

As COVID-19is 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 treated with tocilizumab, an IL-6 blocker (Table 6). This study had no control group. To estimate a control group rate in patients who did not get treatment with tocilizumab, Xu et al. described findings from Yang 2020, which suggested a baseline mortality rate of 60% in critical patients and 11% in severe patients admitted to the ICU [32].

Benefits

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

Harms

Xu et al. reported no serious adverse events [31]. However, patients receiving tocilizumab are often at an increased risk of serious infections (bacterial, viral, invasive fungal infections, and tuberculosis) and hepatitis B reactivation [33]. Cases of anaphylaxis, severe allergic reactions, severe liver damage and hepatic failure, and intestinal perforation have been reported after tocilizumab administration in patients without COVID-19.

Tocilizumab is not metabolized by the cytochrome P450 isoenzyme system, however elevated IL-6 levels seen in inflammatory states have been shown to inhibit these enzymes, thereby slowing the metabolism of drugs through these pathways. As the 3A4 pathway is responsible for metabolism of

many commonly used medications, administration of IL-6 inhibitors like tocilizumab may result in enhanced metabolism in drugs utilizing the cytochrome P450 system [34, 35].

Other considerations

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

Conclusions and research needs for this recommendation

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

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(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
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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-19 convalescent plasma for prophylaxis

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

Ribavirin

There are only *in vitro* data available on the activity of ribavirin on SARS-CoV-2 currently. The 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 guideline will be posted to the IDSA website.

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COI Summary:

The following list is a reflection of what has been reported to the IDSA. To provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the Board of Directors liaison to the Standards and Practice Guideline Committee and, if necessary, the Conflicts of Interest (COI) and Ethics Committee. The assessment of disclosed relationships for possible COI is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. **L.B.** receives research funding from the National Institutes of Health/National Institute of Allergy and Infectious Diseases, Bill and Melinda Gates Foundation, and Wellcome Trust, and serves as chair of the Antimicrobial Drug Advisory Committee of the Food and Drug Administration; **V.C.** 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]

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Figure s1. PRISMA Flow Diagram

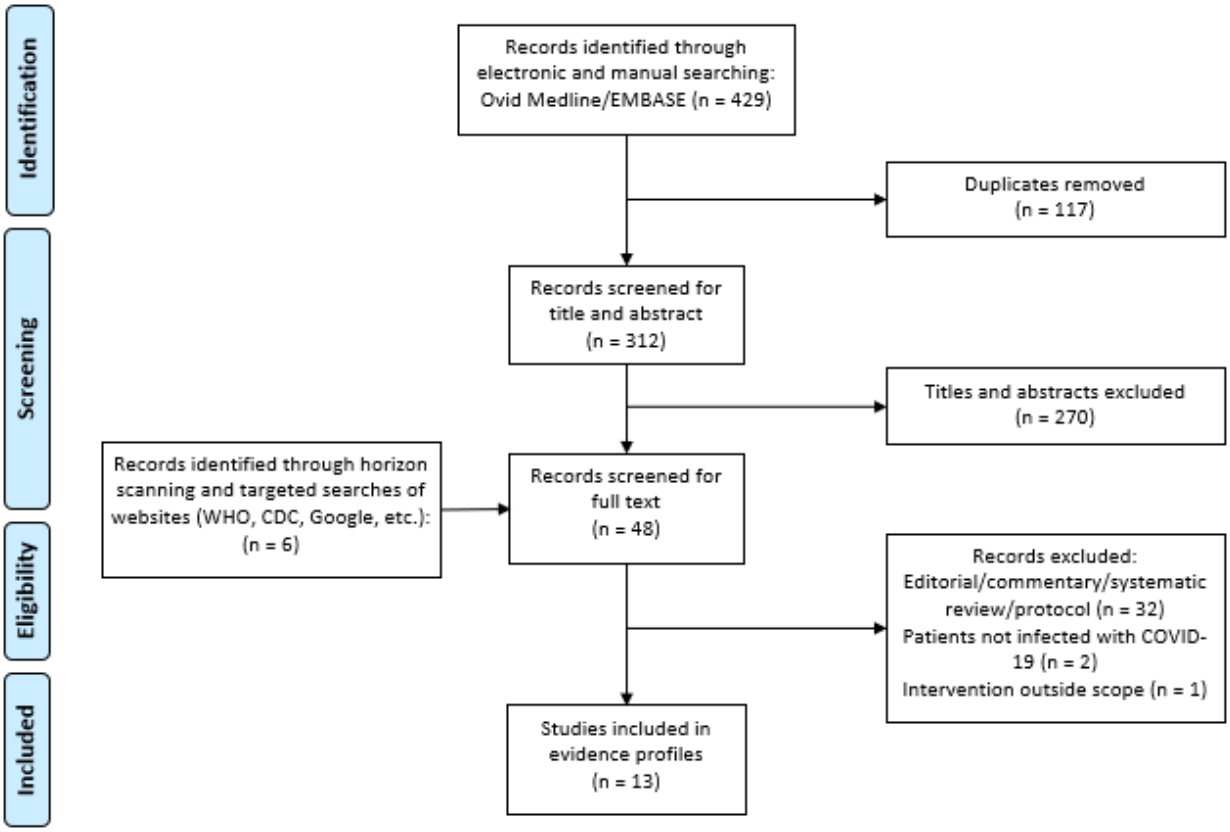
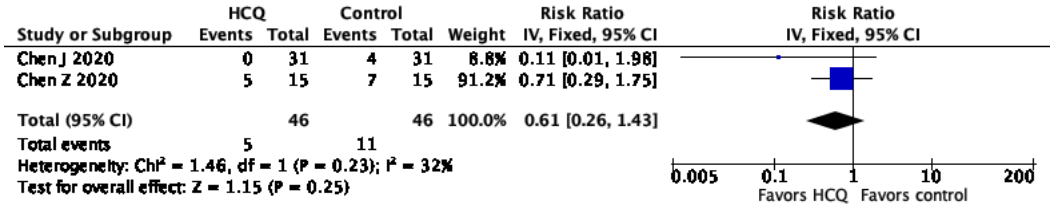


Figure s2: HCQ vs control: pooled estimates

Clinical progression



Any adverse events

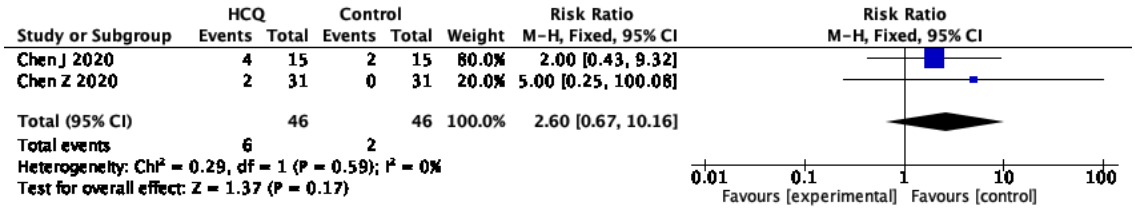
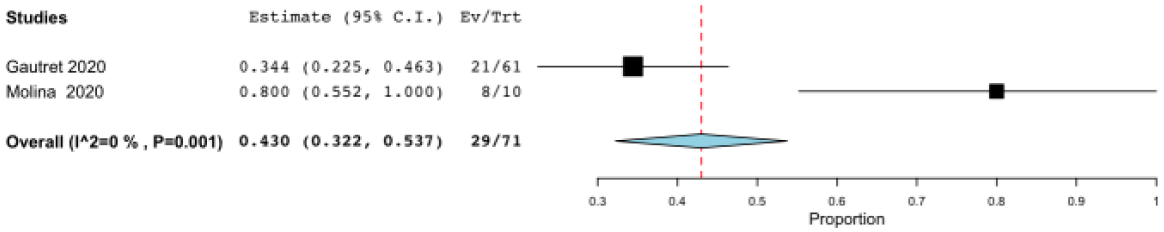


Figure s3: Pooled rates of virological failure using fixed effect model (inverse variance)



Tables s2a – s2f. Characteristics of Included Studies

Table s2a. 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 s2b. 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 s2c. 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 s2d. 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	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	Health and Family Planning Commission of Wuhan Municipality

			tumors, previous 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.				Confounding-by-indication 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	National Natural Science Foundation of China

							analyses (for age and comorbidities)	

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 s2e. 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 s2f. 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	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

				by ELISA) and 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**

Media Release

Roche initiates Phase III clinical trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 pneumonia

Basel, 19 March 2020- Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced we are working with the Food & Drug Administration (FDA) to initiate a randomised, double-blind, placebo-controlled Phase III clinical trial in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), a part of the US Health and Human Services Office of the Assistant Secretary for Preparedness and Response (ASPR), to evaluate the safety and efficacy of Actemra®/RoActemra® (tocilizumab) plus standard of care in hospitalised adult patients with severe COVID-19 pneumonia compared to placebo plus standard of care.

This is the first global study of Actemra/RoActemra in this setting and is expected to begin enrolling as soon as possible in early April with a target of approximately 330 patients globally, including the US. The primary and secondary endpoints include clinical status, mortality, mechanical ventilation and intensive care unit (ICU) variables.

"We are initiating a clinical trial to study Actemra/RoActemra for the treatment of people hospitalised with COVID-19 pneumonia, so that we can better establish the potential role for Actemra/RoActemra in fighting this disease," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "In these unprecedented times, today's announcement is an important example of how industry and regulators can collaborate quickly to address the COVID-19 pandemic, and we will share the results as soon as possible."

To date, there are several independent clinical trials exploring the efficacy and safety of Actemra/RoActemra for the treatment of patients with COVID-19 pneumonia. Actemra/RoActemra has been included in the 7th updated diagnosis and treatment plan for COVID-19 issued by China's National Health Commission (NHC) on March 3, 2020.

However, this new trial is vital because there are no well-controlled studies and limited published evidence on the safety or efficacy of Actemra/RoActemra in the treatment of patients suffering from COVID-19. In addition, Actemra/RoActemra is not currently approved for this use by any health authorities, including the US Food and Drug Administration (FDA).

In addition to initiating this trial, Roche received FDA Emergency Use Authorisation for the cobas® SARS-CoV-2 Test on March 13, 2020, to detect the novel virus that causes COVID-19 disease. Learn more here.

About the Clinical Trial
Roche is initiating a randomised, double-blind, placebo-controlled Phase III study (COVACTA) to evaluate the safety and efficacy of intravenous Actemra/RoActemra added to standard of care in adult patients hospitalised with severe COVID-19 pneumonia compared to placebo plus standard of care. The primary and secondary endpoints include clinical status, mortality, mechanical ventilation and intensive care unit (ICU)

variables. Patients will be followed for 60 days post-randomisation, and an interim analysis will be conducted to look for early evidence of efficacy.

About Actemra/RoActemra
Actemra/RoActemra was the first approved anti-IL-6 receptor biologic available in both intravenous (IV) and subcutaneous (SC) formulations for the treatment of adult patients with moderate-to-severe active rheumatoid arthritis (RA). Actemra/RoActemra can be used alone or with methotrexate (MTX) in adult RA patients who are intolerant to, or have failed to respond to, other disease-modifying anti-rheumatic drugs (DMARDs). In Europe, RoActemra IV and SC are also approved for use in adult patients with severe, active and progressive RA who previously have not been treated with MTX. Actemra/RoActemra IV and SC are approved globally for polyarticular juvenile idiopathic arthritis (pJIA) and in the US and Europe for systemic juvenile idiopathic arthritis (sJIA) in children two years of age and older. Actemra/RoActemra SC injection is also the first approved therapy for the treatment of giant cell arteritis (GCA) in more than 40 countries, including the US and Europe. In the US and Europe, Actemra/RoActemra IV injection is approved for the treatment of chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome (CRS) in people two years of age and older. Actemra/RoActemra was the first approved treatment for CRS in this setting. A prefilled autoinjector ACTPen has been approved in the US and Europe. In Japan, Actemra is also approved for the treatment of Castleman's Disease and Takayasu Arteritis.
Actemra/RoActemra is part of a co-development agreement with Chugai Pharmaceutical Co., Ltd and has been approved in Japan since April 2005. Actemra/RoActemra is approved in more than 110 countries worldwide.

About Roche
Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management.

Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. More than thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Moreover, for the eleventh consecutive year, Roche has been recognised as one of the most sustainable companies in the Pharmaceuticals Industry by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2019 employed about 98,000 people worldwide. In 2019, Roche invested CHF 11.7 billion in R&D and posted sales of CHF 61.5 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the

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ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

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ABSTRACT

BACKGROUND

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

METHODS

We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

RESULTS

Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

CONCLUSIONS

In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Brainard at Gilead Sciences, 333 Lakeside Dr., Foster City, CA 94404, or at diana.brainard@gilead.com.

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Since the first cases were reported in December 2019, infection with the severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a worldwide pandemic.[1,2] Covid-19 — the illness caused by SARS-CoV-2 — is overwhelming health care systems globally.[3,4] The symptoms of SARS-CoV-2 infection vary widely, from asymptomatic disease to pneumonia and life-threatening complications, including acute respiratory distress syndrome, multisystem organ failure, and ultimately, death.[5-7] Older patients and those with preexisting respiratory or cardiovascular conditions appear to be at the greatest risk for severe complications.[6,7] In the absence of a proven effective therapy, current management consists of supportive care, including invasive and noninvasive oxygen support and treatment with antibiotics.[8,9] In addition, many patients have received off-label or compassionate-use therapies, including antiretrovirals, antiparasitic agents, antiinflammatory compounds, and convalescent plasma.[10-13]

Remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Remdesivir has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]) and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses.[14-17] In vitro testing has also shown that remdesivir has activity against SARS-CoV-2. Remdesivir appears to have a favorable clinical safety profile, as reported on the basis of experience in approximately 500 persons, including healthy volunteers and patients treated for acute Ebola virus infection,[18,19] and supported by our data (on file and shared with the World Health Organization [WHO]). In this report, we describe outcomes in a cohort of patients hospitalized for severe Covid-19 who were treated with remdesivir on a compassionate-use basis.

METHODS

PATIENTS

Gilead Sciences began accepting requests from clinicians for compassionate use of remdesivir on January 25, 2020. To submit a request, clinicians completed an assessment form with demographic and disease-status information about their patient (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Approval of requests was reserved for hospitalized patients who had SARS-CoV-2 infection confirmed by reverse-transcriptase–polymerase-chain-reaction assay and either an oxygen saturation of 94% or less while the patient was breathing ambient air or a need for oxygen support. In addition, patients were required to have a creatinine clearance above 30 ml per minute and serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than five times the upper limit of the normal range, and they had to agree not to use other investigational agents for Covid-19.

In approved cases, the planned treatment was a 10-day course of remdesivir, consisting of a loading dose of 200 mg intravenously on day 1, plus 100 mg daily for the following 9 days. Supportive therapy was to be provided at the discretion of the clinicians. Follow-up was to continue through at least 28 days after the beginning of treatment with remdesivir or until discharge or death. Data that were collected through March 30, 2020, are reported here. This open-label program did not have a predetermined number of patients, number of sites, or duration. Data for some patients included in this analysis have been reported previously.[20-22] Details of the study design and conduct can be seen in the protocol (available at NEJM.org).

STUDY ASSESSMENTS

Data on patients' oxygen-support requirements, adverse events, and laboratory values, including serum creatinine, ALT, and AST, were to be reported daily, from day 1 through day 10, and additional follow-up information was solicited through day 28. Although there were no prespecified end points for this program, we quantified the incidence of key clinical events, including changes in oxygen-support requirements (ambient air, low-flow oxygen, nasal high-flow oxygen, noninvasive positive pressure ventilation [NIPPV], invasive mechanical ventilation, and extracorporeal membrane oxygenation [ECMO]), hospital discharge, and reported adverse events, including those leading to discontinuation of treatment, serious adverse events, and death. In addition, we evaluated the proportion of patients with clinical improvement, as defined by live discharge from

the hospital, a decrease of at least 2 points from baseline on a modified ordinal scale (as recommended by the WHO R&D Blueprint Group), or both. The six-point scale consists of the following categories: 1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 5, hospitalized, requiring invasive mechanical ventilation, ECMO, or both; and 6, death.

PROGRAM OVERSIGHT

Regulatory and institutional review board or independent ethics committee approval was obtained for each patient treated with remdesivir, and consent was obtained for all patients in accordance with local regulations. The program was designed and conducted by the sponsor (Gilead Sciences), in accordance with the protocol. The sponsor collected the data, monitored conduct of the program, and performed the statistical analyses. All authors had access to the data and assume responsibility for the integrity and completeness of the reported data. The initial draft of the manuscript was prepared by a writer employed by Gilead Sciences along with one of the authors, with input from all the authors.

STATISTICAL ANALYSIS

No sample-size calculations were performed. The analysis population included all patients who received their first dose of remdesivir on or before March 7, 2020, and for whom clinical data for at least 1 subsequent day were available. Clinical improvement and mortality in the remdesivir compassionate-use cohort were described with the use of Kaplan–Meier analysis. Associations between pretreatment characteristics and these outcomes were evaluated with Cox proportional hazards regression. Because the analysis did not include a provision for correcting for multiple comparisons in tests for association between baseline variables and outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive associations with outcomes. All analyses were conducted with SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

In total, 61 patients received at least one dose of remdesivir on or before March 7, 2020; 8 of these patients were excluded because of missing post-baseline information (7 patients) and an erroneous remdesivir start date (1 patient) (Fig. S1 in the Supplementary Appendix). Of the 53 remaining patients included in this analysis, 40 (75%) received the full 10-day course of remdesivir, 10 (19%) received 5 to 9 days of treatment, and 3 (6%) fewer than 5 days of treatment.

BASELINE CHARACTERISTICS OF THE PATIENTS

Table 1 shows baseline demographic and clinical characteristics of the 53 patients in the compassionate-use cohort. Patients were enrolled in the United States (22 patients), Japan (9), Italy (12), Austria (1), France (4), Germany (2), Netherlands (1), Spain (1), and Canada (1). A total of 40 patients (75%) were men, the age range was 23 to 82 years, and the median age was 64 years (interquartile range, 48 to 71). At baseline, the majority of patients (34 [64%]) were receiving invasive ventilation, including 30 (57%) receiving mechanical ventilation and 4 (8%) receiving ECMO. The median duration of invasive mechanical ventilation before the initiation of remdesivir treatment was 2 days (interquartile range, 1 to 8). As compared with patients who were receiving noninvasive oxygen support at baseline, those receiving invasive ventilation tended to be older (median age, 67 years, vs. 53 years), were more likely to be male (79%, vs. 68%), had higher median serum ALT (48 U per liter, vs. 27) and creatinine (0.90 mg per deciliter, vs. 0.79 [79.6 μmol per liter, vs. 69.8]), and a higher prevalence of coexisting conditions, including hypertension (26%, vs. 21%), diabetes (24%, vs. 5%), hyperlipidemia (18%, vs. 0%), and asthma (15%, vs. 5%). The median duration of symptoms before the initiation of remdesivir treatment was 12 days (interquartile range, 9 to 15) and did not differ substantially between patients receiving invasive ventilation and those receiving noninvasive ventilation (Table 1).

CLINICAL IMPROVEMENT DURING REMDESIVIR TREATMENT

Over a median follow-up of 18 days (interquartile range, 13 to 23) after receiving the first dose

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Invasive Ventilation (N=34)	Noninvasive Oxygen Support (N=19)	Total (N=53)
Median age (IQR) — yr	67 (56–72)	53 (41–68)	64 (48–71)
Age category — no. (%)			
<50 yr	6 (18)	8 (42)	14 (26)
50 to <70 yr	14 (41)	7 (37)	21 (40)
≥70 yr	14 (41)	4 (21)	18 (34)
Male sex — no. (%)	27 (79)	13 (68)	40 (75)
Region — no. (%)			
United States	14 (41)	8 (42)	22 (42)
Japan	8 (24)	1 (5)	9 (17)
Europe or Canada	12 (35)	10 (53)	22 (42)
Oxygen-support category — no. (%)			
Invasive ventilation	34 (100)	—	34 (64)
Invasive mechanical ventilation	30 (88)	—	30 (57)
Extracorporeal membrane oxygenation	4 (12)	—	4 (8)
Noninvasive oxygen support	—	19 (100)	19 (36)
Noninvasive positive-pressure ventilation	—	2 (11)	2 (4)
High-flow oxygen	—	5 (26)	5 (9)
Low-flow oxygen	—	10 (53)	10 (19)
Ambient air	—	2 (11)	2 (4)
Median duration of symptoms before remdesivir therapy (IQR) — days	11 (8–15)	13 (10–14)	12 (9–15)
Coexisting conditions — no. (%)			
Any condition	25 (74)	11 (58)	36 (68)
Hypertension	9 (26)	4 (21)	13 (25)
Diabetes	8 (24)	1 (5)	9 (17)
Hyperlipidemia	6 (18)	0	6 (11)
Asthma	5 (15)	1 (5)	6 (11)
Median laboratory values (IQR)			
ALT — IU per liter	48 (31–79)	27 (20–45)	37 (25–61)
AST — IU per liter	39 (30–76)	35 (28–46)	36 (29–67)
Creatinine — mg per deciliter	0.90 (0.66–1.17)	0.79 (0.63–1.00)	0.89 (0.64–1.08)

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and IQR interquartile range. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

of remdesivir, 36 of 53 patients (68%) showed an improvement in the category of oxygen support, whereas 8 of 53 patients (15%) showed worsening (Fig. 1). Improvement was observed in all 12 patients who were breathing ambient air or receiving low-flow supplemental oxygen and in 5 of 7 patients (71%) who were receiving noninvasive oxygen support (NIPPV or high-flow supplemental oxygen). It is notable that 17 of 30 patients (57%) who were receiving invasive mechanical ventilation were extubated, and 3 of 4 patients (75%) receiving ECMO stopped receiving it; all were alive at last follow-up. Individual patients' changes in the category of oxygen support are shown in Figure 2. By the date of the most recent follow-up, 25 of 53 patients (47%) had been

discharged (24% receiving invasive ventilation [8 of 34 patients] and 89% [17 of 19 patients] receiving noninvasive oxygen support).

By 28 days of follow-up, the cumulative incidence of clinical improvement, as defined by either a decrease of 2 points or more on the six-point ordinal scale or live discharge, was 84% (95% confidence interval [CI], 70 to 99) by Kaplan–Meier analysis (Fig. 3A). Clinical improvement was less frequent among patients receiving invasive ventilation than among those receiving noninvasive ventilation (hazard ratio for improvement, 0.33; 95% CI, 0.16 to 0.68) (Fig. 3B) and among patients 70 years of age or older (hazard ratio as compared with patients younger than 50 years, 0.29; 95% CI, 0.11 to 0.74) (Fig. 3C). Sex, region of enrollment, coexisting conditions, and duration of symptoms before remdesivir treatment was initiated were not significantly associated with clinical improvement (Table S1).

MORTALITY

Seven of the 53 patients (13%) died after the completion of remdesivir treatment, including 6 of 34 patients (18%) who were receiving invasive ventilation and 1 of 19 (5%) who were receiving noninvasive oxygen support (see the Supplementary Appendix for case narratives). The median interval between remdesivir initiation and death was 15 days (interquartile range, 9 to 17). Overall mortality from the date of admission was 0.56 per 100 hospitalization days (95% CI, 0.14 to 0.97) and did not differ substantially among patients receiving invasive ventilation (0.57 per 100 hospitalization days; 95% CI, 0 to 1.2]) as compared with those receiving noninvasive ventilation (0.51 per 100 hospitalization days; 95% CI, 0.07 to 1.1]). Risk of death was greater among patients who were 70 years of age or older (hazard ratio as compared with patients younger than 70 years, 11.34; 95% CI, 1.36 to 94.17) and among those with higher serum creatinine at baseline (hazard ratio per milligram per deciliter, 1.91; 95% CI, 1.22 to 2.99). The hazard ratio for patients receiving invasive ventilation as compared with those receiving noninvasive oxygen support was 2.78 (95% CI, 0.33 to 23.19) (Table S2).

SAFETY

A total of 32 patients (60%) reported adverse events during follow-up (Table 2). The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension. In general, adverse events were more common in patients receiving invasive ventilation. A total of 12 patients (23%) had serious adverse events. The

No. of Patients in Oxygen-Support Group at Baseline (%)

No. of Patients in Oxygen-Support Group after Treatment (%)	Category on ordinal scale	Invasive (N=34)	Noninvasive (N=7)	Low-flow oxygen (N=10)	Ambient air (N=2)
		5	4	3	2
Death	6	6 (18)	1 (14)	0	0
Invasive	5	9 (26)	1 (14)	0	0
Noninvasive	4	3 (9)	0	0	0
Low-flow oxygen	3	0	0	0	0
Ambient air	2	8 (24)	0	0	0
Discharged	1	8 (24)	5 (71)	10 (100)	2 (100)
Improvement		**19 (56)**	**5 (71)**	**10 (100)**	**2 (100)**

Category on ordinal scale

Figure 1. Oxygen-Support Status at Baseline and after Treatment.

For each oxygen-support category, percentages were calculated with the number of patients at baseline as the denominator. Improvement (blue cells), no change (beige) and worsening (gray) in oxygen-support status are shown. Invasive ventilation includes invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or both. Noninvasive ventilation includes nasal high-flow oxygen therapy, noninvasive positive pressure ventilation (NIPPV), or both.

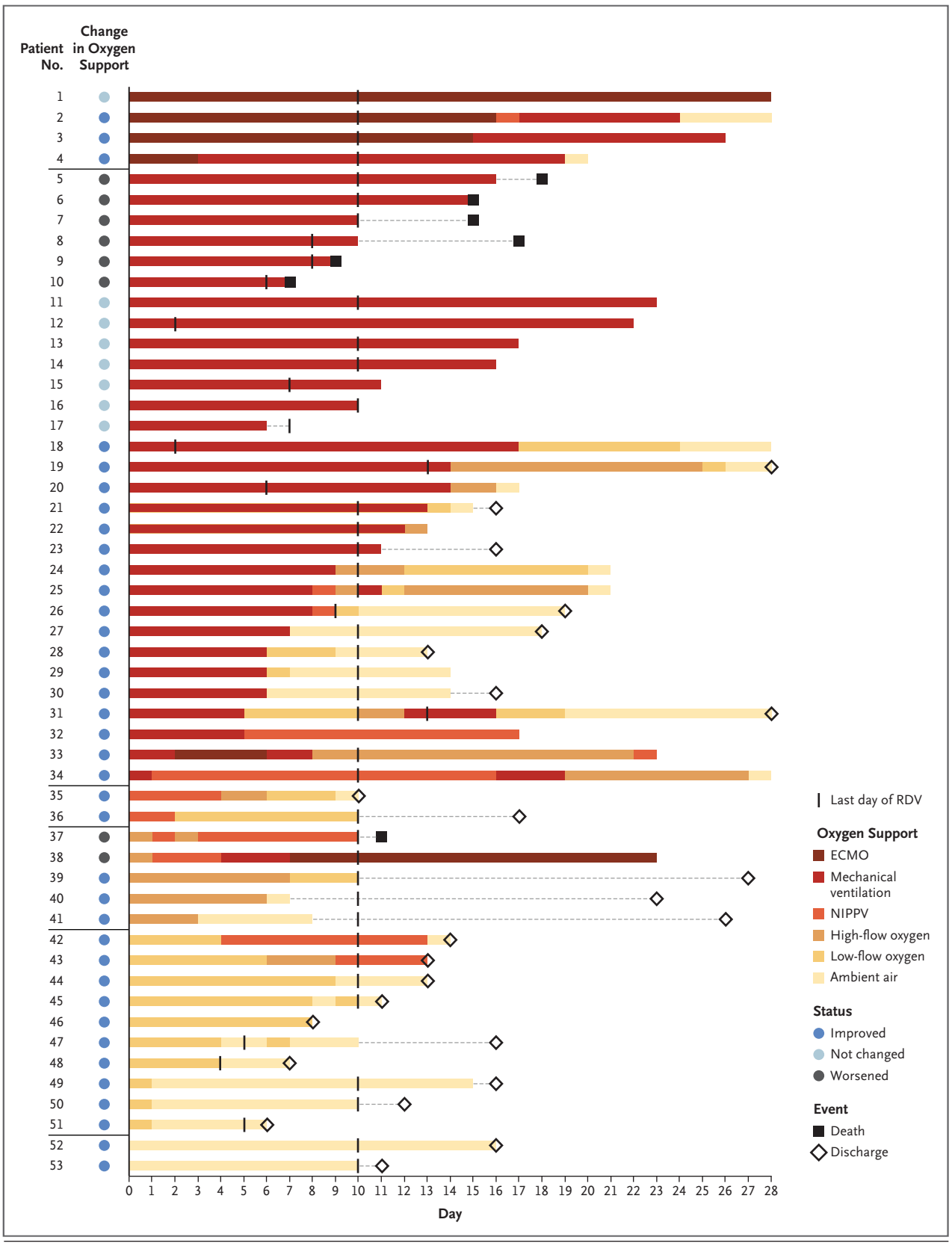

Figure 2 (facing page). Changes in Oxygen-Support Status from Baseline in Individual Patients.

Baseline (day 0) was the day on which treatment with remdesivir (RDV) was initiated. Final oxygen support statuses shown are based on the most recent reported data. For each patient, the colors in the line represent the oxygen-support status of the patient over time. The colored circles to the left of each line indicate the patient's overall change in status from baseline. A patient's status "improved" if the oxygen-support status improved before the last follow-up or the patient was discharged. The vertical black marks show the last day of treatment with RDV. The gray dashed lines represent missing data between the patient's most recent reported oxygen status and an event (death or discharge) or the last dose of RDV. A solid square at the end of a line indicates that the patient died; an open diamond indicates that the patient was discharged from the hospital. If there is neither a square nor a diamond at the end of a line, neither death nor discharge had occurred. Patient 2 was breathing ambient air through day 36. Patients 19 and 31 were discharged on day 44.

most common serious adverse events — multiple-organ-dysfunction syndrome, septic shock, acute kidney injury, and hypotension — were reported in patients who were receiving invasive ventilation at baseline.

Four patients (8%) discontinued remdesivir treatment prematurely: one because of worsening of preexisting renal failure, one because of multiple organ failure, and two because of elevated aminotransferases, including one patient with a maculopapular rash.

LABORATORY DATA

Given the nature of this compassionate-use program, data on a limited number of laboratory measures were collected. Median serum ALT, AST, and creatinine fluctuated during follow-up (Fig. S2).

DISCUSSION

To date, no therapy has demonstrated efficacy for patients with Covid-19. This preliminary report describes the clinical outcomes in a small cohort of patients who were severely ill with Covid-19 and were treated with remdesivir. Although data from several ongoing randomized, controlled trials will soon provide more informative evidence

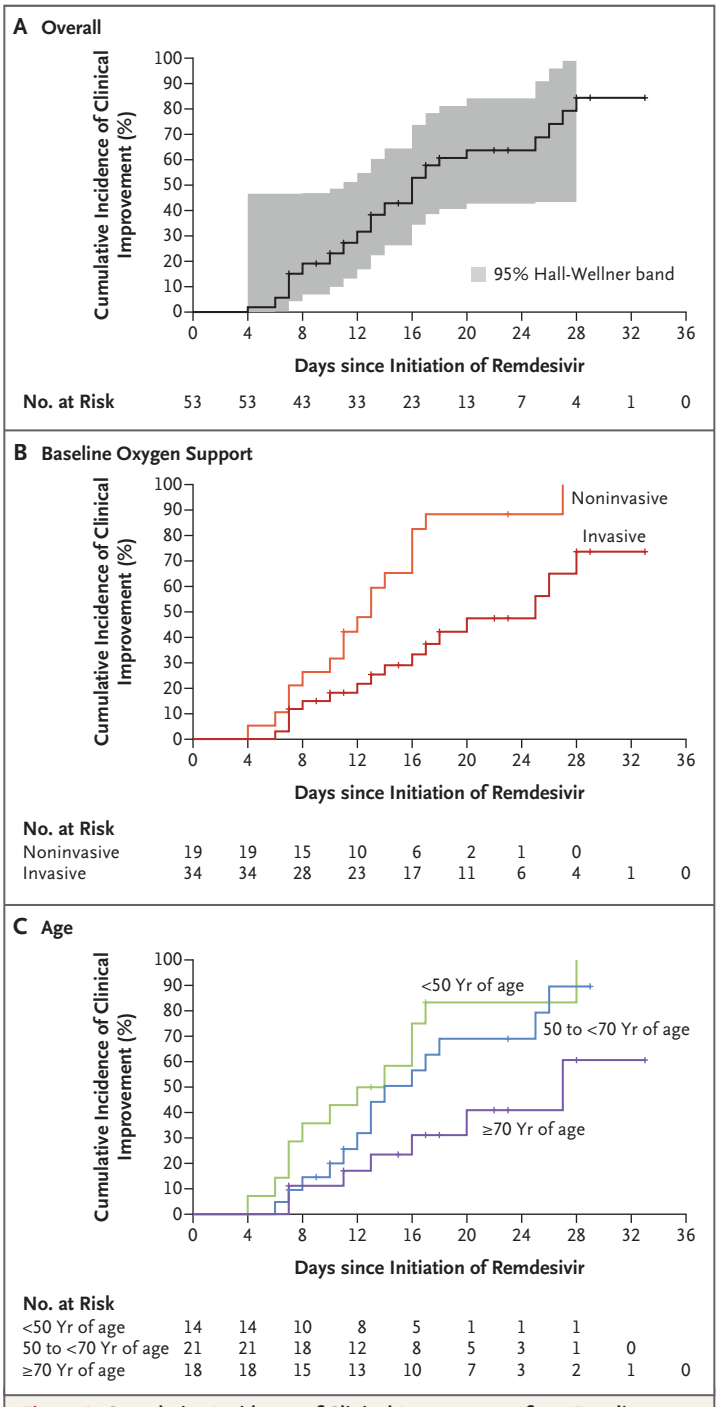

Figure 3. Cumulative Incidence of Clinical Improvement from Baseline to Day 36.

Clinical improvement is shown in the full cohort, in the cohort stratified according to ventilation status at baseline, and in the cohort stratified by age.

Table 2. Summary of Adverse Events.

Event	Invasive Ventilation (N=34)	Noninvasive Oxygen Support (N=19)	Total (N=53)
	number of patients (percent)		
Any adverse event	22 (65)	10 (53)	32 (60)
Adverse events occurring in 2 or more patients			
Hepatic enzyme increased*	8 (24)	4 (21)	12 (23)
Diarrhea	1 (3)	4 (21)	5 (9)
Rash	3 (9)	1 (5)	4 (8)
Renal impairment	4 (12)	0	4 (8)
Hypotension	3 (9)	1 (5)	4 (8)
Acute kidney injury	2 (6)	1 (5)	3 (6)
Atrial fibrillation	2 (6)	1 (5)	3 (6)
Multiple-organ-dysfunction syndrome	3 (9)	0	3 (6)
Hypernatremia	3 (9)	0	3 (6)
Deep-vein thrombosis	3 (9)	0	3 (6)
Acute respiratory distress syndrome	1 (3)	1 (5)	2 (4)
Pneumothorax	2 (6)	0	2 (4)
Hematuria	2 (6)	0	2 (4)
Delirium	1 (3)	1 (5)	2 (4)
Septic shock	2 (6)	0	2 (4)
Pyrexia	1 (3)	1 (5)	2 (4)
Any serious adverse event	9 (26)	3 (16)	12 (23)
Serious events occurring in 2 or more patients			
Multiple-organ-dysfunction syndrome	2 (6)	0	2 (4)
Septic shock	2 (6)	0	2 (4)
Acute kidney injury	2 (6)	0	2 (4)
Hypotension	2 (6)	0	2 (4)

* Adverse-event terms are based on the *Medical Dictionary for Regulatory Activities*, version 22.1. Hepatic enzyme increased includes the following terms: hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased. Elevated hepatic enzymes resulted in discontinuation of remdesivir therapy in 2 patients.

regarding the safety and efficacy of remdesivir for Covid-19, the outcomes observed in this compassionate-use program are the best currently available data. Specifically, improvement in oxygen-support status was observed in 68% of patients, and overall mortality was 13% over a median follow-up of 18 days. In a recent randomized, controlled trial of lopinavir–ritonavir in patients hospitalized for Covid-19, the 28-day mortality was 22%.[10] It is important to note that only 1 of 199 patients in that trial were receiving invasive ventilation at baseline. In case series and cohort studies, largely from China, mortality rates of 17 to 78% have been reported in severe cases, defined by the need for admission to an intensive care unit, invasive ventilation, or both.[23-28] For example, among 201 patients hospitalized in Wuhan, China, mortality was 22% overall and 66% (44 of 67) among patients receiving invasive mechanical ventilation.[7] By way of comparison, the 13% mortality observed in this remdesivir compassionate-use cohort is noteworthy, considering the severity of disease in this patient population; however, the patients enrolled in this compassionate-treatment program are not directly comparable to those studied in these other re-

ports. For example, 64% of remdesivir-treated patients were receiving invasive ventilation at baseline, including 8% who were receiving ECMO, and mortality in this subgroup was 18% (as compared with 5.3% in patients receiving noninvasive oxygen support), and the majority (75%) of patients were male, were over 60 years of age, and had coexisting conditions.

Unfortunately, our compassionate-use program did not collect viral load data to confirm the antiviral effects of remdesivir or any association between baseline viral load and viral suppression, if any, and clinical response. Moreover, the duration of remdesivir therapy was not entirely uniform in our study, largely because clinical improvement enabled discharge from the hospital. The effectiveness of a shorter duration of therapy (e.g., 5 days, as compared with 10 days), which would allow the treatment of more patients during the pandemic, is being assessed in ongoing randomized trials of this therapy.

No new safety signals were detected during short-term remdesivir therapy in this compassionate-use cohort. Nonclinical toxicology studies have shown renal abnormalities, but no clear evidence of nephrotoxicity due to remdesivir therapy was observed. As reported in studies in healthy volunteers and patients infected with Ebola virus, mild-to-moderate elevations in ALT, AST, or both were observed in this cohort of patients with severe Covid-19.[18,19] However, considering the frequency of liver dysfunction in patients with Covid-19, attribution of hepatotoxicity to either remdesivir or the underlying disease is challenging.[29] Nevertheless, the safety and side-effect profile of remdesivir in patients with Covid-19 require proper assessment in placebo-controlled trials.

Interpretation of the results of this study is limited by the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the program, the lack of information on 8 of the patients initially treated, and the lack of a randomized control group. Although the latter precludes definitive conclusions, comparisons with contemporaneous cohorts from the literature, in whom general care is expected to be consistent with that of our cohort, suggest that remdesivir may have clinical benefit in patients with severe Covid-19. Nevertheless, other factors may have contributed to differences in outcomes, including the type of supportive care (e.g., concomitant medications or variations in ventilatory practices) and differences in institutional treatment protocols and thresholds for hospitalization. Moreover, the use of invasive ventilation as a proxy for disease severity may be influenced by the availability of ventilators in a given location. The findings from these uncontrolled data will be informed by the ongoing randomized, placebo-controlled trials of remdesivir therapy for Covid-19.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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JAMA | Review

Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) A Review

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IMPORTANCE The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an unprecedented challenge to identify effective drugs for prevention and treatment. Given the rapid pace of scientific discovery and clinical data generated by the large number of people rapidly infected by SARS-CoV-2, clinicians need accurate evidence regarding effective medical treatments for this infection.

OBSERVATIONS No proven effective therapies for this virus currently exist. The rapidly expanding knowledge regarding SARS-CoV-2 virology provides a significant number of potential drug targets. The most promising therapy is remdesivir. Remdesivir has potent in vitro activity against SARS-CoV-2, but it is not US Food and Drug Administration approved and currently is being tested in ongoing randomized trials. Oseltamivir has not been shown to have efficacy, and corticosteroids are currently not recommended. Current clinical evidence does not support stopping angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with COVID-19.

CONCLUSIONS AND RELEVANCE The COVID-19 pandemic represents the greatest global public health crisis of this generation and, potentially, since the pandemic influenza outbreak of 1918. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of a pandemic. No therapies have been shown effective to date.

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Viewpoint

Related article

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The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019, and has since spread worldwide.[1] As of April 5, 2020, there have been more than 1.2 million reported cases and 69 000 deaths in more than 200 countries. This novel *Betacoronavirus* is similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV); based on its genetic proximity, it likely originated from bat-derived coronaviruses with spread via an unknown intermediate mammal host to humans.[1] The viral genome of SARS-CoV-2 was rapidly sequenced to enable diagnostic testing, epidemiologic tracking, and development of preventive and therapeutic strategies.

Currently, there is no evidence from randomized clinical trials (RCTs) that any potential therapy improves outcomes in patients with either suspected or confirmed COVID-19. There are no clinical trial data supporting any prophylactic therapy. More than 300 active clinical treatment trials are underway. This narrative review summarizes current evidence regarding major proposed treatments, repurposed or experimental, for COVID-19 and provides a summary of current clinical experience and treatment guidance for this novel epidemic coronavirus.

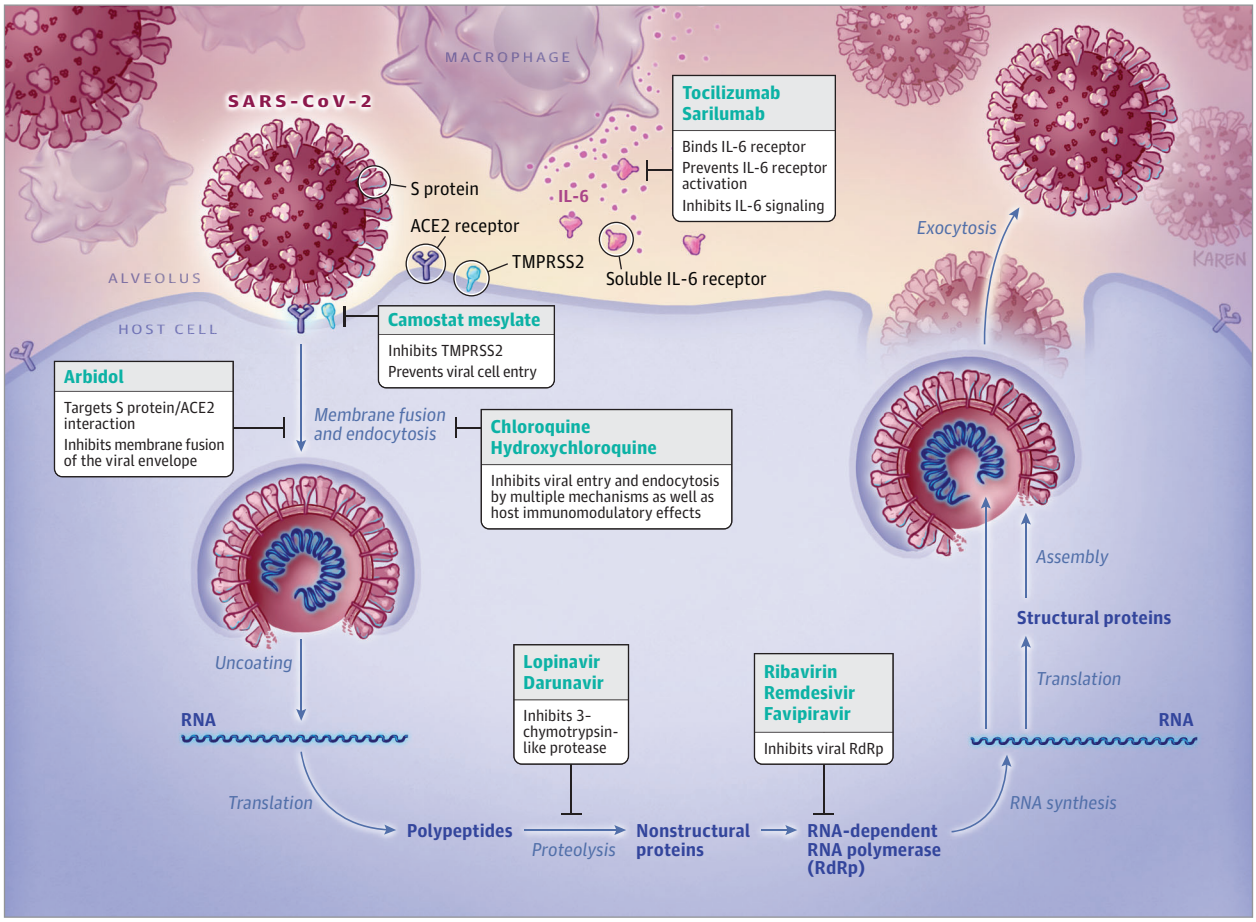
Methods

A literature review was performed using PubMed to identify relevant English-language articles published through March 25, 2020. Search terms included *coronavirus*, *severe acute respiratory syndrome coronavirus 2*, *2019-nCoV*, *SARS-CoV-2*, *SARS-CoV*, *MERS-CoV*, and *COVID-19* in combination with *treatment* and *pharmacology*. The search resulted in 1315 total articles. Due to the lack of RCTs, the authors also included case reports, case series, and review articles. The authors independently reviewed the titles and abstracts for inclusion. Additional relevant articles were identified from the review of citations referenced. Active clinical trials were identified using the disease search term *coronavirus infection* on ClinicalTrials.gov and the index of studies of novel coronavirus pneumonia in the Chinese Clinical Trial Registry.[2]

SARS-CoV-2: Virology and Drug Targets

SARS-CoV-2, a single-stranded RNA-enveloped virus, targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. Following

Figure. Simplified Representation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Viral Lifecycle and Potential Drug Targets



Schematic represents virus-induced host immune system response and viral processing within target cells. Proposed targets of select repurposed and investigational products are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease.

receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 transmembrane serine protease, TMPRSS2, facilitates cell entry via the S protein.[3] Once inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to completion of assembly and release of viral particles.[4-6] These viral lifecycle steps provide potential targets for drug therapy (**Figure**). Promising drug targets include nonstructural proteins (eg, 3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase), which share homology with other novel coronaviruses (nCoVs). Additional drug targets include viral entry and immune regulation pathways.[7,8] **Table 1** summarizes the mechanism of action and major pharmacologic parameters of select proposed treatments or adjunctive therapies for COVID-19.

Ongoing Clinical Trials

The search terms *COVID OR coronavirus OR SARS-COV-2* on ClinicalTrials.gov resulted in 351 active trials, with 291 trials specific to COVID-19 as of April 2, 2020. Of these 291 trials, approximately 109 trials (including those not yet recruiting, recruiting, active, or completed) included pharmacological therapy for the treatment of COVID-19 in adult patients. Of these 109 trials, 82 are interventional studies, with 29 placebo-controlled trials. Per description of the studies, there are 11 phase 4, 36 phase 3, 36 phase 2, and 4 phase 1 trials. Twenty-two trials were not categorized by phase or not applicable.

Review of Selected Repurposed Drugs

Agents previously used to treat SARS and MERS are potential candidates to treat COVID-19. Various agents with apparent in vitro activity against SARS-CoV and MERS-CoV were used during the SARS and MERS outbreaks, with inconsistent efficacy. Meta-analyses of SARS and MERS treatment studies found no clear benefit of any specific regimen.[37,38] Below, the in vitro activity and published clinical experiences of some of the most promising repurposed drugs for COVID-19 are reviewed.

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine have a long-standing history in the prevention and treatment of malaria and the treatment of

Table 1. Summary of Pharmacology for Select Proposed COVID-19 Treatments

Agent	Target	Adult dose/administration	Contraindications	Toxicities	Major drug-drug interactions	Special populations
Repurposed agents						
Chloroquine phosphate (Aralen/generic)[9-14]	Blockade of viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional immunomodulatory effects through inhibition of cytokine production, autophagy, and lysosomal activity in host cells	500 mg by mouth every 12-24 h × 5-10 d. Available as: 250-mg tablets (salt); 500-mg tablets (salt); 500-mg tablets of chloroquine phosphate (salt) = 300-mg chloroquine base. Dose adjustments: Kidney: creatinine clearance <10 mL/min administer 50% of dose. Hepatic: No dose adjustments in hepatic impairment recommended; use with caution. Administration: Preferable to avoid crushing. If needed, may be crushed and mixed with jam, pasteurized yogurt or similar foods	Hypersensitivity to chloroquine, 4-aminoquinoline compounds, or any component of formulation. Presence of retinal or visual field changes of any etiology (unless benefit outweighs risk)	Common: Abdominal cramps, anorexia, diarrhea, nausea, vomiting. Major: Cardiovascular effects (including QTc prolongation), hematologic effects (including hemolysis with G6PD deficiency, use if benefit outweighs risks), hypoglycemia, retinal toxicity, neuropsychiatric and central nervous system effects, idiosyncratic adverse drug reactions	CYP2D6 and CYP3A4 substrate	May be used in pregnancy if benefit outweighs risks
Hydroxychloroquine sulfate (Plaquenil/ generic)[9-11,15-20]	Hydroxychloroquine shares the same mechanism of action as chloroquine	400 mg by mouth every 12 h × 1 d, then 200 mg by mouth every 12 h × 4 d; alternative dosing: 400 mg by mouth daily × 5 d or 200 mg by mouth 3 times/d for 10 d. Available as: 200-mg tablets of hydroxychloroquine sulfate (salt) = 155 mg hydroxychloroquine base. Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution. Administration: Manufacturer does not recommend crushing tablets; however, some sources suggest that tablets can be crushed and dispersed with water OR compounded into an oral solution	Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivative, or any component of the formulation	Adverse drug reactions similar to chloroquine but less common	CYP2D6, CYP3A4, CYP3A5, and CYP2C8 substrate	May be used in pregnancy if benefit outweighs risks
Lopinavir/ritonavir (Kaletra)[21-26]	3CL protease	400 mg/100 mg by mouth every 12 h for up to 14 d. Available as: lopinavir/ritonavir, 200-mg/50-mg tablets; lopinavir/ritonavir, 100-/50-mg tablets; lopinavir/ritonavir 400-mg/100-mg per 5-mL oral solution (can be given via feeding tubes compatible with ethanol and propylene glycol, contains 42% alcohol). Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution in hepatic impairment. Administration: Food restrictions: Tablets, take without regard to meals; oral solution, take with food. Do not crush tablets; oral solution not recommended with polyurethane feeding tubes	Hypersensitivity to lopinavir/ritonavir or any of its ingredients, including ritonavir. Co-administration with drugs highly dependent on CYP4503A. Co-administration with potent CYP450 3A inducers	Common: gastrointestinal intolerance, nausea, vomiting, diarrhea. Major: Pancreatitis, hepatotoxicity, cardiac conduction abnormalities	CYP3A4 inhibitor and substrate; CYP2D6 substrate; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 inducer. P-gp substrate; UGT1A1 inducer	May be used in pregnancy; avoid oral solution if possible due to ethanol content
Umifenovir (Arbidol)[27-29]	S protein/ACE2, membrane fusion inhibitor	200 mg every 8 h by mouth 7-14 d. Available as (not in the US): 50-mg and 100-mg tablets, capsules and granules. Dose adjustments: Kidney: no dose adjustment necessary. Hepatic: No specific recommendations available, caution in those with hepatic impairment. Administration: Bioavailability 40%	Known hypersensitivity to umifenovir	Allergic reaction, gastrointestinal upset, elevated transaminases	Metabolized by CYP3A4, monitor with strong inducers/inhibitors	Contraindicated in children <2 y of age (increased sensitivity)
Investigational agents						
Remdesivir[30-32]	RNA polymerase inhibitor	200 mg × 1, 100 mg every 24 h IV infusion. Available as: 5-mg/mL vial (reconstituted). Dose adjustments: Kidney: Not recommended for GFR <30. No kidney/hepatic dose adjustment currently recommended but holding doses may be considered if significant toxicities occur. Administration: 30-min IV infusion	Exclusion criteria based on specific protocols	Elevated transaminases (reversible), kidney injury	Not a significant inducer/inhibitor of CYP enzymes, monitor with strong inducers/inhibitors	Safety in pregnancy unknown, currently recommended to avoid

(continued)

Table 1. Summary of Pharmacology for Select Proposed COVID-19 Treatments (continued)

Agent	Target	Adult dose/administration	Contraindications	Toxicities	Major drug-drug interactions	Special populations
Favipiravir[33,34]	RNA polymerase inhibitor	Doses vary based on indication, limited data available. Available as (not in the US): 200-mg tablet. Dose adjustments: Kidney: no dose adjustment recommended, limited data available, Hepatic: Dose adjustment considered in Child-Pugh C, increased exposures observed in Child-Pugh class A to C. Administration: Tablet can be crushed or mixed with liquid, bioavailability >95%	Exclusion criteria based on specific protocols	Hyperuricemia, diarrhea, elevated transaminases, reduction in neutrophil count	CYP2C8 and aldehyde oxidase inhibitor, metabolized by aldehyde oxidase and xanthine oxidase	Contraindicated during pregnancy, metabolite found in breast milk
Adjunctive therapies						
Tocilizumab (Actemra)[35,36]	IL-6 inhibition- reduction in cytokine storm	400 mg IV or 8 mg/kg × 1-2 doses. Second dose 8-12 h after first dose if inadequate response. Available as: IV infusion injection: 80 mg/4 mL (20 mg/mL); 200 mg/10 mL (20 mg/mL); 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to IV infusion. Dose adjustments: Kidney: No dose adjustments recommended in mild or moderate kidney impairment. Not studied in patients with severe impairment. Hepatic: No dose adjustments recommended (not studied); initiate based on benefit. Administration: Infuse over 60 min, should not be infused concomitantly in the same IV line with other drugs	Known hypersensitivity to tocilizumab or any components of the formulation. Caution in patients with neutropenia (<500 cells/μL) or thrombocytopenia (<50 000/μL)	Common: Increase in upper respiratory tract infections (including tuberculosis), nasopharyngitis, headache, hypertension, increased AST, infusion related reactions. Major: Hematologic effects, infections, hepatotoxicity, gastrointestinal perforations, hypersensitivity reactions	In vitro data suggested that IL-6 reduces mRNA expression for several CYP450 isoenzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. May decrease levels of substrates	Safety in pregnancy unknown; may cause harm to the fetus

Abbreviations: ACE2, angiotensin-converting enzyme 2; AST, aspartate aminotransferase; 3CL, 3-chymotrypsin-like; COVID-19, coronavirus disease 2019; CYP, cytochrome P450; G6PD, glucose-6-phosphate-dehydrogenase; GFR, glomerular filtration rate; IV, intravenous; P-gp, P-glycoprotein; UGT1A1, UDP glucuronosyltransferase family 1 member A1.

chronic inflammatory diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[7] Chloroquine and hydroxychloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells.[9,10] Chloroquine inhibits SARS-CoV-2 in vitro with a half-maximal effective concentration (EC_{50}) in the low micromolar range. Hydroxychloroquine has in vitro activity with a lower EC_{50} for SARS-CoV-2 compared with chloroquine after 24 hours of growth (hydroxychloroquine: EC_{50} = 6.14 μM and chloroquine: EC_{50} = 23.90 μM).[15]

No high-quality evidence exists for the efficacy of chloroquine/hydroxychloroquine treatment of SARS or MERS. A news briefing from China reported chloroquine was successfully used to treat a series of more than 100 COVID-19 cases resulting in improved radiologic findings, enhanced viral clearance, and reduced disease progression.[39] However, the clinical trial design and outcomes data have not yet been presented or published for peer review, preventing validation of these claims. A recent open-label nonrandomized French study of 36 patients (20 in the hydroxychloroquine group and 16 in the control group) reported improved virologic clearance with hydroxychloroquine, 200 mg, by mouth every 8 hours compared with control patients receiving standard supportive care. Virologic clearance at day 6, measured by nasopharyngeal swabs, was 70% (14/20) vs 12.5% (2/16) for the hydroxychloroquine and control groups, respectively (P = .001). The authors also reported that addition of azithromycin to hydroxychloroquine in 6 patients resulted in numerically superior viral clearance (6/6, 100%) compared with hydroxychloroquine monotherapy (8/14, 57%).[16]

Despite these promising results, this study had several major limitations: a small sample size (only 20 in the intervention arm and only 6 receiving hydroxychloroquine and azithromycin); the removal of 6 patients in the hydroxychloroquine group from analysis due to early cessation of treatment resulting from critical illness or intolerance of the medications; variable baseline viral loads between hydroxychloroquine monotherapy and combination therapy groups; and no clinical or safety outcomes reported. These limitations coupled with concerns of additive cardiotoxicity with combination therapy do not support adoption of this regimen without additional studies. Another prospective study of 30 patients in China randomized patients to hydroxychloroquine, 400 mg, daily for 5 days plus standard of care (supportive care, interferon, and other antivirals) or standard care alone in a 1:1 fashion; there was no difference in virologic outcomes. At day 7, virologic clearance was similar, with 86.7% vs 93.3% clearance for the hydroxychloroquine plus standard of care group and standard care group, respectively (P > .05).[17] Currently, there are several RCTs of both chloroquine and hydroxychloroquine examining their role in COVID-19 treatment. Studies of chloroquine prophylaxis in health care workers (NCT04303507) and hydroxychloroquine for postexposure prophylaxis after high-risk exposures (NCT04308668) are planned or enrolling.[40]

Dosing of chloroquine to treat COVID-19 has consisted of 500 mg orally once or twice daily.[11,12] However, a paucity of data exists regarding the optimal dose to ensure the safety and efficacy of chloroquine. Hydroxychloroquine dosing recommendations for SLE

generally are 400 mg orally daily.[18] However, a physiologically based pharmacokinetic modeling study recommended that the optimal dosing regimen for hydroxychloroquine in COVID-19 treatment is a loading dose of 400 mg twice daily for 1 day followed by 200 mg twice daily.[15] In contrast, alternative recommendations are made for 600 mg total daily dose based on safety and clinical experience for Whipple disease.[11] Further studies are needed to delineate the optimal dose for COVID-19.

Chloroquine and hydroxychloroquine are relatively well tolerated as demonstrated by extensive experience in patients with SLE and malaria. However, both agents can cause rare and serious adverse effects (<10%), including QTc prolongation, hypoglycemia, neuropsychiatric effects, and retinopathy.[41,42] Baseline electrocardiography to evaluate for prolonged QTc is advisable prior to and following initiation of these medications because of the potential for arrhythmias, especially in critically ill patients and those taking concomitant QT-interval prolonging medications such as azithromycin and fluoroquinolones.[13] No significant adverse effects have been reported for chloroquine at the doses and durations proposed for COVID-19.[39] Use of chloroquine and hydroxychloroquine in pregnancy is generally considered safe.[13,18] A review of 12 studies including 588 patients receiving chloroquine or hydroxychloroquine during pregnancy found no overt infant ocular toxicity.[43]

Lopinavir/Ritonavir and Other Antiretrovirals

Lopinavir/ritonavir, a US Food and Drug Administration (FDA)–approved oral combination agent for treating HIV, demonstrated in vitro activity against other novel coronaviruses via inhibition of 3-chymotrypsin-like protease.[21,22] No published SARS-CoV-2 in vitro data exist for lopinavir/ritonavir.[44] A systematic review of lopinavir/ritonavir for the treatment of SARS and MERS found limited available studies, with most of these investigating SARS. Clinical studies in SARS were associated with reduced mortality and intubation rates, but their retrospective, observational nature prevents definitive conclusions. The timing of administration during the early peak viral replication phase (initial 7-10 days) appears to be important because delayed therapy initiation with lopinavir/ritonavir had no effect on clinical outcomes.[45,46]

Early reports of lopinavir/ritonavir for the treatment of COVID-19 are mostly case reports and small retrospective, nonrandomized cohort studies, making it difficult to ascertain the direct treatment effect of lopinavir/ritonavir.[45,46] More recently, Cao and colleagues[23] reported the results of an open-label RCT comparing the efficacy of lopinavir/ritonavir vs standard care in 199 patients with COVID-19. Importantly, the median time from symptom onset to randomization was 13 days (interquartile range [IQR], 11-16), with no between-group difference. The primary outcome of time to clinical improvement defined by a 2-point improvement on a 7-category ordinal scale or hospital discharge was similar in both groups (16 days [IQR, 13-17] vs 16 days [IQR, 15-17]; hazard ratio [HR], 1.31 [95% CI, 0.95-1.85]; $P = .09$). Additionally, no significant differences in viral clearance or 28-day mortality rates (19.2% vs 25.0%; absolute difference, −5.8% [95% CI, −17.3% to 5.7%]) were observed. Although delayed treatment initiation may partially explain the ineffectiveness of lopinavir/ritonavir for treating COVID-19, a subgroup analysis did not find shorter time to clinical improvement for patients who received therapy within 12 days (HR, 1.25 [95% CI, 0.77-2.05]).[23] Although additional RCTs of lopinavir/ritonavir are ongoing, the current data suggest a limited role for lopinavir/ritonavir in COVID-19 treatment.

The most commonly used and studied lopinavir/ritonavir dosing regimen for COVID-19 treatment is 400 mg/100 mg twice daily for up to 14 days.[12,23] Given the significant drug-drug interactions and potential adverse drug reactions (summarized in Table 1), careful review of concomitant medications and monitoring are required if this drug is used. Adverse effects of lopinavir/ritonavir include gastrointestinal distress such as nausea and diarrhea (up to 28%) and hepatotoxicity (2%-10%).[24] In patients with COVID-19, these adverse effects may be exacerbated by combination therapy or viral infection because approximately 20% to 30% of patients have elevated transaminases at presentation with COVID-19.[47] A recent RCT showed approximately 50% of lopinavir/ritonavir patients experienced an adverse effect and 14% of patients discontinued therapy due to gastrointestinal adverse effects.[23] Drug-induced transaminitis is of particular concern because it may exacerbate liver injury resulting from COVID-19. Importantly, alanine transaminase elevations are an exclusion criterion in several COVID-19 investigational trials, meaning that lopinavir/ritonavir-induced hepatotoxicity could limit patients' ability to access these other drugs.[40]

Other antiretrovirals, including protease inhibitors and integrase strand transfer inhibitors, were identified by enzyme activity screening as having SARS-CoV-2 activity.[44] In vitro cell models demonstrated activity of darunavir against SARS-CoV-2. There is no human clinical data in COVID-19 with these drugs, but an RCT of darunavir/cobicistat in China is underway.[40]

Ribavirin

Ribavirin, a guanine analogue, inhibits viral RNA-dependent RNA polymerase. Its activity against other nCoVs makes it a candidate for COVID-19 treatment. However, its in vitro activity against SARS-CoV was limited and required high concentrations to inhibit viral replication, necessitating high-dose (eg, 1.2 g to 2.4 g orally every 8 hours) and combination therapy. Patients received either intravenous or enteral administration in previous studies.[37] No evidence exists for inhaled ribavirin for nCoV treatment, and data with respiratory syncytial virus suggest inhaled administration offers no benefit over enteral or intravenous administration.[48]

A systematic review of the clinical experience with ribavirin for the treatment of SARS revealed inconclusive results in 26 of the 30 studies reviewed, with 4 studies demonstrating possible harm due to adverse effects including hematologic and liver toxicity.[37] In the treatment of MERS, ribavirin, generally in combination with interferons, demonstrated no discernible effect on clinical outcomes or viral clearance.[38,49] A paucity of clinical data with ribavirin for SARS-CoV-2 means its therapeutic role must be extrapolated from other nCoV data.

Ribavirin causes severe dose-dependent hematologic toxicity. The high doses used in the SARS trials resulted in hemolytic anemia in more than 60% of patients.[37] Similar safety concerns were seen in the largest MERS observational trial, with approximately 40% of patients taking ribavirin plus interferon requiring blood transfusions.[49] Seventy-five percent of patients taking ribavirin for SARS experienced transaminase elevations.[37] Ribavirin is also a known teratogen and contraindicated in pregnancy.[50]

The inconclusive efficacy data with ribavirin for other nCoVs and its substantial toxicity suggest that it has limited value for treatment of COVID-19. If used, combination therapy likely provides the best chance for clinical efficacy.

Other Antivirals

Oseltamivir, a neuraminidase inhibitor approved for the treatment of influenza, has no documented in vitro activity against SARS-CoV-2. The COVID-19 outbreak in China initially occurred during peak influenza season so a large proportion of patients received empirical oseltamivir therapy until the discovery of SARS-CoV-2 as the cause of COVID-19.[51] Several of the current clinical trials include oseltamivir in the comparison group but not as a proposed therapeutic intervention.[40] This agent has no role in the management of COVID-19 once influenza has been excluded.

Umifenovir (also known as Arbidol) is a more promising repurposed antiviral agent with a unique mechanism of action targeting the S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope.[27] The agent is currently approved in Russia and China for the treatment and prophylaxis of influenza and is of increasing interest for treating COVID-19 based on in vitro data suggesting activity against SARS.[28] The current dose of 200 mg orally every 8 hours for influenza is being studied for COVID-19 treatment (NCT04260594). Limited clinical experience with umifenovir for COVID-19 has been described in China. A nonrandomized study of 67 patients with COVID-19 showed that treatment with umifenovir for a median duration of 9 days was associated with lower mortality rates (0% [0/36] vs 16% [5/31]) and higher discharge rates compared with patients who did not receive the agent.[29] This observational data cannot establish the efficacy of umifenovir for COVID-19, but ongoing RCTs in China are further evaluating this agent.

Miscellaneous Agents

Interferon-α and -β have been studied for nCoVs, with interferon-β demonstrating activity against MERS.[37,38] Most published studies reported results of therapy combined with ribavirin and/or lopinavir/ritonavir. Similar to other agents, delayed treatment may limit effectiveness of these agents. Given conflicting in vitro and animal data and the absence of clinical trials, the use of interferons to treat SARS-CoV-2 cannot currently be recommended.[52] Current Chinese guidelines list interferons as an alternative for combination therapy.[12] Several other immunomodulatory agents traditionally used for noninfectious indications demonstrate in vitro activity or possess mechanisms purported to inhibit SARS-CoV-2, including, but not limited to, baricitinib, imatinib, dasatinib, and cyclosporine.[53-57] However, no animal or human data exist to recommend their use for COVID-19, and it remains to be seen whether they confer protection for patients already taking them for other indications.

Nitazoxanide, traditionally an antihelminthic agent, has broad antiviral activity and a relatively favorable safety profile. Nitazoxanide has demonstrated in vitro antiviral activity against MERS and SARS-CoV-2.[58,59] Pending further evidence, the antiviral activity, immunomodulatory effects, and safety profile of nitazoxanide warrant its further study as a treatment option for SARS-CoV-2.

Camostat mesylate, an approved agent in Japan for the treatment of pancreatitis, prevents nCoV cell entry in vitro through inhibition of the host serine protease, TMPRSS2.[3] This novel mechanism provides an additional drug target for future research.

SARS-CoV-2 uses the ACE2 receptor for entry into the host cell.[3] This discovery has stimulated discussions about whether ACE inhibitors and/or angiotensin receptor blockers may potentially treat COVID-19 or, conversely, worsen disease.[60] These drugs upregulate ACE2 receptors, which could theoretically lead to worse outcomes if viral entry is enhanced. In contrast, angiotensin receptor blockers could theoretically provide clinical benefit via blockade of ACE2 receptors. Conflicting in vitro data exist to determine if these agents have a detrimental or protective effect in patients with COVID-19. Pending further research, clinical societies and practice guidelines are recommending continuing therapy for patients already taking 1 of these agents.[61,62]

Review of Select Investigational Drugs

Remdesivir

Remdesivir, formally known as GS-5734, is a monophosphate prodrug that undergoes metabolism to an active C-adenosine nucleoside triphosphate analogue. The agent was discovered amidst a screening process for antimicrobials with activity against RNA viruses, such as Coronaviridae and Flaviviridae. Research and development of the agent showed promise during the height of the Ebola virus outbreak due to its low EC_{50} and host polymerase selectivity against the Ebola virus.[30] Currently, remdesivir is a promising potential therapy for COVID-19 due to its broad-spectrum, potent in vitro activity against several nCoVs, including SARS-CoV-2 with EC_{50} and EC_{90} values of 0.77 μM and 1.76 μM, respectively.[31,58] In murine lung infection models with MERS-CoV, remdesivir prevented lung hemorrhage and reduced viral lung titers more than comparator agents.[32]

The safety and pharmacokinetics of remdesivir were evaluated in single- and multiple-dose phase 1 clinical trials.[63] Intravenous infusions between 3 mg and 225 mg were well-tolerated without any evidence of liver or kidney toxicity. Remdesivir demonstrated linear pharmacokinetics within this dose range and an intracellular half-life of greater than 35 hours. Following multiple-dose administrations, reversible aspartate aminotransferase and alanine transaminase elevations occurred. The current dose under investigation is a single 200-mg loading dose, followed by 100-mg daily infusion. No hepatic or kidney adjustments are recommended at this time, but initiation is not recommended in patients with an estimated glomerular filtration rate less than 30 mL/min.

The first clinical use of remdesivir was for the treatment of Ebola[64]; however, successful case reports describing the use of remdesivir for COVID-19 have been reported.[65,66] Clinical trials are ongoing to evaluate the safety and antiviral activity of remdesivir in patients with mild to moderate or severe COVID-19 (NCT04292899, NCT04292730, NCT04257656, NCT04252664, NCT04280705). Of particular importance, the National Institutes of Health is sponsoring an adaptive, randomized, double-blind, placebo-controlled trial that will shed light on the effectiveness of remdesivir compared with supportive care (NCT04280705).[40] As the results from RCTs are anticipated, inclusion of this agent for treatment of COVID-19 may be considered. Notably, remdesivir is not currently FDA-approved and must be obtained via compassionate use (only for children <18 years and pregnant women), expanded access, or enrollment in a clinical trial.

Favipiravir

Favipiravir, previously known as T-705, is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate. The active agent inhibits the RNA polymerase, halting viral replication. Most of favipiravir's preclinical data are derived from its influenza and Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses.[67] In vitro, the EC_{50} of favipiravir against SARS-CoV-2 was 61.88 μM/L in Vero E6 cells.[58]

Various dosing regimens have been proposed based on the type of infectious indication. Dosing variations are likely due to the lower favipiravir EC_{50} values described against influenza compared with Ebola and SARS-CoV-2.[68,69] Doses at the higher end of the dosing range should be considered for the treatment of COVID-19.[69] A loading dose is recommended (2400 mg to 3000 mg every 12 hours × 2 doses) followed by a maintenance dose (1200 mg to 1800 mg every 12 hours). The half-life is approximately 5 hours.[70] The agent has a mild adverse effect profile and is overall well-tolerated, although the adverse event profile for higher-dose regimens is limited.[44,69,71,72] Favipiravir is currently available in Japan for the treatment of influenza, but not available in the United States for clinical use.

Limited clinical experience has been reported supporting the use of favipiravir for COVID-19. In a prospective, randomized, multicenter study, favipiravir (n = 120) was compared with Arbidol (n = 120) for the treatment of moderate and severe COVID-19 infections. Differences in clinical recovery at day 7 were observed in patients with moderate infections (71.4% favipiravir and 55.9% Arbidol, $P = .019$). No significant differences were observed in the severe or severe and moderate (combined) arms.[73] These data support further investigation with RCTs of the efficacy of favipiravir for the treatment of COVID-19.

This review of proposed drugs is by necessity selective. A recent comprehensive review conducted by a division of the American Chemical Society analyzed scientific data related to therapeutic agents and vaccines in human coronaviruses since 2003, using both published literature and patents worldwide.[74] This analysis reported more than 130 patents and more than 3000 potential small molecule drug candidates with potential activity against human coronaviruses. The same analysis identified more than 500 patents for biologic agents with activity against coronaviruses including therapeutic antibodies, cytokines, RNA therapies, and vaccines. Another preprint analysis of SARS-CoV-2–human protein-protein interaction maps identified 332 high-confidence protein-protein interactions, yielding 66 candidate druggable human proteins or host factors targeted by either existing FDA-approved or investigational drugs.[75] This large amount of potential agents will hopefully yield more candidate therapeutics in the race to find effective treatments or preventive strategies against COVID-19.

Adjunctive Therapies

At present in the absence of proven therapy for SARS-CoV-2, the cornerstone of care for patients with COVID-19 remains supportive care, ranging from symptomatic outpatient management to full intensive care support. However, 3 adjunctive therapies that warrant special mention are corticosteroids, anticytokine or immunomodulatory agents, and immunoglobulin therapy.

Corticosteroids

The rationale for the use of corticosteroids is to decrease the host inflammatory responses in the lungs, which may lead to acute lung injury and acute respiratory distress syndrome (ARDS). However, this benefit may be outweighed by adverse effects, including delayed viral clearance and increased risk of secondary infection. Although direct evidence for corticosteroids in COVID-19 is limited, reviews of outcomes in other viral pneumonias are instructive.[76] Observational studies in patients with SARS and MERS reported no associations of corticosteroids with improved survival, but demonstrated an association with delayed viral clearance from the respiratory tract and blood and high rates of complications including hyperglycemia, psychosis, and avascular necrosis.[37,77] Additionally, a 2019 meta-analysis of 10 observational studies with 6548 patients with influenza pneumonia found that corticosteroids were associated with an increased risk of mortality (risk ratio [RR], 1.75 [95% CI, 1.3-2.4]; $P < .001$) and a 2-fold higher risk of secondary infections (RR, 1.98 [95% CI, 1.0-3.8]; $P = .04$).[78] While the efficacy of corticosteroids in ARDS and septic shock more generally remains debated, Russell and colleagues[76] argued that those most likely to benefit from corticosteroids are those with bacterial rather than viral infections. A recent retrospective study of 201 patients with COVID-19 in China found that, for those who developed ARDS, treatment with methylprednisolone was associated with a decreased risk of death (23/50 [46%] with steroids vs 21/34 [62%] without; HR, 0.38 [95% CI, 0.20-0.72]).[47] However, the authors noted that bias and residual confounding between those who did or did not receive steroids may exist in this observational study. Therefore, the potential harms and lack of proven benefit for corticosteroids cautions against their routine use in patients with COVID-19 outside an RCT unless a concomitant compelling indication, such as chronic obstructive pulmonary disease exacerbation or refractory shock exists.

Anticytokine or Immunomodulatory Agents

Monoclonal antibodies directed against key inflammatory cytokines or other aspects of the innate immune response represent another potential class of adjunctive therapies for COVID-19. The rationale for their use is that the underlying pathophysiology of significant organ damage in the lungs and other organs is caused by an amplified immune response and cytokine release, or "cytokine storm."[79] IL-6 appears to be a key driver of this dysregulated inflammation based on early case series from China.[80] Thus, monoclonal antibodies against IL-6 could theoretically dampen this process and improve clinical outcomes. Tocilizumab, a monoclonal antibody IL-6 receptor antagonist, is FDA approved to treat RA and cytokine release syndrome following chimeric antigen receptor T-cell therapy. Given this experience, tocilizumab has been used in small series of severe COVID-19 cases with early reports of success. A report of 21 patients with COVID-19 showed receipt of tocilizumab, 400 mg, was associated with clinical improvement in 91% of patients as measured by improved respiratory function, rapid defervescence, and successful discharge, with most patients only receiving 1 dose.[35] The lack of a comparator group limits the interpretation of the drug-specific effect and warrants caution until more rigorous data are available. Several RCTs of tocilizumab, alone or in combination, in patients with COVID-19 with severe pneumonia are underway in China (NCT04310228, ChiCTR2000029765), and it is included in the current Chinese national treatment guidelines.[12]

Table 2. Summary of Treatment and Clinical Outcomes From Early COVID-19 Clinical Series

Source	Huang et al, 2020[91]	Chen et al, 2020[92]	Wang et al, 2020[51]	Yang et al, 2020[93]	Young et al, 2020[94]	Kujawski et al, 2020[66]	Guan et al, 2020[95]
Study setting and region	Wuhan Jinyintan Hospital, China (12/16/19-1/2/20)	Wuhan Jinyintan Hospital, China (1/1/20-1/20/20)	Zhongnan Hospital, Wuhan, China (1/1/20-1/28/20)	Wuhan Jinyintan Hospital, China (12/24/19-1/26/20)	4 Singapore hospitals (1/23/20-2/3/20)	US-confirmed cases (1/20/20-2/5/20)	National Chinese cases (12/19/19-1/29/20)
No. of patients	41 Hospitalized	99 Hospitalized	138 Hospitalized	52 (All ICU)	18 Hospitalized	12 (Only 7 hospitalized)	1096 Hospitalized
Age, median (IQR), y	49 (41-58)	Mean (SD), 55.5 (13.1)	56 (42-68)	Mean (SD), 59.7 (13.3)	47 (31-73)	53 (21-68)	47 (35-58)
Sex, No. (%)							
Male	30 (73)	67 (68)	75 (54)	35 (67)	9 (50)	8 (67)	637 (58)
Female	11 (27)	32 (32)	63 (46)	17 (33)	9 (50)	4 (33)	459 (42)
ICU status/ complications, No. (%)	ICU: 13 (32); ARDS: 12 (29); MI: 5 (12); AKI: 3 (7); shock: 3 (7); secondary infection: 4 (10)	ICU: 23 (23); ARDS: 17 (17); AKI: 3 (3); shock: 4 (4); VAP: 1 (1)	ICU: 36 (26); ARDS: 27 (20); MI: 10 (7.2); arrhythmia: 23 (17); AKI: 5 (3.6); shock: 12 (8.7)	ICU: 52 (100); ARDS: 35 (67); MI: 12 (23); AKI: 15 (29); bacterial infection: 8 (15)	ICU: 2 (11); ARDS: 0 (0); secondary bacterial infection: (0)	ICU: 1 (8); culture-positive secondary bacterial infection: 0 (0)	ICU: 55 (5); ARDS: 37 (3.4); AKI: 6 (0.5); shock: 12 (1.1)
Treatments, No. (%)							
Supportive care	NIV/HFNC: 10 (24); MV: 2 (5); ECMO: 2 (5); KRT: 3 (7)	NIV: 13 (13); MV: 4 (4); ECMO: 3 (3); KRT: 9 (9)	NIV: 15 (10.9); MV: 17 (12); ECMO: 4 (2.9); KRT: 2 (1.5)	NIV: 29 (56); MV: 22 (42); ECMO: 6 (12); KRT: 9 (17)	Supplemental oxygen: 6 (33); MV: 1(6)	Supplemental oxygen: 4 (33)	Oxygen: 454 (41); NIV: 56 (5); MV: 25 (2); ECMO: 5 (0.5); KRT: 9 (0.8)
Specific agents	Antivirals (oseltamivir): 38 (99); antibacterials: 41 (100); corticosteroids: 9 (22)	Antivirals (oseltamivir, ganciclovir, or lopinavir/ ritonavir): 75 (76); antibacterials: 70 (71); antifungals: 15 (15); corticosteroids: 19 (19); IVIG: 27 (27)	Antivirals (oseltamivir): 124 (90); antibacterials: moxifloxacin: 89 (64), ceftriaxone: 34 (23), azithromycin: 25 (18); corticosteroids: 62 (45)	Antivirals: 23 (44); antibacterials: 49 (94); corticosteroids: 30 (58); IVIG: 28 (54)	Antivirals (lopinavir/ ritonavir): 5 (42); other antivirals or antibacterials: NR	Antivirals (remdesivir): 3 (25); antibacterials: 5 (42); corticosteroids: 2 (17)	Antivirals (oseltamivir): 393 (36); antibacterials: 637 (58); antifungals: 31 (2.8); corticosteroids: 204 (19); IVIG: 144 (13)
Discharged alive, No. (%)	28 (68)	31 (31)	47 (34)	NR	8 (75)	100 (100)	55 (5)
Deaths, No. (%)	6 (15)	11 (11)	6 (4.3)	32 (62)	0	0	15 (1.4)

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; ICU, intensive care unit; IQR, interquartile range; IVIG, intravenous immunoglobulins; MI, myocardial infarction; MV, invasive mechanical ventilation; KRT, kidney replacement therapy; NIV, noninvasive ventilation; NR, not reported; VAP, ventilator-associated pneumonia.

Sarilumab, another IL-6 receptor antagonist approved for RA, is being studied in a multicenter, double-blind, phase 2/3 trial for hospitalized patients with severe COVID-19 (NCT04315298).[81] Other monoclonal antibody or immunomodulatory agents in clinical trials in China or available for expanded access in the US include bevacizumab (anti–vascular endothelial growth factor medication; NCT04275414), fingolimod (immunomodulator approved for multiple sclerosis; NCT04280588), and eculizumab (antibody inhibiting terminal complement; NCT04288713).[40]

Immunoglobulin Therapy

Another potential adjunctive therapy for COVID-19 is the use of convalescent plasma or hyperimmune immunoglobulins.[82] The rationale for this treatment is that antibodies from recovered patients may help with both free virus and infected cell immune clearance. Anecdotal reports or protocols for convalescent plasma have been reported as salvage therapy in SARS and MERS.[83,84] A 2009 prospective observational study in 93 critically ill patients with H1N1 influenza A, 20 of whom received convalescent plasma, demonstrated that receipt of convalescent plasma vs nonreceipt was associated with a reduction in mortality (20% vs 54.8%; $P = .01$).[85] As part of a 2015 systematic review, Mair-Jenkins and colleagues[86] conducted a post hoc meta-analysis of 8 observational studies including 714 patients with either SARS or severe influenza. Administration of convalescent plasma and hyperimmune immunoglobulin was associated with reduction in mortality (odds ratio, 0.25 [95% CI, 0.14-0.45]; $I^2 = 0\%$) with relatively few harms, although study quality was generally low and at risk of bias.[86] In theory, the benefits of this therapy would accrue primarily within the first 7 to 10 days of infection, when viremia is at its peak and the primary immune response has not yet occurred. Although current commercial immunoglobulin preparations likely lack protective antibodies to SARS-CoV-2, this modality warrants further safety and efficacy trials as the pool of patients who have recovered from COVID-19 increases globally. Indeed, the first reported uncontrolled case series of 5 critically ill patients with COVID-19 treated with convalescent plasma in China was recently published.[87] Additionally, a case series of 3 patients with COVID-19 in Wuhan, China, treated with intravenous immunoglobulin at a dose of 0.3 to 0.5 g/kg/d for 5 days was recently published.[88] On March 24, 2020, the FDA released

Box 1. Clinical Treatment Guidance and Other Useful Resources

International and Select National or Institutional Clinical Management Guidance

World Health Organization Clinical Management Guidance (interim guidance, updated March 13, 2020)
https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

US Centers for Disease Control and Prevention COVID-19 clinical care (interim guidance, updated March 7, 2020)
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

Chinese National Health Commission novel coronavirus pneumonia diagnosis and treatment plan (provisional 7th edition, updated March 3, 2020)
Chinese original: http://www.gov.cn/zhengce/zhengceku/2020-03/04/5486705/files/ae61004f930d47598711a0d4cbf874a9.pdf
English translation: https://www.chinalawtranslate.com/wp-content/uploads/2020/03/Who-translation.pdf

Italian Society of Infectious and Tropical Diseases handbook for care of people with COVID-19 (edition 2.0, updated March 13, 2020)
Italian original: http://www.simit.org/IT/simit/sezioni-regionali.xhtml/sezione/112-lombardia/comunicazioni/1
English translation: https://drive.google.com/file/d/1eXE6espkYp6_k2XCyTf_6kgT6tFbnQjg/view

University of Washington
https://covid-19.uwmedicine.org/Pages/default.aspx

JAMA Network COVID-19 site
https://jamanetwork.com/journals/jama/pages/coronavirus-alert

Clinical Trials Registries/Resources

Clinical trials (US)
https://clinicaltrials.gov/ct2/search

Clinical trials (China)
http://www.chictr.org.cn/searchprojen.aspx

National Institutes of Health COVID-19 page
https://www.nih.gov/health-information/coronavirus

Drug-Drug Interaction Websites

University of Liverpool
https://www.covid19-druginteractions.org/

Micromedex (version 2.0)
https://www.micromedexsolutions.com/

Clinical Pharmacology
https://www.clinicalpharmacology.com

Facts and Comparisons 4.0/Lexicomp
https://fco.factsandcomparisons.com
https://online.lexi.com

Epocrates
https://epocrates.com

Medscape drug reference
https://reference.medscape.com

Guidance for Special Populations

Solid organ transplantation
https://www.myast.org/covid-19-information#

Surviving Sepsis Campaign: guideline on the management of critically ill adults with COVID-19
https://jamanetwork.com/journals/jama/fullarticle/2763879

Care of patients with cancer during COVID-19 pandemic
https://jnccn.org/fileasset/jnccn1804-Ueda_20118_preprint.pdf

Pregnancy
https://www.acog.org/topics/covid-19

Persons with HIV
https://aidsinfo.nih.gov/guidelines/html/8/covid-19-and-persons-with-hiv--interim-guidance-/0

guidance for requesting an emergency investigational new drug application and screening donors for COVID-19 convalescent plasma.[89] There are also early preprint reports describing preclinical development of a human monoclonal antibody against a common epitope to block SARS-COV-2 (and SARS-CoV) infection.[90]

The most effective long-term strategy for prevention of future outbreaks of this virus would be the development of a vaccine providing protective immunity. However, a minimum of 12 to 18 months would be required before widespread vaccine deployment. A comprehensive review of vaccine research for SARS-CoV-2 is beyond the scope of this review.

Current Clinical Treatment Experience and Recommendations

The published clinical treatment experience, outside the few clinical trials mentioned, mostly consists of descriptive reports and case series from China and other countries affected early in this pandemic. Therefore, outcomes including case-fatality rates must be interpreted with caution given the presence of confounding and selection bias as well as the shifting demographics, testing, and treatment approaches. **Table 2** summarizes the clinical severity, complications, treatments, and clinical outcomes from early reported COVID-19 case series.

The current Centers for Disease Control and Prevention guidance for clinical care of patients with COVID-19 (as of March 7, 2020) highlights that no specific treatment for COVID-19 is available, and emphasizes that management should include "prompt implementation of recommended infection prevention and control measures and supportive management of complications."[96] The guidance from the Centers for Disease Control and Prevention specifically mentions that corticosteroids should be avoided unless indicated for other reasons. Investigational therapeutics, specifically remdesivir, are mentioned as options through either compassionate use or ongoing clinical trials.

Similarly, the current World Health Organization (WHO) clinical management guidance document (as of March 13, 2020) states "there is no current evidence to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19."[97] The guidance emphasizes the role of supportive care based on severity of illness, ranging from symptomatic treatment for mild disease to evidence-based ventilatory management for ARDS and early recognition and treatment of bacterial infections and sepsis in critically ill patients. They recommend to "not routinely give systemic corticosteroids for treatment of viral pneumonia outside clinical trials" and state "investigational

Box 2. COVID-19 Clinical Management: Frequently Asked Questions

1. Have any medical therapies been definitively shown to improve outcomes in a patient with COVID-19?
At this time there are no medical therapies that have been definitively shown to improve outcomes in patients with COVID-19. A number of drugs have demonstrated in vitro activity against the SARS-CoV-2 virus or potential clinical benefits in observational or small, nonrandomized studies. Adequately powered randomized clinical trials are currently enrolling and needed to establish the efficacy of these proposed therapies.

2. Should hydroxychloroquine and/or azithromycin be prescribed for patients with severe symptoms from COVID-19?
The reported clinical benefits of the combination of hydroxychloroquine and azithromycin for patients with COVID-19 come either from media reports or nonrandomized trials with small numbers of participants (<100 patients). The documented benefit of hydroxychloroquine with or without azithromycin is very limited, especially in severe disease. While these medications, individually or in combination, may prove efficacious, these benefits need to be established with randomized clinical trials prior to widespread adoption of these treatments.

3. Should I stop ARBs/ACE inhibitors in my older patients and those at high risk for severe illness from COVID-19?
Major institutions and societies, including the Centers for Disease Control and Prevention, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology recommend continuation of ACE inhibitors or ARB medications for all patients already prescribed those medications for another indication. There is currently no human evidence establishing a link between the use of these medications with an increased risk of COVID-19 acquisition or illness severity.

4. What is the role of immunomodulatory drugs such as IL-6 receptor antagonists or corticosteroids in the management of patients with COVID-19?
Given the important role the immune response plays in the complications of COVID-19, active clinical trials are evaluating immunomodulatory drugs (such as IL-6 receptor antagonists) in this disease. In patients with "cytokine storm," characterized by marked elevation in inflammatory markers, use of IL-6 receptor antagonists can be considered, preferably in the context of a clinical trial, although these medications can increase risk of secondary infections. The role of corticosteroids remains controversial, and current guidelines from the World Health Organization do not recommend their use unless another concomitant indication exists such as chronic obstructive pulmonary disease exacerbation or pressor-refractory shock. However, their utility in patients with severe COVID-19 with acute respiratory distress syndrome should be further investigated in clinical trials.

5. Which medications have been repurposed to treat COVID-19?
Numerous agents demonstrate in vitro activity against novel coronaviruses, including SARS-CoV-2. Small molecule database screens identified thousands of potential agents. Of these, several repurposed agents used to treat a variety of other disease states (eg, HIV and autoimmune diseases) have been proposed as possible treatment options for COVID-19. Lopinavir/ritonavir and chloroquine or hydroxychloroquine are the medications with the most clinical evidence, either positive or negative, in the treatment of COVID-19. To date, available clinical trials have not demonstrated that any of these drugs are clearly effective.

6. Are there investigational drugs available to treat COVID-19?
Remdesivir is available to COVID-19–infected patients through enrollment in a clinical trial or application for emergency access. In the United States, there are 3 ongoing clinical trials differentiated by severity of disease (eg, moderate vs severe infection) and study design (eg, placebo-controlled). Emergency access is available through an expanded access program. Sites without access to a clinical trial may obtain the drug this way. Also, individual compassionate use for pregnant women and children younger than 18 years of age with confirmed COVID-19 and severe manifestations of the disease may obtain the drug in this manner. Favipiravir is not currently available in the United States.

7. How do I decide if a patient with COVID-19 needs a specific treatment or should receive only supportive care?
The priority should be to enroll a patient in a clinical trial if they qualify. If this is not possible, patients who are stable as an outpatient or have no evidence of oxygen requirement or pneumonia by imaging can generally be managed with supportive care alone. Patients who have evidence of hypoxia or pneumonia, especially those with risk factors for disease progression such as age older than 65 years, cardiac or pulmonary comorbidities, and immunosuppression, can be considered for specific COVID-19 therapy after discussing the risks and benefits with the patient and in accordance with local hospital treatment guidance.

8. What are the limitations of repurposing medications to treat COVID-19?
The use of repurposed medications relies on the assumption that the benefits (in vitro/clinical evidence) outweigh associated risks (adverse drug reactions). One limitation to using repurposed agents is the propensity of these agents to cause acute toxicity. This acute toxicity may outweigh the undefined benefit of a specific antiviral agent. Augmented toxicity with combination therapy, such as heart or liver toxicity, creates potential additional risk and need for close risk vs benefit analysis. Overall, the paucity of evidence demonstrating a clear benefit may not justify the risk of the repurposed agent(s). This is of upmost concern in patients at high risk for toxicity and in situations where adverse events may preclude entry into investigational trials.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials." In this regard, the WHO recently announced plans to launch a global "megatrial" called SOLIDARITY with a pragmatic trial design that will randomize confirmed cases into either standard care or 1 of 4 active treatment arms (remdesivir, chloroquine or hydroxychloroquine, lopinavir/ritonavir, or lopinavir/ritonavir plus interferon-β) based on local drug availability.[98]

Box 1 provides links to major US and international guidance documents for clinical treatment and other useful resources for drug-drug interactions and guidance in special populations. **Box 2** answers

frequently asked questions for clinicians about clinical management of patients with COVID-19.

Limitations

This review has several limitations to note. First, the tremendous volume and fast pace of published literature on the treatment of COVID-19 means that research findings and recommendations are constantly evolving as new evidence arises. Second, the published treatment data to date derive exclusively from observational data or small clinical trials (none with more than 250 patients), introducing higher risks of bias or imprecision regarding the magnitude of treatment effect size. Third, our review focused only on adult patients and the data may not be applicable to pediatric populations. Fourth, the articles were limited to English-language publications or translations so relevant international data could be lacking.

Conclusions

The COVID-19 pandemic represents the greatest global public health crisis of this generation and, potentially, since the pandemic influenza outbreak of 1918. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of a pandemic. No therapies have been shown effective to date.

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Brief communication

Clinical trials on drug repositioning for COVID-19 treatment

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ABSTRACT

The World Health Organization (WHO) was informed on December 2019 about a coronavirus pneumonia outbreak in Wuhan, Hubei province (China). Subsequently, on March 12, 2020, 125,048 cases and 4,614 deaths were reported. Coronavirus is an enveloped RNA virus, from the genus *Betacoronavirus*, that is distributed in birds, humans, and other mammals. WHO has named the novel coronavirus disease as COVID-19. More than 80 clinical trials have been launched to test coronavirus treatment, including some drug repurposing or repositioning for COVID-19. Hence, we performed a search in March 2020 of the clinicaltrials.gov database. The eligibility criteria for the retrieved studies were: contain a clinicaltrials.gov base identifier number; describe the number of participants and the period for the study; describe the participants' clinical conditions; and utilize interventions with medicines already studied or approved for any other disease in patients infected with the novel coronavirus SARS-CoV-2 (2019-nCoV). It is essential to emphasize that this article only captured trials listed in the clinicaltrials.gov database. We identified 24 clinical trials, involving more than 20 medicines, such as human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, favipiravir, lopinavir, ritonavir, oseltamivir, methylprednisolone, bevacizumab, and traditional Chinese medicines (TCM). Although drug repurposing has some limitations, repositioning clinical trials may represent an attractive strategy because they facilitate the discovery of new classes of medicines; they have lower costs and take less time to reach the market; and there are existing pharmaceutical supply chains for formulation and distribution.

Keywords Drug repositioning; clinical trials as topic; coronavirus infection; virus diseases; pneumonia, viral; pandemics.

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The World Health Organization (WHO) was informed on December 31, 2019, about a pneumonia outbreak in Wuhan, Hubei province (China), a city with 11 million inhabitants. By March 12, 2020, there were 125 048 cases and 4 614 deaths (nearly 3.7% of cases) reported for the novel coronavirus (1), named 2019-novel coronavirus (2019-nCoV), and later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). The WHO named this novel coronavirus disease as COVID-19 (1,2), and there have been confirmed cases in 117 countries or territories outside China, including Japan, the United States of America, Italy, Iran, and Brazil (1). Coronavirus is an enveloped RNA virus, from the genus *Betacoronavirus*, that is distributed in birds, humans, and other mammals (3,4). New evidence indicates a link between SARS-CoV-2 and bat coronavirus (3). Six species of coronavirus are known as infectious in humans, four of which (229E, OC43, NL63, and HKU1) cause common cold symptoms (4). However, some authors have claimed that SARS-CoV-2 is even related to the coronavirus species responsible for the severe acute respiratory syndrome (SARS-CoV) as well as Middle East Respiratory Syndrome (MERS-CoV), which have zoonotic origins linked to severe significant illness with higher mortality (3,4). For example, in July 2003, the WHO reported 8 437 SARS-CoV cases, especially in China and Hong Kong, with 813 related deaths (5). Concerning MERS-CoV, from June 2012 to April 2018, 2 206 people were infected in 27 countries, 1 831 cases in Saudi Arabia, with 787 deaths (6). Unfortunately, there are no vaccines or medicines approved for the novel coronavirus infection (7), but more than 80 clinical trials have been launched to test coronavirus treatments, including some drug repurposing or repositioning for COVID-19 (8). Drug repositioning for other neglected diseases is an essential and universal strategy in the development of new drugs due to: *a)* lower costs and reduced time to reach the market because some clinical trial steps might not be required, especially concerning phases I and II; *b)* existing pharmaceutical supply chains are available for formulation and distribution; *c)* the possibility of combinations with other drugs in treatments that are more effective than monotherapy; and *d)* may facilitate the discovery of new mechanisms of action for old drugs and new classes of medicines (9,10).

On the other hand, this repurposing strategy has some limitations, including patent barriers, the complexity of regulatory pathways, absence of funding opportunities, greater access to data from other industry-sponsored clinical trials, and the heterogeneity of the population for new clinical studies (10). Nevertheless, drug repurposing is still a tool for the discovery of entirely new classes of medicines (10,11). Hence, considering this scenario, we felt that it is of interest to be aware of the drug repositioning in clinical tests for the COVID-2019 treatment.

METHODS

We performed a search on March 12, 2020, at the clinicaltrials.gov database, with the descriptor [coronavirus] in the simple search field "conditions or disease" search, without restrictions on languages, disease conditions, results, or locations. The eligibility criteria for the retrieved studies were: contain a clinicaltrials.gov base identifier number; describe the number of participants and the study period; describe the patient's clinical conditions; and interventions utilize medicines already studied or approved for any other disease in patients with COVID-19. ClinicalTrials.gov is a resource from the US National Library of Medicine, and it contains clinical studies conducted by 209 countries.

RESULTS AND DISCUSSION

We identified 24 clinical trials (**Table 1**), in which 19 studies were at clinical phases 2, 3, or 4. The pharmaceutical interventions found for COVID-19 treatment include human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, oseltamivir, favipiravir, carrimycin, methylprednisolone, bevacizumab, thalidomide, vitamin C, pirfenidone, bromhexine, fingolimod, danoprevir, ritonavir, darunavir, cobicistat, lopinavir, xiyanping, and traditional Chinese medicines (TCM).

Chloroquine and **hydroxychloroquine** are antimalarial drugs. They have antiviral effects against human immunodeficiency virus (HIV), namely by inhibiting virus entry into host cells. Another antiviral mechanism is related to the post-translation alteration of newly synthesized proteins via glycosylation inhibition (12). Hydroxychloroquine is already being used in clinical trials on acquired immune deficiency syndrome (AIDS) treatment (13). In a recent trial with patients on COVID-19 treatment (14), 100% of patients treated with hydroxychloroquine in combination with the macrolide antibiotic **azithromycin** were virologically cured comparing with 57.1% in patients treated with hydroxychloroquine alone, and 12.5% in the control group. Currently, chloroquine and hydroxychloroquine will be tested (15,16) in patients with pneumonia caused by 2019-nCoV and chloroquine as preventative medicine for COVID-19, as shown in Table 1.

Immunoglobulins are useful in several diseases, such as idiopathic thrombocytopenia purpura (ITP), Guillain-Barre Syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), Kawasaki disease, and in multiple neurological autoimmune disorders refractory to standard immunosuppressive treatments (17). Broadly neutralizing antibodies can recognize a wide variety of glycoproteins (GPs) in virus surfaces or the protein shell of a non-enveloped virus. However, HIV-1, dengue virus (DENV), influenza viruses, hepatitis C

virus (HCV), and Ebola virus (EBOV) can mutate superficial GPs in order to evade the antibody response, an obstacle in the development of new therapies against such infections (18). Trial NCT04261426 (19) is utilizing human immunoglobulin in patients with pneumonia caused by 2019-nCoV (Table 1).

Two clinical studies refer to the use of **remdesivir** in severe (20) or mild (21) respiratory infections by SARS-CoV-2. Remdesivir is a nucleotide analog inhibitor of the EBOV RNA-polymerase RNA-dependent (RdRp). Dyer et al. 2019 (22) described preliminary findings of a mortality rate of 33% in 499 patients treated with remdesivir against the EBOV disease in early infection stages. The same authors noted a mortality rate of 75% (almost 1 900 people) of non-treated infected patients during the same epidemic period (22). Wang et al. 2020 (23) presented data showing that remdesivir is effective against the 2019-nCoV in Vero E6 cells (EC_{90} 1.76 µM). The suggested mechanism for remdesivir involves the host cells' post-entry stage (23).

Arbidol, also known as **umifenovir,** is approved in Russia and China for the treatment of influenza virus infections; it does not have significant adverse effects and is patented for SARS treatment (24). As shown in Table 1, four clinical trials will be conducted for COVID-19 treatment: one with arbidol in comparison with the basic treatment (25), and the other three studies comparing effects with oseltamivir (26,27), lopinavir-ritonavir (27), and carrimycin (28). The arbidol anti-viral mechanism against influenza A and B involves viral fusion inhibition with the targeted membrane, which blocks virus entry into the cell (24). **Oseltamivir** is another drug approved for influenza A and B treatment; it inhibits the viral neuraminidase and, consequently, blocks the release of viral particles from host cells, reducing the spread in the respiratory tract (29). Additionally, the use of oseltamivir was already reported during the COVID-19 epidemic in China, either with or without antibiotics and corticosteroids (30). Oseltamivir is also used in a clinical trial with multiple combinations with chloroquine and **favipiravir** (31), a nucleoside analog that is well-known as a broad-spectrum antiviral drug; it has shown (23) an EC_{50} of 61.88 µM against SARS-CoV-2 and low toxicity (CC50 >400 µM).

The **lopinavir-ritonavir** combination is approved for AIDS treatment in several countries. Both drugs are HIV protease inhibitors, but ritonavir is also a cytochrome P450 and GP inhibitor, a fact that endorses the lopinavir pharmacokinetic and pharmacodynamic activities against HIV (32). Such a combination, plus β-1b interferon, is in phase 2 for the MERS treatment (33). Several trials involve lopinavir-ritonavir treatment in comparison with the use of other drugs for COVID-19: arbidol (26,27), carrimycin (28), TCM (34,35), xiyanping (36,37), danoprevir-ritonavir (38) and interferon inhalation (34,38). Nevertheless, one previous article argued

that in a clinical trial with 199 patients with laboratory-confirmed SARS-CoV-2 infection, the lopinavir-ritonavir combination was not associated with clinical improvement comparing with standard care procedures (39).

Carrimycin is a macrolide antibiotic with effects against some gram-positive bacteria and *in vitro* effects on *Mycobacterium tuberculosis* (40).

Danoprevir is an HCV NS3 protease inhibitor approved in China for the treatment of non-cirrhotic genotype 1b chronic hepatitis C, in combination with ritonavir, peginterferon-α, and ribavirin (41).

Traditional Chinese medicine (TCM) uses phytotherapeutic formulations such as teas, pills, powders or tinctures, and cultural components that originated 5000 years ago in Chinese medicine (42). TCMs were already used for SARS-CoV infection in 2002 as coadjuvant therapy with the enhancement of patients' symptoms, increased oxyhemoglobin arterial saturation; they proved useful in the early stages of this infection (42).

Interferons (IFNs) are proteins that bind to cellular surfaces' receptors and initiate JAK-STAT signaling cascades, with transcriptional regulation of genes controlled by interferons and effects against some viruses like hepatitis B virus and HCV (43).

Xiyanping is a TCM preparation with andrographolide as a principal component; it has significant antibacterial and antiviral effects (44).

Darunavir, in combination with **cobicistat,** will be used in trial number NCT04252274 (45) in patients with COVID-19 pneumonia. The United States Food and Drug Administration (FDA) currently approves such a combination in AIDS treatment. Darunavir is another HIV protease inhibitor, and cobicistat, like ritonavir, is a booster for enhancing the pharmacokinetics and pharmacodynamics of darunavir by cytochrome P450 (CYP3A) inhibition (46,47).

Recombinant human interferon α2β is described to have inhibitory effects on MERS-CoV and SARS-CoV (48), and the purpose of the clinical trials found for this paper is to evaluate the efficacy and safety of recombinant human interferon α2β in treating patients with new coronavirus infection (49).

Thalidomide will be used in two trials against COVID-19 (49, 50). Thalidomide has an anti-inflammatory action due to its ability to speed up the degradation of messenger RNA in blood cells and thus reduce tumor necrosis factor-α (TNFα). Furthermore, thalidomide can increase the secretion of interleukins, such as IL-12, and activate natural killer cells (51).

The corticosteroid **methylprednisolone** will be tested against COVID-19 (52). Long et al. 2016 (53) reported that corticosteroid therapy (methylprednisolone, dexamethasone, and hydrocortisone) is beneficial

in treating SARS-CoV patients; it significantly prolongs the survival time of clinical cases. Nevertheless, other authors described the use of corticosteroids in the early stages of SARS infection with increasing values of viral load (54). Furthermore, studies with corticosteroids in the adjuvant therapy of MERS-CoV infection were unable to prove efficacy because all patients died (55). Methylprednisolone has already been used in COVID-19 patients in combination with antibiotics, oseltamivir, and oxygen therapy (56).

Finally, vitamin C (ascorbic acid), pirfenidone, bevacizumab, fingolimod, and bromhexine hydrochloride are going to be tested on COVID-19 (57-61). **Vitamin C** has antioxidant activity and may reduce oxidative stress and inflammation (57,62), effects that improve vasopressor synthesis, enhance immune cell function, improve endovascular function, and provide epigenetic immunologic modifications. Clinical trials have demonstrated promising data on mortality improvement in sepsis, but more extensive studies are necessary to validate these conclusions (63). **Pirfenidone** has been used in the treatment of idiopathic pulmonary fibrosis diseases due to anti-inflammatory and anti-oxidant effects, namely by inhibiting IL-1β and IL-4 (58). Trial NCT04282902 claimed (58) that anti-inflammatory effects may be helpful in SARS-CoV-2 infection. **Bevacizumab** is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF) (59,63), and it may reduce the levels of VEGF caused by hypoxia, severe inflammation, and upregulation of the infected respiratory tract epithelium, all of which might suppress the edema in patients with COVID-19 (63). **Fingolimod** is a sphingosine-1-phosphate receptor regulator (FTY720) with an effective immunology modulator that is useful in multiple sclerosis (60). According to some pathological findings of pulmonary edema and hyaline membrane formation, the use of immune modulators, together with ventilator support, should be considered for severe patients to prevent the development of acute respiratory distress syndrome (ARDS). Study NCT04280588 aims to determine the efficacy of fingolimod for COVID-19 (60). **Bromhexine** is a transmembrane protease serine inhibitor; such a protease is responsible for the activation of S-glycoprotein of SARS-CoV and MERS-CoV for viral entry through the plasma membrane (61,64). One study (60) will evaluate the efficacy of bromhexine combined with standard treatment/standard treatment in patients with COVID-19.

In conclusion, the WHO declared an epidemic of pneumonia caused by the SARS-CoV-2 in 2020. In this review, we found 24 clinical trials that have already started with the repositioning of more than 20 medicines for COVID-19 treatment, such as human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, favipiravir, oseltamivir, thalidomide, methylprednisolone, bevacizumab, and TCM. The Hydroxychloroquine-azithromycin combination was the first drug repurposed with excellent results in clinical

trials against SARS-CoV-2, but further, more extended studies, with a higher number of patients, are needed to confirm these results. Besides its limitations, repositioning clinical trials are still an attractive strategy: they may facilitate the discovery of new classes of medicines; they may reduce the costs and time to reach the market; there is an existing pharmaceutical supply chain for formulation and distribution; and there is the possibility of combinations with other drugs in treatments that are more effective than monotherapy. Most of the studies found in this article are scheduled to end in 2020, and we hope these repositioning trials may help to find solutions for COVID-19 treatment by this year.

Conflicts of interest. None declared.

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Table 1. Clinical trials identified at Clinicaltrials.gov related to drug repositioning for COVID-19 treatment

Intervention	Clinical condition	Sponsor	N° test / Status	Beginning / Estimated end	Phase
Hydroxychloroquine	30 participants with pneumonia caused by 2019-nCoV	Shanghai Public Health Clinical Center	NCT04261517 / Recruiting patients	6-2-2020 / 31-12-2020	3
Chloroquine	10000 participants in a prophylaxis study for COVID-19	University of Oxford	NCT04303507 / Not yet recruiting	May 2020 / May 2022	N/A
Human immunoglobulin	Pneumonia caused by 2019-nCoV with 80 participants	Peking Union Medical College Hospital	NCT04261426 / Not yet recruiting patients	10-2-2020 / 30-06-2020	2 and 3
Remdesivir	Severe respiratory infection caused by 2019-nCoV with 452 participants	Capital Medical University	NCT04257656 / Recruiting patients	6-2-2020 / 31-05-2020	3
Remdesivir	308 participants with mild/moderate respiratory infection caused by 2019-nCoV	Capital Medical University	NCT04252664 / Recruiting patients	05-02-2020 / 27-04-2020	3
Arbidol (umifenovir)	Pneumonia caused by 2019-nCoV with 380 participants	Jieming QU, Ruijin Hospital	NCT04260594 / Not yet recruiting patients	7-02-2020 / 30-12-2020	4
Arbidol or l**opinavir-ritonavir** or o**seltamivir**	400 participants infected with 2019-nCoV	Tongji Hospital	NCT04255017 / Recruiting patients	01-02-2020 / 01-07-2020	4
Arbidol or **lopinavir-ritonavir**	125 participants infected with 2019-nCoV	Guangzhou 8th People's Hospital	NCT04252885 / Recruiting patients.	28-01-2020 / 31-07-2020	4
Darunavir-cobicistat combination	Pneumonia caused by 2019-nCoV with 30 participants	Shanghai Public Health Clinical Center	NCT04252274 / Recruiting patients	30-01-2020 / 31-12-2020	3
TCM combination with **lopinavir-ritonavir, α-interferon** via aerosol	150 participants infected with 2019-nCoV	Beijing 302 Hospital	NCT04251871 / Recruiting patients	22-01-2020 / 22-01-2021	N/A
Recombinant human interferon α2β	328 participants with COVID-19	Tongji Hospital	NCT04293887 / Not yet recruiting	01-03-2020 / 30-06-2020	1
Carrimycin or **lopinavir-ritonavir** or **arbidol** or **chloroquine phosphate**	520 participants with COVID-19	Beijing YouAn Hospital	NCT04286503 / Not yet recruiting	23-02-2020 / 28/02-2021	4
Danoprevir-ritonavir and **interferon** inhalation or **lopinavir-ritonavir** or **TCM** plus **interferon** inhalation	50 participants with pneumonia caused by 2019-nCoV	The Ninth Hospital of Nanchang	NCT04291729 / Recruiting	14-02-2020 / 30-04-2020	4
Xiyanping or **lopinavir-ritonavir-interferon** inhalation	384 participants with pneumonia caused by 2019-nCoV	Jiangxi Qingfeng Pharmaceutical Co. Ltd.	NCT04275388/ Not yet recruiting	19-02-2020 / 14-12-2020	N/A
Xiyanping combined with **lopinavir-ritonavir**	80 participants with COVID-19	Jiangxi Qingfeng Pharmaceutical	NCT04295551 / Not yet recruiting	14-03-2020 / 14-04-2021	N/A
Combinations of **oseltamivir, favipiravir**, and c**hloroquine**	80 participants with COVID-19	Rajavithi Hospital	NCT04303299 / Not yet recruiting	15-03-2020 / 30-11-2020	3
Thalidomide	40 participants with COVID-19	First Affiliated Hospital of Wenzhou Medical University	NCT04273581 / Not yet recruiting	18-02-2020 / 30-05-2020	2
Thalidomide	100 participants with pneumonia caused by 2019-nCoV	First Affiliated Hospital of Wenzhou Medical University	NCT04273529 / Not yet recruiting	20-02-2020 / 30-06-2020	2
Vitamin C	140 participants with severe pneumonia caused by 2019-nCoV	ZhiYong Peng	NCT04264533 / Recruiting	14-02-2020 / 30-09-2020	2
Methylprednisolone	80 participants infected with 2019-nCoV	Peking Union Medical College Hospital	NCT04244591 / Recruiting patients	26-01-2020 / 25-12-2020	2
Pirfenidone	294 participants with severe pneumonia caused by 2019-nCoV	Huilan Zhang	NCT04282902 / Recruiting	04-02-2020 / 01-06-2020	3
Bromhexine hydrochloride	60 participants with suspected and mild pneumonia caused by 2019-nCoV	Second Affiliated Hospital of Wenzhou Medical University	NCT04273763 / Enrolling by invitation	16-02-2020 / 30-04-2020	N/A
Bevacizumab	20 participants with severe COVID-19 pneumonia	Qilu Hospital of Shandong University	NCT04275414 / Recruiting	February 2020 / May 2020	2 and 3
Fingolimod	30 participants with COVID-19	1° Affiliated Hospital of Wenzhou Medical University	NCT04280588 / Recruiting	22-02-2020 / 01-06-2020	2

COVID-19, coronavirus disease 2019; 2019-nCoV, novel coronavirus 2019; TCM, traditional Chinese medicine

Ensayos clínicos de reposicionamiento de medicamentos para el tratamiento de la COVID-19

RESUMEN

En diciembre de 2019 fue informado a la Organización Mundial de la Salud (OMS) un brote de neumonía por coronavirus en Wuhan, provincia de Hubei, China. Al 12 de marzo de 2020, se habían notificado 125 048 casos y 4 614 muertes. El coronavirus es un virus ARN envuelto del género *Betacoronavirus* distribuido en aves, seres humanos y otros mamíferos. La OMS ha denominado a la nueva enfermedad por coronavirus COVID-19. Se han puesto en marcha más de 80 ensayos clínicos para evaluar un tratamiento para el coronavirus, que incluyen algunos ensayos de reposicionamiento de medicamentos para la COVID-19. En marzo de 2020 se llevó a cabo una búsqueda de los ensayos clínicos registrados en la base de datos clinicaltrials.gov. Los criterios de elegibilidad para los estudios recuperados fueron tener un número de identificación de la base de datos clinicaltrials.gov; describir el número de participantes y el período del estudio; describir las condiciones clínicas de los participantes; y emplear intervenciones con medicamentos ya estudiados o aprobados para cualquier otra enfermedad en pacientes infectados con el nuevo coronavirus SARS-CoV-2 (2019-nCoV). Es esencial destacar que este artículo solo recoge los ensayos que figuran en la base de datos clinicaltrials.gov. Se identificaron 24 ensayos clínicos relacionados con más de 20 medicamentos, como inmunoglobulina humana, interferones, cloroquina, hidroxicloroquina, arbidol, remdesivir, favipiravir, lopinavir, ritonavir, oseltamivir, metilprednisolona, bevacizumab y medicina tradicional china. Aunque el reposicionamiento de medicamentos tiene algunas limitaciones, el reposicionamiento de los ensayos clínicos puede representar una estrategia atractiva porque facilita el descubrimiento de nuevas clases de medicamentos; estos tienen costos más bajos y tardan menos en llegar al mercado; y existen cadenas de suministro farmacéutico que apoyan la formulación y la distribución.

Palabras clave Reposicionamiento de medicamentos; ensayos clínicos como asunto; infecciones por coronavirus; virosis; neumonía viral; pandemias.

Ensaios clínicos de reposicionamento de medicamentos para o tratamento do COVID-19

RESUMO

A Organização Mundial da Saúde (OMS) foi informada, em dezembro de 2019, sobre um surto de pneumonia por coronavírus em Wuhan, província de Hubei (China). Posteriormente, em 12 de março de 2020, 125 048 casos e 4 614 mortes haviam sido registrados. O coronavírus é um vírus RNA envelopado do gênero *Betacoronavírus*, distribuído em aves e em humanos e

outros mamíferos. A OMS designou a nova doença por coronavírus como COVID-19. Mais de 80 ensaios clínicos foram iniciados para testar tratamentos para o coronavírus, incluindo alguns de reposicionamento de medicamentos para o COVID-19. Assim, em março de 2020 realizou-se uma busca na base de dados clinicaltrials.gov. Os critérios de elegibilidade para os estudos recuperados foram: conter o número identificador da base de dados clinicaltrials.gov; descrever o número de participantes e o período do estudo; descrever as condições clínicas dos participantes; e utilizar intervenções para tratamento de doentes infectados com o novo coronavírus SARS-CoV-2 (2019-nCoV) com medicamentos já estudados ou aprovados para qualquer outra doença. É essencial salientar que este artigo apenas capturou ensaios listados na base de dados clinicaltrials.gov. Foram identificados 24 ensaios clínicos envolvendo mais de 20 medicamentos, tais como imunoglobulina humana, interferons, cloroquina, hidroxicloroquina, arbidol, remdesivir, favipiravir, lopinavir, ritonavir, oseltamivir, metilprednisolona, bevacizumabe e medicamentos chineses tradicionais. Embora o reposicionamento de medicamentos tenha algumas limitações, os ensaios clínicos de reposicionamento podem representar uma estratégia atraente, porque facilitam a descoberta de novas classes de medicamentos, têm custos mais baixos, levam menos tempo para chegar ao mercado e se beneficiam de cadeias de fornecimento farmacêutico já existentes para formulação e distribuição.

Palavras-chave Reposicionamento de medicamentos; ensaios clínicos como assunto; infecções por coronavirus; viroses; pneumonia viral; pandemias.