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REVIEW

COVID-19: Before the Fall, An Evidence-Based Narrative Review of Treatment Options

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ABSTRACT

The 2019 novel coronavirus (COVID-19) has quickly become one of the most dire international pandemic crises since the 1918 Spanish flu. Evidence for COVID-19 pharmacological therapies has shown rapid growth and a diverse array of results, but an assessment of the value of each piece of evidence must be reinforced. This article aims to review utilized therapies, the evidence level supporting these therapies, as well as drugs under investigation for the treatment of COVID-19. Primary scrutinized therapies include antiviral regimens, such as remdesivir, hydroxychloroquine/chloroquine, lopinavir/ritonavir, immunomodulating drugs, such as corticosteroids and interleukin (IL) inhibitors, and other therapies including convalescent plasma. Only one therapy, dexamethasone, has shown a mortality benefit in randomized controlled trials and summarized evidence for other therapies show limited positive results. Reviewing these therapies in a historical way shows how limited evidence can drive therapy decisions. A broad summary of available evidence can assist clinicians in a return to hierarchical assessments of evidence which can lead to safer patient outcomes, improved distribution of resources, and better targets for appropriate therapy decisions.

Keywords: Coronavirus; COVID; COVID-19; Evidence; Narrative review; Pharmacologic; Review; Therapy; Treatment

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Key Summary Points

Evidence for COVID-19 pharmacological therapies has shown rapid growth and a diverse array of results, but an assessment of the value of each piece of evidence must be reinforced

This article aims to review utilized therapies, the evidence level supporting these therapies, as well as drugs under investigation for the treatment of COVID-19

Only one therapy, dexamethasone, has shown a mortality benefit in randomized controlled trials and summarized evidence for other therapies show limited positive results

A broad summary of available evidence can assist clinicians in a return to hierarchical assessments of evidence

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13536953.

INTRODUCTION

The newly discovered betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has quickly become one of the most dire international pandemic crises since the 1918 Spanish flu, which resulted in 20 million deaths, including 500,000 in the USA [1]. First discovered in Wuhan, China in December 2019, SARS-CoV-2 has now spread to nearly every country across the globe, with the USA leading the charge in the number of confirmed cases by country. As of December 1, 2020, the number of confirmed cases has climbed to over 60,000,000 with almost 1.5 million deaths worldwide [2]. The virus manifests as an acute viral respiratory infection referred to as coronavirus disease 2019 (COVID-19) primarily characterized by cough, fever, shortness of breath, muscle pain, loss of taste or smell, and/or no symptoms at all [3]. Management of COVID-19 is similar to many viral respiratory illnesses in that therapy is largely supportive, but respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality. Studies suggest that 20–30% of hospitalized patients with COVID-19 disease progress to ARDS [4, 5]. Currently, there are still no US Food and Drug Administration (FDA)-approved therapies for the treatment of SARS-CoV-2 except for an emergency use authorization for remdesivir and scattered data supporting other agents such as dexamethasone. As a result of scant data early in the course of the pandemic, many institutions had implemented treatment algorithms based on observational trials and in vitro activity against SARS-CoV-2 and similar coronaviruses, such as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome (MERS). Many treatment options have been suggested, utilized, and are in trials for their effectiveness against SARS-CoV-2, but the level of evidence varies between these therapies.

This article aims to review recently utilized therapies, the evidence supporting these therapies, as well as drugs under investigation for the treatment of COVID-19. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The authors agree with both the Infectious Diseases Society of America (IDSA) and National Institutes of Health (NIH) guidelines on the treatment and management of patients with COVID-19, which encourage more experimental therapies to be performed within the context of a clinical trial [6]. To this end, a comprehensive understanding of current treatment evidence will help providers assess risks and benefits, identify gaps in research, and direct attention towards the most promising drugs being screened to treat COVID-19.

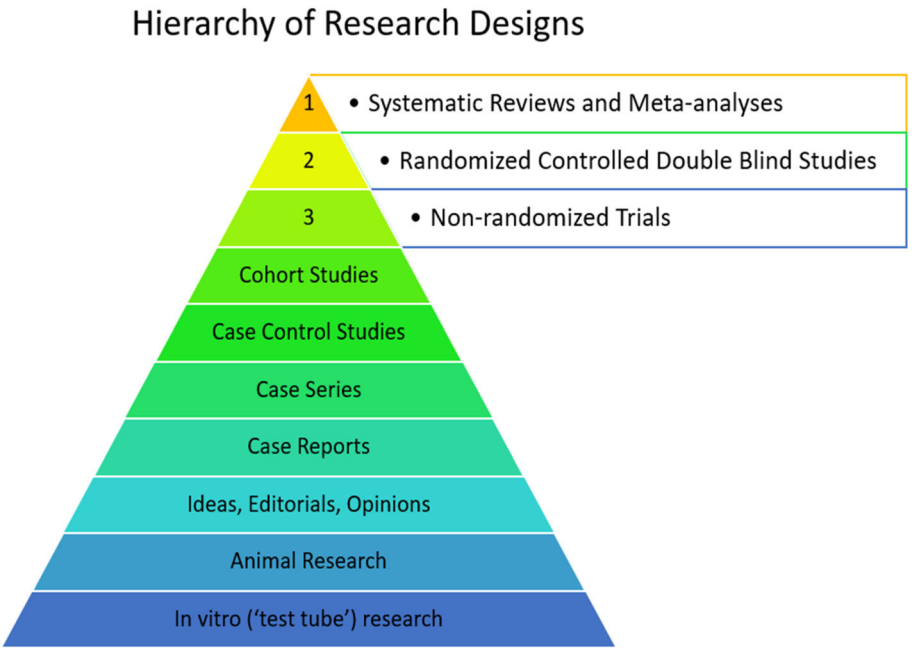

Fig. 1 Chart adapted from Guide to Research Methods: The Evidence Pyramid. SUNY Downstate Medical Center. Medical Research Library of Brooklyn EBM Resources

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GENERAL PRINCIPLES

When discussing evidence between pharmacologic therapies, one must remember the hierarchy of evidence (Fig. 1). It is vital to not let desperation replace evidence when recommending potential therapies. Too often, there is harm perpetrated with the best of intentions, before there can be adequate data to assess the therapy. This can be seen in prior pandemics and early harmful "therapies" for human immunodeficiency virus (HIV) and other respiratory viruses [7, 8]. With COVID-19 entering 11 months since its characterization as a pandemic, more studies and randomized controlled trial (RCT) results are surfacing regarding treatment for COVID-19. As clinicians and researchers, we should refer patients and healthcare professionals to well-performed RCTs to make decisions as to whether these antimalarials and/or antibiotics should be utilized in the treatment of COVID-19. Trials that only provide a low to moderate level of evidence can deprive high-level trials of potential subjects. Also therapies that are not sufficiently evidence-based can bias the populations for RCTs that consider the definition of "standard of care". Understanding how to categorize and assess scientific evidence is important when discussing the strengths and weaknesses of studies that have been used for the IDSA and NIH recommendations, and it is important to prioritize high-level evidence in these discussions. An updated review of the evidence behind COVID-19 therapies can help more providers understand the breadth and depth of historical COVID-19 treatment evidence and assess gaps and potential research for the future pharmacologic treatments.

The driving forces behind many of the early therapies for COVID-19 were prior studies among SARS and MERS viruses. The initial

Table 1 Key parameters used for comparing in vitro data

Term	Definition
EC_{50}	Effective concentration needed to achieve 50% of maximal response (50% viral inhibition)
IC_{50}	Inhibitory concentration needed to inhibit a process by 50% (usually intended for antagonist drug potency, but often interchanged with EC_{50} when discussing antiviral therapy)
CC_{50}	Cytotoxic concentration needed to cause death among 50% of host cells
SI	CC_{50}/EC_{50}; selectivity index to describe a given drug's therapeutic window

studies with SARS and MERS revealed certain agents that could effectively inhibit coronaviruses at achievable concentrations in cell or animal models [9–11]. When comparing efficacy for various therapies with little RCT data behind them, often the discussion begins around comparing in vitro data. The main principles of comparing in vitro data involve quantifying an agent's half-maximal effective concentration (EC_{50}), half-maximal inhibitory concentration (IC_{50}) (EC_{50} and IC_{50} are sometimes interchanged when the substance is intended to inhibit viral replication), and 50% cytotoxic concentration (CC_{50}) (Table 1) [12].

One can assess higher levels of evidence by building on these definitions for comparing in vitro research. Much of the same definitions are used in animal research, where EC_{50} can apply to the clinical syndrome in an animal and CC_{50} can apply to a population of animals. However, there are assumptions in targeting EC_{50} values which have not been borne out by scientific evidence. It is unclear whether EC_{50} values are important targets, and in one of the only true pharmacodynamic studies there was a lack of antiviral effect of a drug despite having serum and lung concentrations above the EC_{50} value. One must keep the primary target of the human host in mind and ensure outcomes are evaluated rather than abstract EC_{50} values which may not predict outcomes [13]. The level of evidence rises when the data is derived from human hosts, with larger sample sizes, and more controlled randomized trials associated with eliminating confounders and bias.

Taking the recommendation rating scheme and adapting it from the NIH guidelines, one can apply a simple way to assess many different types of clinical evidence (Table 2). A systematic search was undertaken from March 2020 to September 2020 utilizing PubMed search terms of "covid", "covid-19", and "covid treatment" including pharmacologic studies only. This narrative review will focus on the quality of evidence and the positive or negative effects of each therapy in evidence. The strength of the recommendations will remain with the NIH and IDSA given their consensus guidelines among a panel of experts. Each study will be evaluated on a quality of evidence scale from I for an RCT as the highest level of evidence to VI for in vitro research or P for pending investigation (Table 3). The studies will also be evaluated on a strength of effect scale across a range from $(- - -)$ for strong ($\geq$ 5%) negative effect on mortality to $(+ + +)$ for strong ($\geq$ 5%) positive effect on mortality (Table 3).

TREATMENT OPTIONS

Antiviral Therapies

Remdesivir

Remdesivir is an adenosine nucleotide analogue that interferes with the action of viral RNA polymerases that ultimately decreases viral RNA production. It was originally developed to treat Ebola virus and has been found to have inhibitory effects on other viruses. With demonstrated in vitro activity against SARS-CoV-2 and in vivo activity against similar coronaviruses, remdesivir became an early contender among the potential treatment options against SARS-CoV-2 (Table 4) [24, 79]. As a result of high demand, the manufacturer (Gilead Sciences, Inc.) transitioned from individual compassionate use requests to an expanded access program in concert with the FDA [80]. New individual compassionate use requests were accepted specifically for pregnant women and children

Table 2 Recommendation rating scheme for NIH COVID-19 assessment of evidence. Chart adapted from NIH Table 1 in ref. [14]

Strength of recommendation		Quality of evidence for recommendation	
A	Strong recommendation for the statement	I	One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B	Moderate recommendation for the statement	II	One or more well-designed, non-randomized trials or observational cohort studies
C	Optional recommendation for the statement	III	Expert opinion

under 18 years of age [81]. On April 29, 2020, the FDA granted emergency use authorization (EUA) for the investigational intravenous antiviral drug to treat severe COVID-19 (defined as oxygen saturation $\leq$ 94%). An EUA is intended to provide the availability of a drug during an emergency. It is a temporary approval and does not take the place of the formal new drug application submission, review, and approval process.

Multiple clinical trials remain underway to assess remdesivir's role in the treatment of COVID-19 [16, 18–23]. It was also the first COVID-19 therapy used in the first documented patient case in the USA [22]. Initially, the data for compassionate use of remdesivir was released for patients hospitalized with severe COVID-19 to support its use. The design was an observational study of patients who were provided compassionate use remdesivir, with no control group. There were 53 patients who received at least one dose (200 mg or 100 mg IV) of remdesivir with analyzable data at different clinical sites, 30/53 (57%) were mechanically ventilated and 4/53 (8%) were on extracorporeal membrane oxygenation (ECMO). At a median of 18-day follow-up, 36/53 (68%) had an improvement in oxygen-support class, 25/53 (47%) of patients were discharged, and 7/53 (13%) patients died. While 68% of patients improved on therapy defined as oxygen-support class, it is difficult to assess the significance of results with the lack of a control group [21].

However, the EUA that came after the order for compassionate use was based on a stronger set of data from the Adaptive COVID-19 Treatment Trial (ACTT) group in an RCT. In one of the strongest volumes of evidence to date, the National Institute of Allergy and Infectious Diseases (NIAID) ACTT-1 Study was a randomized, double-blind, placebo-controlled clinical trial evaluating remdesivir (200 mg daily $\times$ 1 day followed by 100 mg daily $\times$ 9 days, up to 10 days total) in hospitalized adult patients with COVID-19. The trial enrolled 1063 hospitalized patients who received remdesivir or placebo allocated in a 1:1 ratio. In a preliminary analysis of the primary endpoint after 606 recoveries were attained, the median time to recovery was 11 days in the remdesivir group compared to 15 days in the placebo group (HR 1.31; 95% confidence interval [CI] 1.12–1.54, $p < 0.001$). All-cause mortality was 8.0% for the remdesivir group versus 11.6% for the placebo group ($p = 0.059$) [16]. This study provided initial strong evidence for a modest benefit of remdesivir. Subsequently to this, Gilead Sciences, Inc. has given drug to the federal government to distribute to in-need hospitals while ramping up production for more cases. Another of Gilead's clinical trials compared 5 days versus 10 days of therapy for remdesivir. The randomized, open-label, multicenter study (GS-US-540-5773) suggested that patients receiving a 10-day treatment course had similar improvement in clinical status compared with those receiving a 5-day treatment course (10-day vs. 5-day odds ratio 0.76; 95% CI 0.51–1.13 on day 14). This gives rise to the suggestion of a 5-day duration, with possible extension to 10 days if no clinical improvement is demonstrated in an intensive care unit (ICU) setting [82]. The NIH guidelines have provided specific recommendations for 5 days

Table 3 Evidence assessment scheme for assessment of evidence for review

Quality of evidence		Effect size strength (only evidence I–II)	
I	Randomized trial with clinical outcomes and/or validated laboratory endpoints	+ + +	Strong positive effect on mortality (≥ 5%)
II	Non-randomized trial or observational cohort study	+ +	Positive effect on mortality (< 5%)
III	Single-arm study or case series/reports	+	Some positive effect on an outcome
IV	Editorials/expert opinion	0	No significant effect noted from treatment
V	Animal or animal-model research	−	Some negative effect/increased adverse events
VI	In vitro research or AI-based drug selection	− −	Negative effect on mortality (< 5%)
P	In-progress clinical trials	− − −	Strong negative effect on mortality (≥ 5%)
		N/A	Not applicable

of remdesivir when on supplemental oxygen but not mechanical ventilation, while NIH recommended 10 days for those patients on mechanical ventilation or ECMO.

After this set of initial studies and results, remdesivir's portfolio of evidence became further filled with completed trials. The full results for the ACTT-1 trial have been released that finalized a total of 1062 patients' results and provide the strongest piece of evidence for utilizing remdesivir. The primary results showed that the median recovery time for the remdesivir group was 10 days compared to standard of care's 15 days (RR for recovery 1.29; 95% CI 1.12–1.49, $p < 0.001$) and showing 29-day mortality of 11.4% in the remdesivir group and 15.2% in the placebo group (HR 0.73; 95% CI 0.52–1.03). Adverse events were lower at 24.6% who received remdesivir and at 31.6% for placebo [17]. Over 15 RCTs are being conducted to determine the efficacy and safety of remdesivir in the treatment of COVID-19 [83]. In stark contrast to the positive results from ACTT-1 in the USA, in one of the most recent and broadest clinical trials to date, the World Health Organization (WHO) international SOLIDARITY trial allocated 2750 patients to remdesivir and 4088 to no study drug and found a 28-day mortality relative risk ratio of 0.95 (95% CI 0.81–1.11, $p = 0.50$) which showed no statistically significant reduction in mortality. Total 28-day mortality was 12%, and this was measured along Kaplan–Meier curves. SOLIDARITY, when gathering the great amount of patients in combination with the finalized ACTT-1 results, has shown that there is no statistically significant difference in mortality with remdesivir use [15]. While initial results with the ACTT-1 trial seemed promising, final results in combination with the SOLIDARITY trial have shown remdesivir has limited utility in curbing mortality rates and that it may have limited efficacy. This complete picture of evidence has complicated many healthcare centers' aggressive uptake of this drug as one of the few pharmacological options for patients with COVID-19. Guidelines have split on remdesivir's ultimate use, with the NIH and IDSA guidelines advocating for remdesivir's use in severe COVID-19, and WHO issuing a conditional recommendation against remdesivir's use in hospitalized patients given the lack of evidence that it improves survival or has an important effect on need for mechanical ventilation or time to clinical improvement [14, 84]. The dosing table below provides complete context on how the drug should be used

Table 4 Evidence review summary of pharmacologic treatment for COVID-19

Drug class	Drug	Evidence/studies	Interventions	Quality of evidence (I–VI)	Effect size strength (only evidence I–II)
Antiviral	Remdesivir	SOLIDARITY, Pan et al. [15]	RDV vs. PBO, HCQ vs. PBO, LPV/r vs. PBO, LPV/r + INF vs. PBO, INF vs. PBO	I	0
		ACTT-1, Beigel et al. [16, 17]	RDV vs. PBO	I	+
		Wang et al. [18]	RDV vs. PBO	I	0
		Goldman et al. [19]	RDV 5d vs. RDV 10d	I	0
		Spinner et al. [20]	RDV 5d vs. RDV 10d vs. Std	I	RDV 5d +
					RDV 10d 0
		Grein et al. [21]	RDV	II	N/A
		Holshue et al. [22]	Case report	III	
		Williamson et al. [23]	RDV in rhesus macaques	V	
		Wang et al. [24]	RDV, CLQ in vitro	VI	
	Hydroxychloroquine/ chloroquine	SOLIDARITY, Pan et al. [15]	RDV vs. PBO, HCQ vs. PBO, LPV/r vs. PBO, LPV/r + INF vs. PBO, INF vs. PBO	I	0
		Cavalcanti et al. [25]	Std vs. HCQ vs. HCQ + AZI	I	HCQ −
					HCQ + AZI −
		HCQ: RECOVERY trial, Horby et al. [26]	Std vs. HCQ	I	−
		Tang et al. [27]	Std vs. HCQ	I	−
		Chen et al. [28]	Std vs. HCQ	I	+
		Magagnoli et al. [29]	Std vs. HCQ vs. HCQ + AZI	II	HCQ − −
					HCQ + AZI 0
		Mahevas et al. [30]	HCQ vs. PBO	II	0
		Rosenberg et al. [31]	Std vs. HCQ vs. AZI vs. HCQ + AZI	II	HCQ 0
					AZI 0
					HCQ + AZI −
		Arshad et al. [32]	Std vs. HCQ vs. AZI vs. HCQ + AZI	II	HCQ + +
					AZI 0
					HCQ + AZI +
		Yu et al. [33]	Std vs. HCQ	II	+ + +
		Ip et al. [34]	Outpt: Std vs. HCQ	II	+
		Geleris et al. [35]	Std vs. HCQ	II	0
		Castelnuovo et al. [36]	Std vs. HCQ	II	+ +
		Gautret et al. [37, 38]	Std vs. HCQ ± AZI	III	
		Molina et al. [39]	HCQ + AZI PCR-time	III	
		Wang et al. [24]	RDV, CLQ in vitro	VI	
	Favipiravir	Cai et al. [40]	FPV vs. LPV/r	II	+
	Galidesivir	BioCryst [41]	Phase I and II	I	P
	Lopinavir/ritonavir	Li et al. [42]	Std vs. LPV/r vs. arbidol	I	−
		SOLIDARITY, Pan et al. [15]	RDV vs. PBO, HCQ vs. PBO, LPV/r vs. PBO, LPV/r + INF vs. PBO, INF vs. PBO	I	0
		RECOVERY trial [43]	Std vs. LPV/r	I	0
		Cao et al. [44]	Std. vs. LPV/r	I	0
	Sofosbuvir/daclatasvir	Eslami et al. [45]	SOF/DCV vs. RBV	II	+ + +
	Oseltamivir	Tan et al. [46]	In vitro	VI	
Immunomodulators	Colchicine	Deftereos et al. [47]	Std vs. Colc	I	+

Table 4 continued

Drug class	Drug	Evidence/studies	Interventions	Quality of evidence (I–VI)	Effect size strength (only evidence I–II)
Corticosteroids	Dexamethasone	Dex: RECOVERY trial, Horby et al. [48]	Std vs. Dex	I	+ +
	Methylprednisolone	METCOVID, Jeronimo et al. [49]	Std vs. MP	I	0
		Corral-Gudino et al. [50]	Std vs. MP	I	+
IL-1 inhibitors	Anakinra	Huet et al. [51]	Std vs. Ana	II	+ +
		Cavalli et al. [52]	Std vs. Ana-high vs. Ana-low	II	Ana-H + Ana-L 0
		Aouba et al. [53]	Ana	III	
IL-6 inhibitors	Tocilizumab	Stone et al. [54]	Std vs. Toci	I	0
		Salvarani et al. [55]	Std vs. Toci	I	0
		CORIMUNO-19, Hermine et al. [56, 57]	Std vs. Toci	I	0
		COVACTA trial [58, 59]	Std vs. Toci	I-P, stopped	0
		Guaraldi et al. [60]	Std vs. Toci	II	+ + +
		Biran et al. [61]	Std vs. Toci	II	+ + +
		Sciascia et al. [62]	Toci	III	
		Xu et al. [63]	Tocilizumab pts	III	
	Sarilumab	REGENERON/ SANOFI trial [64]	Std vs. Sari	I-P, stopped	0
JAK inhibitors	Ruxolitinib	Cao et al. [65]	Rux vs. PBO	I	+
		Rosee et al. [66]	Rux	III	
	Tofacitinib	I-TOMIC [67]	Std vs. Toci	I-P	
	Baricitinib	Cantini et al. [68]	Bar + LPV/r vs. HCQ + LPV/r	II	0
BTK inhibitors	Acalabrutinib	Rochewski et al. [69]	Acalabrutinib	II	+
	Ibrutinib	Treon et al. [70]	Ibrutinib	III	
Antibodies	Convalescent plasma	Gharbharan et al. [71]	Std vs. CP	I	0
		Li et al. [72]	Std vs. CP	I	0
		Shen et al. [73]	CP	III	
Monoclonal antibody	LY-CoV555	BLAZE-1 [74, 75]	Outpt: Std. vs. LY-Low vs. LY-Med vs. LY-High	I	LY-Low 0 LY-Med + LY-High 0
Antibiotics	Azithromycin	Rosenberg et al. [31]	Std vs. HCQ vs. AZI vs. HCQ + AZI	II	HCQ 0 AZI 0 HCQ + AZI −
		Arshad et al. [32]	Std. vs. HCQ vs. AZI vs. HCQ + AZI	II	HCQ + + AZI 0 HCQ + AZI +
Vitamin/mineral	Zinc	Carlucci et al. [76, 77]	HCQ + AZI vs. HCQ + AZI + Zn	II	+
Combination	Remdesivir + baricitinib	ACTT-2, NCT04401579 [78]	RDV + Bara vs. RDV	I-P	N/A

RDV remdesivir, *PBO* placebo, *Std* standard of care, *CLQ* chloroquine, *HCQ* hydroxychloroquine, *AZI* azithromycin, *FPV* favipiravir, *LPV/r* lopinavir/ritonavir, *SOF/DCV* sofosbuvir/daclatasvir, *RBV* ribavirin, *Dex* dexamethasone, *INF* interferon-β1a, *pt* patient, *Ana* anakinra, *Sari* sarilumab, *Rux* ruxolitinib, *Toci* tofacitinib, *Bar* baricitinib, *CP* convalescent plasma, *5d* 5 days of therapy, *10d* 10 days of therapy, *N/A* not applicable

and is the current recommended dosage under the NIH guidelines.

- Remdesivir dosing table

Dosing	200 mg IV once × 1 day, 100 mg IV QD × 4 or 9 days
Duration	5 days (≤ 94% SpO2, and not requiring mechanical ventilation and/or ECMO)
	Can extend to (if no clinical improvement demonstrated) 10 days (mechanical ventilation and/or ECMO)
Adverse effects	Adverse events were mostly mild–moderate: hepatic enzyme elevations, diarrhea, rash, etc. [21]

IV intravenous, *QD* daily, *ECMO* extracorporeal membrane oxygenation

Chloroquine/Hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) are pharmacologic therapies exhibit in vitro antiviral activity against SARS-CoV-2 [24]. HCQ is a derivative of chloroquine with an extra hydroxyl group and has been shown to be less toxic than CQ in animal studies [85]. Initially, both agents had been used as antimalarial drugs as derivatives of quinine, then later became used as immunomodulatory drugs for autoimmune and rheumatic diseases upon approval in 1956. In addition to their immunoregulatory and anti-inflammatory properties, their proposed antiviral effects are thought to be mediated by changes in the cell membrane pH necessary for viral fusion and interference of glycosylation of viral proteins [86]. The chloroquine analogues seemed to emerge in clinical trials as potential treatment options against the novel coronavirus [87]. Initially, chloroquine had been studied in 23 clinical trials in China, in addition to promising in vitro research. Hydroxychloroquine, alone and in combination, had even more results available in late spring 2020. This initial treatment use for hydroxychloroquine and chloroquine was driven by a lower quality of evidence until RCTs confirmed the lack of efficacy of the treatment [15, 24–27, 37].

One such early study, a non-randomized trial, emerged in mid-March from a group of researchers in Marseille, France, which described the preliminary use of HCQ (200 mg TID) ± azithromycin (AZI) (500 mg on day 1 followed by 250 mg per day, the next 4 days) in 26 patients compared to a control group, which received supportive care only [37]. The addition of azithromycin in this trial is interesting for its noted anti-inflammatory properties, but additional data suggested potential antiviral mechanisms [88]. Viral clearance in nasopharyngeal swabs was achieved in 6/6 (100%) patients in the HCQ + AZI group and 8/14 (57%) in the HCQ monotherapy group [37]. This study drove much of the fervent interest in HCQ and AZI as a potential combination therapy for COVID-19. However, while preprint popularity drove initial use, full results have been published along with other results from similar studies. In the full results of the Gautret study, 80 patients were included with no control group, and the results can only be interpreted by inference to other studies on COVID-19 patients with standard supportive care. The final polymerase chain reaction (PCR) results in the complete study were less impressive with roughly 40% of 80 patients having a PCR-positive sample at day 5 compared with 0% in the interim results of HCQ + AZI above [37, 38].

The full Gautret study did not have a control group, so interpreting treatment efficacy is a challenge and represents a significant limitation of the study. However, since the publishing of the initial study results in Marseille, a group in Paris, France failed to replicate the positive preliminary results of Gautret and colleagues in a prospective study designed to assess both virologic and clinical outcomes in patients with severe COVID-19. The study included 11 patients who received hydroxychloroquine (600 mg/day for 10 days) and azithromycin (500 mg day 1 and 250 mg days 2–5) using the same dosing regimen reported by Gautret et al. Repeated nasopharyngeal swabs at days 5–6 after treatment initiation were still positive in

8/10 patients (80%, 95% CI 49–94). The virologic results contrast those reported by Gautret, et al., which left unanswered questions regarding the role of this combination therapy in the treatment of COVID-19 [39]. After this series of studies, prospective randomized trials began to result, beginning in late March. The first of these came from Wuhan with somewhat positive results. In this study, 31 patients were randomized to 5 days of hydroxychloroquine (400 mg/day) and 31 patients were randomized to placebo. In the treatment group, chest CTs significantly improved in 25/31 (80.6%) patients from day 0 to 6, compared with the control group of 17/31 (54.8%) [28]. While promising, the trial was underpowered to detect a significant outcome, and it was intended to recruit 300 patients at the outset, instead of the published 62 patients. In early May with the Tang study, RCTs began to illuminate the treatment's lack of efficacy more clearly and adverse events came to be more clearly documented. This trial had 75 participants in each group, HCQ and standard of care, across 16 hospital sites in China in February. Results focused on negative conversion of SARS-CoV-2 by 28 days, which was non-significantly different between the two groups, because only two patients with severe COVID-19 were enrolled for clinical outcome analysis. Frequency of adverse events was 9% in the standard of care group and 30% in the HCQ group [27]. The lack of efficacy and higher adverse event results continued in three further large RCTs for hydroxychloroquine [15, 25, 26].

At the time of this review, there are now at least five significant RCTs evaluating the use of hydroxychloroquine and azithromycin [15, 25–28]. The RCTs have shown a lack of efficacy of hydroxychloroquine or azithromycin, in comparison to results from some non-randomized clinical retrospective trials [32, 33, 36]. Indeed, the addition of azithromycin may cause more harm than intended given the noted QT prolongation that can occur [89]. Hydroxychloroquine, chloroquine, and azithromycin have now fully fallen out of favor because of the overall study results. The SOLIDARITY trial in combination with other RCTs like ACTT-1 has now settled the question of any therapeutic efficacy for hydroxychloroquine. For historical dosing reference when they were utilized, refer to the hydroxychloroquine dosing table for a brief review on regimens.

- Hydroxychloroquine dosing table

Note: Most dosing regimens have been extrapolated from pharmacokinetics (PK) parameters described in patients with rheumatic diseases or healthy volunteers; therefore, PK studies are still needed to determine the optimal dosing regimen in patients with COVID-19 [90].

Dosing strategies	Reference/indication
800 mg followed by 400 mg at 6, 24, 48, 72, and 96 h	FDA approved adult dosing for treatment of acute malaria extended to 5 days.
3 days (acute malaria treatment) 5–10 days	Recommended most reasonable, efficacious, and safest approach by Downes' dosing simulations [91]
400 mg BID × 2 doses, then 200 mg PO BID 5 days Prefer to give with food	Optimal regimen recommended by Yao et al. [92]
200 mg TID × 10 days	Dosing from Gautret et al. [37]
400 mg QD × 10 days	Maximal approved adult dosing for rheumatologic conditions
800 mg on day 1, then 200 mg BID for 7 days	For ICU patients with COVID-19, recommended from prospective study describing PK of HCQ in 13 patients [90]
Adverse effects: Usually mild severity—GI intolerances, cytopenias, QT prolongation, headaches, dizziness	

Table b continued

Dosing strategies	Reference/indication
Warning: A recent cohort study found that the addition of azithromycin to hydroxychloroquine was associated with greater changes in QTc as compared to hydroxychloroquine alone. Close monitoring of QTc should be utilized with concomitant medication usage	[89]

FDA Food and Drug Administration, *PO* by mouth, *BID* twice a day, *GI* gastrointestinal, *TID* three times a day, *QD* daily, *ICU* intensive care unit

Lopinavir/Ritonavir

Lopinavir/ritonavir (LPV/r) is a combination drug that is FDA approved for the treatment of HIV infection. It combines a protease inhibitor and a pharmacokinetic enhancer, where the enhancer is used to increase the effectiveness and concentration of lopinavir. Lopinavir/ritonavir has been identified as a potential treatment option against SARS-CoV-2 given its documented in vitro antiviral activity against SARS-CoV-1 [93]. The proposed mechanism of action suggests lopinavir inhibits the main protease of SARS-CoV-1, which stops viral replication [94]. One of the first RCTs evaluating lopinavir/ritonavir's efficacy was conducted in patients with severe COVID-19 in January to February in China, with results published mid-March. This study helped to temper any enthusiasm for lopinavir/ritonavir as a potential treatment early in the US COVID-19 treatment experience. The study included 199 patients and compared the clinical outcomes between patients who received LPV/r and supportive care only. The study found no significant difference mortality at 28 days or viral clearance, nor did it identify an association between the addition of LPV/r and clinical improvement, defined as improvement of two points on a seven-category ordinal scale or discharge from the hospital. However while primary results showed little efficacy, post hoc analyses found statistical significance in median time to clinical improvement for the LPV/r group (1 day shorter, HR 1.39, 95% CI 1.00–1.91) when removing patients that experienced death before getting the drug and for patients receiving therapy within 12 days of onset of symptoms [44]. This minor positive signal in the data would continue questions of efficacy around lopinavir/ritonavir until further studies confirmed the lack of a benefit. One study conducted in China evaluated LPV/r in mild–moderate COVID-19 and compared this against usual care with a comparator arm of umifenovir (Arbidol), a broad antiviral medication used against influenza. The study was limited by its low sample size of 86 patients, but found no benefit of LPV/r in the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid or improvement in symptoms or imaging. In fact, the therapy only increased adverse events from primarily diarrhea and loss of appetite in the LPV/r arm [42].

While a somewhat positive signal for treatment deep in the data from the Cao et al. study may have been present, any question of therapeutic benefit has since been ended with the RECOVERY trial results from over 4500 patients. With 1596 patients randomized to LPV/r and 3376 randomized to standard of care, it was found that there was no significant difference in mortality, progression to mechanical ventilation, or length of hospital stay in either group [43]. In addition to the RECOVERY trial results, results were further solidified with the subsequent SOLIDARITY trial data which showed a lack of any mortality benefit to lopinavir/ritonavir. The SOLIDARITY trial involved 1411 patients randomized to lopinavir, 651 to interferon plus lopinavir, and 4088 no study drug at 405 hospitals in 30 countries. Lopinavir showed no statistically significant effect on mortality (RR1.00, CI 0.79–1.25, $p = 0.97$) [15]. Given the volume of patients involved in these two major trials, this has since shuttered further research into this drug being of benefit to patients with COVID-19. The dosing for lopinavir/ritonavir is

documented below for completeness and historical sake, but it is no longer considered a viable treatment option for COVID-19.

- Lopinavir/ritonavir dosing table

Dosing	PO: 400/100 mg (2 tabs) BID
Duration	5–10 days. Up to 14 total days of therapy have been reported, but most patients have adverse effects requiring early termination of drug combination
Adverse effects	Occur in most patients and can be moderate/severe—GI intolerance, hepatitis, and LFT abnormalities

PO by mouth, *BID* twice a day, *GI* gastrointestinal, *LFT* liver function

Other Antiviral Drugs

Other antiviral drugs have been studied for the treatment of COVID-19, and these include favipiravir, umifenovir (Arbidol), galidesivir, drugs currently utilized against influenza (oseltamivir, etc.), and sofosbuvir/daclatasvir. These antiviral drugs have not shown significant data to support their use. Some, like oseltamivir, have been ruled out as agents to use for COVID-19 given the lack of positive in vitro data and absence of plausible mechanism of action [46]. Favipiravir and umifenovir are broad antivirals approved in countries outside the USA that were used as anti-influenza agents. Both drugs have had limited clinical data supporting their use, although there has been some in vitro data [40, 42, 95, 96]. Sofosbuvir/daclatasvir is a treatment for hepatitis C infection that has also been found to bind to SARS-CoV-2 [97]. In a limited non-randomized study, it was found to have positive outcomes in COVID-19. However the trial was of limited participants and the comparison group was against ribavirin, which had significantly more adverse events as a therapy and it is not one commonly used in COVID-19 [45].

Immunomodulating Drugs

Literature from prior acute viral respiratory illnesses suggests that patients can progress to ARDS quite rapidly, as a result of the patient's own immune system becoming activated in a mechanism similar to sepsis. In addition, emerging evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine release syndrome (CRS), which is characterized by a substantial release of proinflammatory cytokines including interleukins (IL)-6, IL-1, tumor necrosis factor-α (TNFα), and others [98]. This hyperinflammatory state when induced from COVID-19 can often lead to poor outcomes and ICU admission [99]. This section of drug therapy discusses immunomodulating drugs which aim to affect the immune response to SARS-CoV-2 and hope to limit hyperinflammatory responses which can further exacerbate a patient's illness.

Corticosteroids

Corticosteroids are a broadly acting immunosuppressant at high doses that work to limit the hyperactive response in the immune system. These drugs were initially thought to be a poor choice due to data from SARS and MERS outbreaks that showed variable outcomes and higher mortality [8]. However, large RCT data from the RECOVERY trial has shown mortality benefit with dexamethasone. Among 2104 patients allocated to dexamethasone 6 mg given once daily for up to 10 days compared with 4321 patients allocated to usual care, a significant decrease in 28-day mortality was noted in the treatment arm (21.6% vs. 24.6%, RR 0.83, CI 0.74–0.92) [48]. These results extend chiefly to those patients who were receiving invasive mechanical ventilation and those patients receiving oxygen support. Given differences in steroids used, questions remain whether this mortality benefit extends to other corticosteroids besides dexamethasone. The GLUCOCOVID study was a study involving 34 patients randomized with 22 patients preferred by clinicians to receive methylprednisolone (MP) 40 mg every 12 h × 3 days then 20 mg every 12 h × 3 days. This was compared against 29

patients in the control group. The composite endpoint was of death, admission to the ICU, and ventilation requirement, which was significant between groups in intention-to-treat analysis (RR 0.55, CI 0.33–0.91) [50]. However, the use of methylprednisolone was further complicated with results from the METCOVID RCT where 393 patients were ultimately analyzed between methylprednisolone at 0.5 mg/kg twice daily for 5 days versus placebo. METCOVID did not show a mortality difference at day 28 between the groups, and only showed a difference in the subgroup analysis in patients over 60 years old, who had a lower mortality rate. METCOVID also provided evidence on adverse events with worsening diabetes evident from patients in the MP group who required more insulin therapy [49]. These data, especially from the high-powered RECOVERY trial, suggest that corticosteroids (specifically dexamethasone) are one of the mainstays of treatment for COVID-19 to reduce mortality. The data from METCOVID and GLUCOCOVID provides some conflicting evidence whether other corticosteroids can be used, such as methylprednisolone, yet this question explains why healthcare practice and guidelines specify dexamethasone over other alternative corticosteroids.

IL Inhibitors

One of the sets of proinflammatory cytokines, interleukins (IL), have been identified as a risk factor for worsened illness in COVID-19 and as a possible target for inhibition. Primary biomarkers and targets of interest lie with IL-1 and IL-6 [99]. In analysis of patients with severe COVID-19 illness, it was found that patients with more severe illness had higher IL-6 levels and this biomarker seemed to correlate with worse outcomes [4]. As a result, investigation began into the use of IL inhibitors, specifically tocilizumab and subsequently sarilumab for IL-6 and anakinra for IL-1, to identify their role in patients with severe COVID-19.

One of the first studies to document the use of IL inhibitors was with tocilizumab. Reported from China, a single-arm study included 21 patients who received one dose of tocilizumab 400 mg IV in addition to standard of care. Although the follow-up period was relatively short at 2 weeks, 75% of patients experienced improved respiratory function after treatment [63]. This initial trial led many institutions internationally to use IL inhibitors because there were few data to support any COVID-19 treatments at the time. Many centers began using these agents and studying retrospectively whether these agents did indeed lower mortality and lead to better outcomes. Retrospective studies involving tocilizumab used in a non-randomized method with statistical analysis adjusting for propensity scores and illness severity showed favorable outcomes regarding mortality [60, 61]. However, when IL-6 inhibitors were studied in an RCT environment, these results were not replicated. The COVACTA trial was a global, randomized, double-blind, placebo-controlled phase III trial studying whether tocilizumab leads to improved clinical status in COVID-19. An interim report on July 29, 2020, by the trial sponsors showed that there was no difference regarding improved clinical status on a seven-point scale between tocilizumab and placebo (OR [odds ratio] 1.19, 95% CI 0.81, 1.76), no difference in percentage of patients who died by week 4 in either group (difference 0.3%, 95% CI − 7.6%, 8.2%; $p = 0.9410$), and no difference in ventilator-free days [58, 59]. The full results would be submitted for publication in a peer-reviewed journal, but the study was halted at that report after its primary endpoint showed no difference. Simultaneously with this tocilizumab trial that occurred, a phase II–III trial of sarilumab at 400 mg was begun along with minor recruitment of a second cohort of sarilumab at 800 mg compared against placebo. The primary analysis group included 194 patients who were critically ill with COVID-19 and were receiving mechanical ventilation at time of enrollment. This trial with sarilumab was also subsequently halted because it did to not meet its primary endpoint of improvement on a seven-point scale. Detailed results are also pending submission [64]. While initial use of IL inhibitors seemed positive according to early reports and retrospective analyses, RCTs have thus far failed to find any significant outcomes from this treatment. Three subsequent RCTs that have

finalized results for tocilizumab (using 8 mg/kg IV) versus placebo have all failed to find any significant mortality difference with tocilizumab use or any statistical improvement on the WHO clinical progression scale (measuring symptoms/disease progression) [54–57]. While initial hopes for this treatment were high, subsequent RCT data has tempered hopes for this pharmacologic treatment modality. With limited evidence to support the use of tocilizumab, the treatment should now only be used in a restricted manner in the context of further clinical trials.

- Tocilizumab dosing table

Dosing	Initial dose of 400 mg (flat dose) [63] or 4–8 mg/kg (rheum) infused over more than 60 min If initial dose not effective, may administer second dose (in same dosage as initial dose) after 12 h No more than 2 doses should be given; maximum single dose is 800 mg
Adverse effects	Increased risk of infection, injection site reactions, elevated liver enzymes, risk of GI perforation

GI gastrointestinal

Kinase Inhibitors

Both Janus kinase (JAK) inhibitors and Bruton tyrosine kinase (BTK) inhibitors interfere with cytokine signaling by inhibiting their respective enzymes. By impairing the production of pro-inflammatory cytokines, their theorized mechanism of action in the treatment of COVID-19 is to reduce inflammation and frequency of immunopathologies [100].

JAK Inhibitors As described in the following studies, ruxolitinib has demonstrated positive results in recent clinical trials and serves as another potential agent to be considered for patients with COVID-19-associated cytokine storm. After recent completion of a phase II trial, in which 22 patients received ruxolitinib 5 mg PO BID, the results demonstrated safety and efficacy in a small subset of patients with significant improvement on the follow-up chest CT scans at day 14 and a significant decrease in cytokine levels [65]. As a result, phase III clinical trial, named RUXCOVID (NCT04362137), has been initiated and is currently recruiting patients to further assess the safety and efficacy of ruxolitinib 5 mg PO BID or placebo plus standard of care for a total of 14 days in patients with COVID-19-associated cytokine storm [101]. Higher doses, including up to 20 mg BID, have been reported in small, non-randomized, prospective cohort studies without serious adverse effects [66, 102]. However, an Expanded Access Program is open for enrollment of eligible patients with COVID-19-associated cytokine storm, in which they will receive ruxolitinib 5 mg PO twice daily [103]. The remaining JAK inhibitor under investigation for treatment of COVID-19 is tofacitinib, which is FDA approved for the treatment of rheumatoid arthritis [104]. Tofacitinib is currently under a phase II trial, given the name I-TOMIC (NCT04415151), which is recruiting patients for the treatment of moderate COVID-19 [105]. The intervention will be tofacitinib administered in a dose of 10 mg PO BID until return to their clinical baseline (as defined by need for supplementary oxygen), and will continue to be administered at 5 mg PO BID for a total duration of therapy of 14 days. Another JAK inhibitor to mention is baricitinib, which is currently being investigated in the phase III clinical trial ACTT-2 (NCT04401579), which will evaluate the combination of remdesivir and baricitinib compared to remdesivir alone [78]. So far, only the results from a small non-randomized study examining the safety and clinical impact of baricitinib therapy plus lopinavir/ritonavir compared to standard of care (combination lopinavir/ritonavir and hydroxychloroquine) has shown a significant decrease in C-reactive protein (CRP) levels and shorter time to improvement of COVID-19 symptoms [68]. However, this study was unable to demonstrate any efficacy

standard because of the lack of a proper control group.

BTK Inhibitors Acalabrutinib is currently being investigated in an active phase II trial, called CALAVI US (NCT04380688), which aims to assess the safety, efficacy, and pharmacokinetics of acalabrutinib in patients with COVID-19 [106]. Similarly, phase II randomized trial, named iNSPIRE (NCT04375397), is currently recruiting patients to assess safety as well as the impact of ibrutinib on the incidence of respiratory failure in patients with COVID-19 [107]. Until now, the data to support the use of BTK inhibitors for COVID-19 treatment has stemmed from various retrospective trials with small sample sizes, which also lack control groups [69, 70]. Unless data becomes available from the aforementioned phase II trials, the NIH recommends, at this time, against the use of BTK and JAK inhibitors for the treatment of COVID-19, except in a clinical trial [14].

OTHER THEORETICAL/POTENTIAL TREATMENTS

There are a growing number of potential therapies that show in vitro activity, potential in vitro activity, biologically plausible mechanisms of inhibition, and theoretical benefit in patients who are infected or may become infected. The treatments mentioned in Table 4 are by no means a comprehensive list, but it is a list to identify other potential medications that have had increased scrutiny during this pandemic but are somewhat less well known or discussed. All other therapies not mentioned in the above sections show even less evidence of efficacy and safety. Some treatments such as convalescent plasma have been investigated with little evidence of benefit in randomized clinical trials [71, 72]. However, the FDA has released an EUA for convalescent plasma, citing these RCTs among other non-randomized data, concluding that the "potential benefits of the product outweigh the known" risks [108]. The current NIH guidelines do not support the use of convalescent plasma outside of a clinical trial, and the evidence for its broad use in patients to treat COVID-19 is lacking. This treatment, among others, should be assessed with the utmost care regarding risks over benefits, with preference to avoid any therapy in non-clinical trial scenarios until further evidence supporting use is elucidated.

The road to effective COVID-19 pharmacologic options has been a difficult one, and one in which we still do not have robust exciting answers. Dexamethasone remains the drug for treatment of severe COVID-19 that may decrease mortality, and remdesivir has proven to have less of a positive clinical benefit than once thought. Many of the treatments above were used liberally in the early stages of the pandemic with little supportive evidence, and this review should provide context on how evidence can change and evolve when correctly focusing on high-level RCTs to determine treatment efficacy and safety.

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