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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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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.

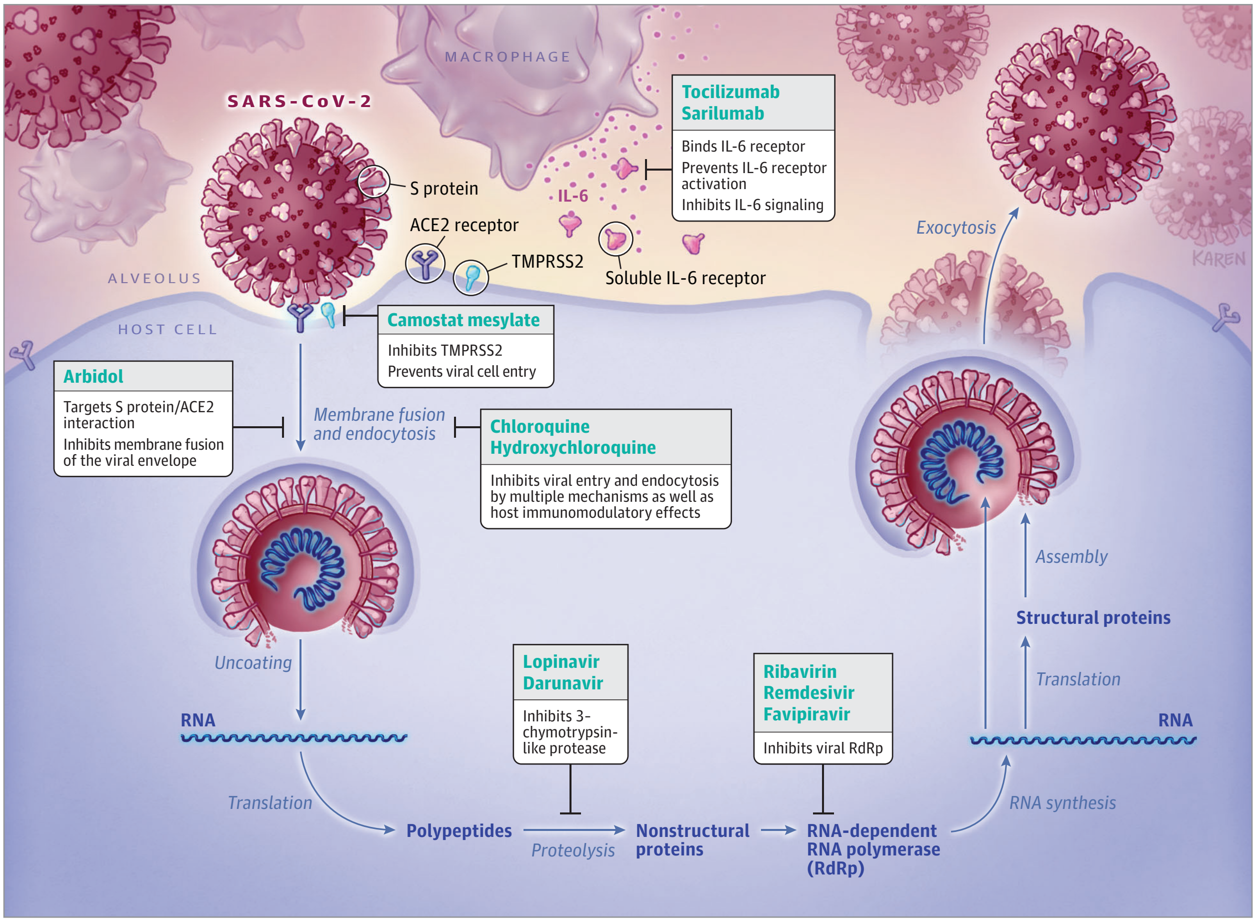
Methods

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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