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Review Article

Overview of Pharmacotherapy for COVID-19 Management

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ABSTRACT

Introduction: the current epidemic of COVID-19 requires a lot of efforts to be controlled involving pharmacotherapy and clinical pharmacology studies. Aim: to introduce a brief review of drugs under investigation for COVID-19. **Methodology:** Our project is a systematic review of many medications being studied for their effectiveness and safety in COVID-19 management. **Results:** Antiviral drugs (osletmivir, ramdisvir), corticosteroids (dexamethasone), immunomodulators (anakinera, toculizumab), antithrombotic (antiplatletes, anticoagulants) are still under investigation although preliminary results are promising. **Conclusion:** Yet, few medications have been approved by FDA for management of COVID-19 but drugs have been used in clinical trials under FDA emergency use authorization. Ongoing clinical trials are essential to establish their long-term safety and effectiveness. Key points: 1. Scientists are testing different medicines, such as antivirals, steroids, immune-boosting drugs, and blood thinners, to see if they can help treat COVID-19. 2. Some of these drugs show early promise, but only a few have official approval for use. 3. More research and clinical trials are needed to make sure these treatments are safe and work well in the long run.

Keywords: COVID-19, Antiviral therapy, Corona virus.

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INTRODUCTION

Coronaviruses (CoVs) are a family of RNA viruses classified under the subfamily Orthocoronavirinae, within the Coronaviridae family and the order Nidovirales. This group includes alpha-, beta-, gamma-, and delta-coronaviruses. Notably, beta-coronaviruses have been responsible for three major outbreaks in the past two decades: Severe Acute Respiratory Syndrome (SARS-CoV) in 2002, Middle East Respiratory Syndrome (MERS-CoV) in 2012, and the ongoing COVID-19 pandemic caused by SARS-CoV-2, first identified in late 2019 (Banerjee *et al*., 2019; The Lancet Oncology, 2020).

As of July 31, 2020, the World Health Organization (WHO) had received extensive global reporting on COVID-19 cases (Figure 1; World Health Organization, 2020). These data underscore the importance of robust clinical and pharmacological responses to curb the pandemic.

Objectives

To introduce a brief review of medications under investigation for COVID-19 management showing their efficacy and safety with evidence by clinical trials

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METHODOLOGY

Our study is a systematic review of many medications being studied for their effectiveness and safety in COVID-19 management. We used PubMed search tool using term "management of COVID-19 by pharmacotherapy" resulting in many clinical trials and few systematic review.

Literature Review

Nutritional interventions

Nutritional Supportive Therapies

Nutritional approaches have gained attention for their potential to modulate immune responses in patients with COVID-19. Vitamins and minerals such as vitamin C, D, and zinc may help reinforce the host defense mechanisms against viral infections. These agents play a supportive role in recovery and are commonly recommended as adjunctive therapy, especially in cases involving immune dysregulation (Figure 2; Zhang and Liu, 2020).

Coronavirus-specific treatments

Coronavirus-specific treatments are shown in Figures 3 and 4 shows a recommendation rating scheme.

Chloroquine/Hydroxychloroquine

These antimalarial compounds initially showed promise due to their ability to interfere with viral entry via the ACE2 receptor. However, data from clinical trials have yielded inconsistent efficacy and raised concerns over cardiac safety, particularly QT interval prolongation, limiting their use to experimental settings

(Savarino *et al*., 2003; Vincent *et al*., 2005; Fang *et al*., 2020; Borba *et al*., 2020; CredibleMeds, 2020; Rosa and Santos, 2020; Chorin *et al*., 2020).

Promazine

As an older antipsychotic, promazine has demonstrated potential antiviral activity by disrupting the viral entry process, but it has not progressed beyond preclinical evaluation (Zhang and Yap, 2004).

Antiviral treatments

Summary of antiviral agents is shown in Figures 5-7.

Lopinavir/ritonavir (Kaletra)

This protease inhibitor combination, used in HIV management, showed modest efficacy in early coronavirus outbreaks. Its use in COVID-19 has been discouraged outside clinical trials due to pharmacokinetic challenges and limited clinical improvement (Tsang and Zhong, 2003; Kim *et al*., 2016; Cao *et al*., 2020).

Remdesivir

A nucleotide analog with broad antiviral properties, remdesivir has demonstrated inhibition of coronavirus replication in animal and human studies. It is frequently administered to hospitalized patients requiring respiratory support, typically in a 5- to 10-day course depending on clinical status (Agostini *et al*., 2018; Sheahan *et al*., 2020; Beigel *et al*., 2020; Goldman *et al*., 2020).

Nelfinavir

Another HIV medication, nelfinavir has shown *in vitro* suppression of SARS-CoV replication and is being considered for further exploration against COVID-19 (Yamamoto *et al*., 2004).

Azithromycin

Known for its anti-inflammatory and immunomodulatory effects, azithromycin has been combined with hydroxychloroquine in early studies. However, this regimen has not shown consistent benefits and may increase cardiac risks (Gautret *et al*., 2020; Molina *et al*., 2020).

Niclosamide and Ivermectin

These antiparasitic agents have shown antiviral activity *in vitro*. Ivermectin, in particular, has demonstrated a rapid reduction in viral RNA levels, but clinical evidence remains limited (Wu *et al*., 2004; Caly *et al*., 2020).

Oseltamivir

Primarily used for influenza, oseltamivir has been included in some investigational combinations against COVID-19, although its individual efficacy remains unclear (Rosa and Santos, 2020).

Immune-Based Therapy Under Evaluation for Treatment of COVID-19

Convalescent Plasma and Immune Globulins

There is currently a lack of conclusive data either supporting or opposing the use of convalescent plasma or SARS-CoV-2-specific immune globulins in treating COVID-19 (Ahn *et al*., 2020; Wang *et al*., 2020; Ye *et al*., 2020; Zeng *et al*., 2020).

Interleukin-1 Inhibitors

Medications like anakinra, which target IL-1, are being investigated for their potential in managing COVID-19-related inflammation. However, data remain insufficient to recommend their use outside of clinical trials (Shakoory *et al*., 2016; Aouba *et al*., 2020; Cavalli *et al*., 2020).

Interleukin-6 Inhibitors

Agents such as tocilizumab, sarilumab, and siltuximab target IL-6 pathways involved in cytokine release syndromes. Despite their theoretical benefits, current evidence is inadequate to suggest routine use in COVID-19 (Press Release, 2020; Sciascia *et al*., 2020).

Interferons (Alfa, Beta)

The COVID-19 Treatment Guidelines Panel advises against the use of interferons in COVID-19 management except within the context of formal clinical trials (Al-Tawfiq *et al*., 2014; Arabi *et al*., 2019).

Janus Kinase Inhibitors (e.g., Baricitinib)

JAK inhibitors, including baricitinib, are not currently recommended for general COVID-19 treatment and should only be administered under controlled clinical research (Richardson *et al*., 2020).

Antithrombotic Therapy in Patients with COVID-19

Chronic Anticoagulant and Antiplatelet Therapy

Patients already prescribed antithrombotic therapy for other conditions should continue their regimen upon COVID-19 diagnosis (AIII).

Venous Thromboembolism Prophylaxis and Screening

Non-hospitalized individuals with COVID-19 should not receive anticoagulation prophylaxis unless another indication exists (AIII). Hospitalized patients should receive standard VTE prophylaxis, but routine post-discharge prophylaxis is not recommended unless specific high-risk factors apply (BI).

Screening and Management

Routine screening for thrombotic events in asymptomatic COVID-19 patients is not supported by current evidence (BIII).

However, if there is rapid clinical deterioration suggestive of thromboembolism, further evaluation and management are warranted (AIII).

Treatment

In cases of confirmed or highly suspected thromboembolism where imaging is not feasible, standard anticoagulant therapy should be initiated (AIII). Patients undergoing ECMO, CRRT, or catheter-based interventions should also receive antithrombotic therapy as per institutional protocols (AIII).

Selection of Anticoagulant or Antiplatelet Drugs for Patients with COVID-19

For hospitalized patients, low molecular weight or unfractionated heparin is preferred due to better control and fewer interactions (AIII). Outpatients on warfarin with limited INR access may transition to direct oral anticoagulants unless contraindicated (American Society of Hematology, 2020).

Other compounds

α-Lipoic acid (ALA)

ALA, long used for liver and nerve-related disorders, exhibits strong antioxidant properties by enhancing intracellular glutathione and neutralizing oxidative stress. It may mitigate viral infectivity by counteracting oxidative damage and G6PD-related vulnerabilities to coronaviruses (Sachse and Willms, 1980; Tibullo *et al*., 2017; El-Senousey *et al*., 2018; Wu *et al*., 2008).

Dexamethasone

As a potent corticosteroid, dexamethasone has shown benefit in reducing inflammation and improving outcomes in patients with severe COVID-19. The RECOVERY trial demonstrated improved survival among ventilated patients or those needing supplemental oxygen (Horby *et al*., 2020). Dexamethasone is not advised in cases without oxygen support (AI) (Molina *et al*., 2020). Chronic corticosteroid users for underlying conditions should continue therapy, possibly with stress-dose adjustments (AIII) (Kaiser *et al*., 2020).

WHO Region	New cases in last 7 days (%)	Change in new cases in last 7 days	Cumulative cases (%)	New deaths in last 7 days (%)	Change in new deaths in last 7 days*	Cumulative deaths (%)
Europe	927 433 (38%)	25%	8 027 954 (20%)	8 386 (23%)	29%	256 540 (23%)
Americas	798 794 (33%)	-1%	18 800 094 (47%)	16 283 (45%)	-21%	608 727 (55%)
South-East Asia	513 444 (21%)	-11%	8 546 666 (21%)	6 864 (19%)	-11%	135 275 (12%)
Eastern Mediterranean	144 133 (6%)	4%	2 786 477 (7%)	3 492 (10%)	10%	70 902 (6%)
Africa	31 473 (1%)	11%	1 267 664 (3%)	1 058 (3%)	8%	28 469 (3%)
Western Pacific	28 317 (1%)	8%	688 737 (2%)	464 (1%)	-27%	14 823 (1%)
† Other	-	-	741 (<1%)	-	-	13 (<1%)
Global	**2 443 594 (100%)**	**6%**	**40 118 333 (100%)**	**36 547 (100%)**	**-8%**	**1 114 749 (100%)**

**Percent change in the number of newly confirmed cases/deaths in past seven days, compared to seven days prior. Regional percentages rounded to the nearest whole number, global totals may not equal 100%.*

Figure 1: COVID-19 Situation in numbers 20/10/2020 (by WHO Region) (Al-Tawfiq *et al*., 2014).

Options	Virus targeted and functions related
2.1. Nutritional interventions	
2.1.1. Vitamin A	Measles virus, human immunodeficiency virus, avian coronavirus
2.1.2. B vitamins	MERS-CoV; ventilator-induced lung injury
2.1.3. Vitamin C	Avian coronavirus; lower respiratory tract infections
2.1.4. Vitamin D	Bovine coronavirus
2.1.5. Vitamin E	Coxsackievirus, bovine coronavirus
2.1.6. Omega-3 polyunsaturated fatty acids (PUFA)	Influenza virus, human immunodeficiency virus
2.1.7. Selenium	Influenza virus, avian coronavirus; viral mutations
2.1.8. Zinc	Measles virus, SARS-CoV
2.1.9. Iron	Viral mutations
2.2. Immunoenhancers	
2.2.1. Interferons	SARS-CoV, MERS-CoV
2.2.2. Intravenous gammaglobulin	SARS-CoV
2.2.3. Thymosin α-1	Increase resistance to glucocorticoid-induced death of thymocyte
2.2.4. Thymopentin	Restore antibody production
2.2.5. Levamisole	Immunostimulant agent or immunosuppressive agent
2.2.6. Cyclosporine A	SARS-CoV, avian infectious bronchitis virus
2.2.7. Chinese medicine	SARS-CoV, avian infectious bronchitis virus

Abbreviations: MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus.

Figure 2: General supportive treatments of COVID-19 (Amici *et al.*, 2006).

Empiric Broad-Spectrum Antimicrobial Therapy

In patients with COVID-19 and intense or vital illness, there are inadequate records to endorse empiric broad-spectrum antimicrobial therapy in the absence of any other indication (BIII).

If antimicrobials are initiated, the Panel recommends that their use must be reassessed every day so that you can decrease the unfavorable effects of needless antimicrobial therapy (AIII).

Considerations for Certain Concomitant Medications in Patients with COVID-19

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

Persons with COVID-19 who are taking NSAIDs for a comorbid condition should continue therapy as previously directed by their physician (AIII). The Panel recommends that there be no distinction in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) among patients with or without COVID-19 (AIII; Patel and Verma, 2020; American College of Cardiology, 2020).

Ibuprofen

Ibuprofen, a Nonsteroidal Anti-Inflammatory Drug (NSAID), is an activator of ACE2 receptors, similar to ACE inhibitors or ARBs. Their utilization can result in an increased hazard of contracting COVID-19 (Fang *et al.*, 2020). Since fatal lung failure triggered through SARS-CoV infections can be managed through blocking the renin-angiotensin pathway (Kuba *et al.*, 2005), ibuprofen might not be harmful. However, there is no strong evidence suggesting a link between NSAID use and worsening symptoms due to SARS-CoV-2 infection.

Indomethacin

Amici *et al.*, (2006) demonstrated that indomethacin, a widely used NSAID and a potential Cyclooxygenase (COX) inhibitor, exhibits antiviral activity against SARS-CoV. Remarkable inhibition of SARS-CoV-infected cells by more than 99% at non-toxic concentrations was also observed. This suggests probable efficacy of indomethacin against SARS-CoV-2.

RESULTS

Nutritional intervention: Vitamins, minerals, and immunomodulators play an important role in enhancing the body's immunity against several viruses, including SARS-CoV (Zhang and Liu, 2020). Chloroquine and hydroxychloroquine are potent inhibitors of SARS coronavirus infection but are not recommended for use outside clinical trials (Savarino *et al.*, 2003).

Currently, many trials are testing the effect of azithromycin in conjunction with hydroxychloroquine on the course of disease in people with SARS-CoV-2, showing its efficacy (Gautret *et al.*, 2020; Molina *et al.*, 2020). However, the azithromycin and hydroxychloroquine combination is not recommended for use outside clinical trials due to potential interactions (e.g., prolonged QT-interval) (Borba *et al.*, 2020; CredibleMeds, 2020; Rosa and Santos, 2020).

Although lopinavir/ritonavir showed potential during the early disease phase in conjunction with interferons, studies have

since shown limited benefit in COVID-19 patients due to poor pharmacokinetics (Cao *et al*., 2020).

Remdesivir has shown efficacy in preclinical studies by reducing viral load and improving lung function. It is currently recommended for hospitalized patients requiring oxygen or mechanical support (Agostini *et al*., 2018; Sheahan *et al*., 2020; Beigel *et al*., 2020).

Nelfinavir has also demonstrated significant inhibitory effects on SARS-CoV replication and may be a candidate for further COVID-19 trials (Yamamoto *et al*., 2004). Oseltamivir, while effective against influenza, is being studied in combination with other drugs for potential use against SARS-CoV-2 (Rosa and Santos, 2020).

Niclosamide and ivermectin both show strong *in vitro* antiviral properties, with ivermectin reducing viral RNA by thousands-fold within 48 hr (Caly *et al*., 2020; Wu *et al*., 2004).

ALA acts as an antioxidant, potentially reducing oxidative stress and related complications during viral infection, including COVID-19 (Tibullo *et al*., 2017; Wu *et al*., 2008).

Dexamethasone has proven clinical benefit in patients requiring respiratory support by dampening systemic inflammation (Horby *et al*., 2020).

Use of broad-spectrum antibiotics is discouraged unless secondary infection is suspected. Convalescent plasma, IL-1/IL-6 inhibitors, interferons, and baricitinib remain under investigation and are not yet recommended for routine care (Ahn *et al*., 2020; Shakoory *et al*., 2016; Cavalli *et al*., 2020; Sciascia *et al*., 2020; Al-Tawfiq *et al*., 2014; Richardson *et al*., 2020).

Convalescent Plasma and Immune Globulins

There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immune globulins for the treatment of COVID-19 (Ahn *et al*., 2020; Ye *et al*., 2020; Zeng *et al*., 2020).

3.1. Coronavirus protease inhibitors
3.1.1. Chymotrypsin-like (3C-like) inhibitors
3.1.1.1. Cinanserin
3.1.1.2. Flavonoids
3.1.2. Papain-like protease (PLP) inhibitors
3.1.2.1. Diarylheptanoids

3.2. Spike (S) protein-angiotensin-converting enzyme-2 (ACE2) blockers
3.2.1. Human monoclonal antibody (mAb)
3.2.2. Chloroquine
3.2.3. Emodin
3.2.4. Promazine
3.2.5. Nicotianamine

Figure 3: Coronavirus-specific treatments (Amici *et al*., 2006).

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, nonrandomized trials or observational cohort studies
C: Optional recommendation for the statement	**III:** Expert opinion

Figure 4: Recommendation Rating Scheme.

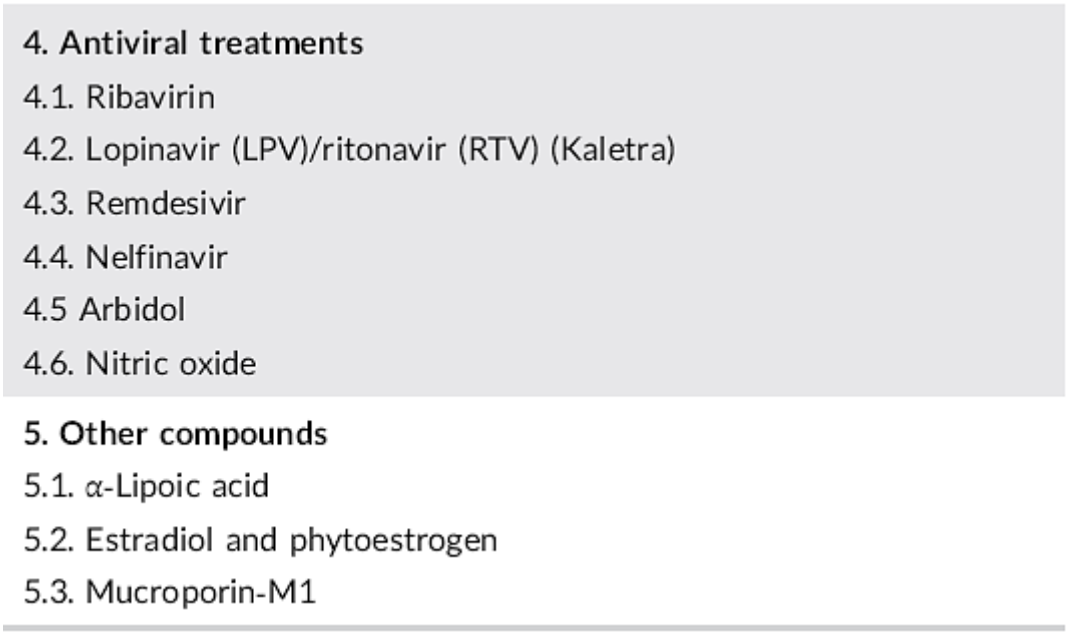

Figure 5: Antiviral drugs for COVID-19.

Antithrombotic Therapy

Antithrombotic interventions, including heparins and oral anticoagulants, are used only when clinically indicated. Choice of drug depends on the patient's condition and setting, with LMWH and UFH preferred in hospitalized patients (American Society of Hematology, 2020).

Anakinra

There are insufficient data to recommend either for or against the use of interleukin-1 (IL-1) inhibitors, such as anakinra, for the treatment of COVID-19 (Aouba *et al*., 2020; Cavalli *et al*., 2020).

Tocilizumab

There are insufficient data to recommend either for or against the use of interleukin-6 (IL-6) inhibitors (tocilizumab) for the treatment of COVID-19 (Press Release, 2020; Sciascia *et al*., 2020).

Interferons

It is not recommended to use interferons for the treatment of COVID-19, except in the context of a clinical trial (Al-Tawfiq *et al*., 2014; Arabi *et al*., 2019).

Baricitinib

It is not recommended to use Janus kinase (JAK) inhibitors (e.g., baricitinib) for the treatment of COVID-19, except in the context of a clinical trial (Richardson *et al*., 2020).

Antithrombotic Therapy

Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease at a time when imaging is not possible should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19. Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy per institutional protocols. Low molecular weight heparin or unfractionated heparin may be preferred in hospitalized, critically ill patients because of their shorter half-lives, ability to be administered intravenously or subcutaneously, and fewer drug-drug interactions compared with oral anticoagulants. Outpatients receiving warfarin who are unable to get international normalized ratio monitoring during isolation may be candidates for direct oral anticoagulant therapy. Patients with mechanical heart valves, ventricular assist devices, valvular atrial fibrillation, or antiphospholipid antibody syndrome or patients who are lactating should continue treatment with warfarin therapy (American Society of Hematology, 2020).

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

It is not recommended to use ACE inhibitors or ARBs for the treatment of COVID-19 outside the setting of a clinical trial (Patel and Verma, 2020).

HMG-CoA Reductase Inhibitors (Statins)

It is not recommended to use statins for the treatment of COVID-19 outside the setting of a clinical trial (Fedson *et al*., 2020).

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Azithromycin (When Used with Hydroxychloroquine)	500 mg PO once on Day 1, then 250 mg PO daily on Days 2–5	• Gastrointestinal effects (e.g., diarrhea, nausea, vomiting) • Hepatotoxicity	• Baseline/follow-up ECG • Hepatic panel, SCr, potassium, magnesium	Additive effect with other drugs that prolong the QTc interval (including HCQ and CQ)	• The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Half-life of up to 72 hours • A list of clinical trials is available here: Azithromycin
Chloroquine	**Dose Previously Suggested in an EUA for Adults and Adolescents Weighing ≥50 kg:** • 1 gm PO once on Day 1, then 500 mg PO once daily for 4–7 days of total treatment based on clinical evaluation.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting, diarrhea, hepatitis) • Hypoglycemia • Hemolysis (especially in patients with G6PD deficiency) • Myopathy • Rash • Given the risk of heart rhythm problems, the FDA cautions against using CQ to treat COVID-19 outside of a hospital or a clinical trial.[1]	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline/follow-up ECG if CQ is given with concomitant QTc-prolonging drugs or if the patient has underlying cardiac disease • Perform G6PD testing; CQ **is not recommended** in patients with G6PD deficiency. Consider using HCQ instead of CQ while awaiting G6PD test results.	• Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• The Panel **recommends against** the use of CQ for the treatment of COVID-19, except in a clinical trial **(AII)**. • The Panel **recommends against** using high-dose CQ (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**. • Dose-dependent toxicity • CQ is not commercially available in the United States • A list of clinical trials is available here: Chloroquine
Hydroxychloroquine	**Adults:** • Various loading and maintenance doses have been reported in studies or in clinical care. **Dose Previously Suggested in an EUA for Hospitalized Adults and Adolescents Weighing ≥50 kg:** • 800 mg PO once on Day 1, then 400 mg PO once daily for 4–7 days of total treatment based on clinical evaluation.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia • Myopathy • Anxiety, agitation, hallucinations, psychosis • Allergic reaction/rash • Given the risk of heart rhythm problems, the FDA cautions against the use of HCQ to treat COVID-19 outside of a hospital or a clinical trial.[1]	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if HCQ is given with concomitant QTc-prolonging drugs (e.g., AZM) or if the patient has underlying cardiac diseases	• Additive effect with other drugs that prolong the QTc interval (including AZM) or cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• The Panel **recommends against** HCQ for the treatment of COVID-19, except in a clinical trial **(AII)**. • The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Available through EUA for hospitalized patients who cannot access HCQ via clinical trials. • Long elimination; half-life is 40–55 days. • Dose-dependent toxicity • A list of clinical trials is available here: Hydroxychloroquine

A

Lopinavir/Ritonavir	**Adults:** • LPV/r 400 mg/100 mg PO twice daily for 10–14 days **Neonates Aged ≥14 Days with a PMA ≥42 Weeks and Children Aged <18 Years:** • LPV 300 mg/m² plus RTV 75 mg/m² (maximum: LPV/r 400 mg/100 mg per dose) PO twice daily for a total of 7 days	• Nausea, vomiting, diarrhea • Transaminase elevation • QTc interval prolongation and Torsades de Pointes have been reported. • PR interval prolongation	• HIV antigen/ antibody testing at baseline • Serum transaminase levels • Consider monitoring ECG when LPV/r is given with other QTc-prolonging medications.	**High Drug Interaction Potential** *Lopinavir:* • CYP3A4 inhibitor and substrate *Ritonavir:* • CYP3A4 > 2D6 substrate • Potent CYP3A4 and 2D6 inhibitor • Inducer of UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19	• The Panel **recommends against** the use of LPV/r and other HIV PIs for the treatment of COVID-19, except in a clinical trial **(AI)**. • Liquid formulation is commercially available. Crushing LPV/r tablets may result in significantly decreased drug exposure (AUC ↓ 45%).[2] • Use with caution in patients with hepatic impairment. • A list of clinical trials is available here: Lopinavir/ Ritonavir
Remdesivir *Investigational drug. Remdesivir is not approved by the FDA; however, it is available through an EUA,[a] a clinical trial, or the manufacturer's emergency access program.*	**In Patients Who Are Participating in Clinical Trials:** • Dose according to clinical trial protocol. **Panel's Recommendations for Adult and Pediatric Patients Weighing >40 kg** *For Patients with Severe COVID-19 Who Are Not Intubated:* • RDV 200 mg IV over 30–120 minutes for one dose, followed by RDV 100 mg IV on Day 2 through Day 5 **(AI)**. *For Mechanically Ventilated Patients, Patients on ECMO, and Patients Who Have Not Shown Adequate Improvement After 5 Days of Therapy:* • There are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, and	• Transient elevations in ALT or AST levels (Grade 1 or 2), typically after multiple days of therapy[3] • Mild, reversible PT prolongation without INR change or hepatic effects[3] • Drug vehicle is SBECD, which has been associated with renal toxicity. Potential for SBECD accumulation in patients with moderate to severe renal impairment • Gastrointestinal symptoms (e.g., nausea, vomiting)	• Monitor for infusion reactions. • Renal and hepatic function • **Do not administer** RDV if eGFR <30 mL/min (or if patient is receiving dialysis) or if ALT or AST level is >5 times ULN	• RDV levels are unlikely to be markedly altered by CYP2C8, CYP2D6, or CYP3A4 enzymes, or by P-gp or OATP drug transporters. RDV may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP or P-gp.	**For Patients with Severe COVID-19:** • The Panel recommends RDV for treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on ambient air (at sea level) or those who require supplemental oxygen **(AI)**, and in patients who are on mechanical ventilation or ECMO **(BI)**. **For Patients with Mild to Moderate COVID-19:** • There are insufficient data to recommend for or against RDV for the treatment of patients with mild or moderate COVID-19.
Remdesivir, continued	patients who have not shown adequate improvement after 5 days of therapy. Some experts extend the total RDV treatment duration to up to 10 days **(CIII)**. **Note:** The EUA recommends 10-day therapy for patients on mechanical ventilation or ECMO. **Suggested Dose in EUA[b] for Pediatric Patients Weighing 3.5 to <40 kg** *Requiring Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg mg IV over 30–120 minutes for one dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 10 *Not Requiring Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg mg IV over 30–120 minutes for one dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 5. If no clinical improvement, may extend treatment for up to 5 additional days (for a total treatment duration of 10 days)			• Strong induction of P-gp is expected to modestly reduce RDV levels. The clinical relevance of lower RDV levels is unknown. The use of RDV with known inducers of P-gp (e.g., rifampin) **is not recommended**.	**Availability:** • RDV is available through an EUA[b] for the treatment of hospitalized adults and children with severe COVID-19. • RDV is also available for other patient populations through expanded access and compassionate use programs. • A list of clinical trials is available here: Remdesivir

[a] The FDA EUA permits the emergency use of the investigational product RDV for the treatment of suspected COVID-19 or laboratory-confirmed COVID-19 in adults and children who have been hospitalized with severe disease. Severe disease is defined as COVID-19 in patients with SpO_2 ≤94% on ambient air (at sea level) or in patients who require supplemental oxygen, mechanical ventilation, or ECMO.

B

Figure 6: Characteristics of Potential Antiviral Agents Under Evaluation for COVID-19 (Food and Drug Administration, 2020).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

There should be no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 (Food and Drug Administration, 2020; Bancos *et al*., 2009).

Ibuprofen is an activator of ACE2 receptors; its usage can lead to increased risk of contracting COVID-19 (Fang *et al*., 2020).

Indomethacin

Indomethacin exhibits antiviral activity against SARS-CoV. Remarkable inhibition against SARS-CoV-infected Vero cells by more than 99% at concentrations that were non-toxic for uninfected cells has also been observed. This suggests probable efficacy of indomethacin against SARS-CoV-2 (Amici *et al*., 2006).

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood Products					
COVID-19 Convalescent Plasma and SARS-CoV-2 Immune Globulins	Single or multiple transfusions based on patient response	• TRALI and TACO have been reported.[1] • Fever, allergic reactions ranging from urticaria to anaphylaxis (rare) • Transmission of infectious pathogens • Antibody-mediated enhancement of infection • Red cell alloimmunization	Monitor for transfusion-related reactions. Observe the patient and measure vital signs at baseline and during and after transfusion.	Drug products **should not be added** to the IV infusion line for the blood product.	• There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immune globulins for the treatment of COVID-19. • The FDA has provided guidance for the use of COVID-19 convalescent plasma under an emergency IND application. • The FDA has approved a national expanded access program for the use of convalescent plasma for the treatment of patients with COVID-19. Clinicians can refer to the National COVID-19 Convalescent Plasma Project website for more information. People who have fully recovered from COVID-19 for at least 2 weeks and are interested in donating plasma can contact their local blood donor or plasma collection center or refer to the American Red Cross website. • A list of clinical trials is available: Convalescent Plasma and Immune Globulin
Blood Products, continued					
Non-SARS-CoV-2 Specific Intravenous Immune Globulin	Doses vary based on indication and formulation.	• Thrombotic events • Renal dysfunction and acute renal failure (more common with certain products) • Flu-like symptoms, dermatologic effects, arrhythmia, TRALI, anaphylaxis, aseptic meningitis, and hemolysis • AEs may be precipitated by high dose, rapid infusion, or underlying conditions, including IgA-deficiency. AEs may vary between formulations. • Consider the risks and benefits of the high-dose regimen in patients with increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.	• Observe the patient and measure vital signs at baseline and during and after infusion. • Discontinue if renal function deteriorates during treatment.	IVIG may interfere with immune response to certain vaccines.	• The Panel **recommends against** the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in a clinical trial (**AIII**). This should not preclude the use of IVIG when otherwise indicated for treatment of complications that arise during COVID-19. • A list of clinical trials is available: Intravenous Immunoglobulin

A

Interferons					
Interferon Alfa	Peginterferon alfa-2a 180 mcg SQ once weekly for 2 weeks for MERS[2,3]	Flu-like symptoms (e.g., fever, fatigue, myalgia), injection site reactions, liver function abnormalities, decreased blood counts, worsening of depression, insomnia, irritability, nausea, vomiting, and hypertension[4]	• CBC with differential • LFTs (ALT); avoid if Child-Pugh Score >6 • Depression, psychiatric symptoms • Reduce dose in patients with CrCl <30 mL/min.	• Low potential for drug interactions • Inhibition of CYP1A2	• The Panel **recommends against** the use of IFN alfa, except in a clinical trial **(AIII)**. • For MERS, SQ formulation used in combination with ribavirin. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN; discontinue if accompanied by increase in bilirubin. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon
Interferon Beta	**IFN Beta-1a:** • 44 mcg SQ three times weekly[3] for MERS • Duration for COVID-19 unknown • SNG001 (this formulation delivered by nebulization is not approved in the United States). **IFN Beta-1b:** • 0.25 mg SQ every 48 hours for MERS[5] • Duration unknown	Flu-like symptoms (e.g., fever, fatigue, myalgia), leukopenia, neutropenia, thrombocytopenia, lymphopenia, increased liver enzymes (ALT > AST), injection site reactions, headache, hypertonia, pain, rash, and worsening of depression[6,7]	• LFTs • CBC with differential • Worsening CHF • Depression, suicidal ideation	Low potential for drug interactions	• The Panel **recommends against** use of IFN beta, except in a clinical trial **(AIII)**. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • Several products are available in the United States; doses differ between products. **IFN Beta-1a Products:** • Avonex, Rebif **IFN Beta-1b Products:** • Betaseron, Extavia • A list of clinical trials is available: Interferon
Interleukin-1 Inhibitor					
Anakinra	• Standard adult dose is 100 mg SQ once daily • Duration unknown	• Neutropenia (particularly in combination with other agents that can cause neutropenia) • Anaphylaxis • Headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, and abdominal pain • Injection site reactions	• CBC • Renal function (reduce dose in patients with CrCl <30 mL/min)	Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	• There are insufficient data for the Panel to recommend for or against the use of IL-1 inhibitors (e.g., anakinra) for the treatment of COVID-19. • A list of clinical trials is available: Anakinra
Tocilizumab[11]	**Clinical Trial Dosing:** • 8 mg/kg IV once • Dose **should not exceed** 800 mg. • Dose may be repeated once, 12 hours later, if clinical symptoms worsen or show no improvement (see NCT04320615).	• Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and LFTs • Hepatitis B reactivation	• Monitor for HSR • Monitor for infusion reactions • Neutrophils, platelets • LFTs	• Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• There are insufficient data for the Panel to recommend for or against the use of tocilizumab for the treatment of COVID-19. • SQ formulation **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab
Janus Kinase Inhibitor					
Baricitinib[12]	• 2 mg PO once daily for rheumatoid arthritis • Duration unknown	• Lymphoma and other malignancies • Thrombosis • Gastrointestinal perforation • Treatment-related changes in lymphocytes, neutrophils, hemoglobin, liver enzymes • Herpes simplex • Herpes zoster	• Treatment-related decreases in neutrophils, lymphocytes, and hemoglobin • Renal and hepatic function • Monitor for new infections	Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor.	• The Panel **recommends against** the use of baricitinib, except in a clinical trial **(AIII)**. • **Not recommended** in patients with severe hepatic or renal impairment. • A list of clinical trials is available here: Baricitinib

B

Figure 7: Characteristics of Immune-Based Therapy Under Evaluation for Treatment of COVID-19 (Food and Drug Administration, 2020).

DISCUSSION

As shown in our results, clinical trials are still in progress and until now there are no definitive results for the efficacy of studied medications for management of COVID-19. Although preliminary findings for some medications are promising, others show that harms may outweigh benefits.

Nutritional interventions should be initiated as early as diagnosis is suspected to enhance patient immunity against respiratory viruses and any opportunistic bacterial respiratory infections (Zhang and Liu, 2020).

Chloroquine, hydroxychloroquine, lopinavir/ritonavir, anakinra, tocilizumab, interferons, baricitinib, ACE inhibitors, ARBs, and statins are still not recommended for COVID-19 management except in clinical trials (Vincent *et al*., 2005; Cao *et al*., 2020; Aouba *et al*., 2020; Cavalli *et al*., 2020; Sciascia *et al*., 2020; Al-Tawfiq *et al*., 2014; Arabi *et al*., 2019; Richardson *et al*., 2020; Patel and Verma, 2020; Fedson *et al*., 2020).

Remdesivir, nelfinavir, azithromycin, niclosamide, ivermectin, oseltamivir, indomethacin, convalescent plasma, and immune globulins have shown antiviral activity against SARS-CoV-2, though clinical trials are still in progress (Rosa and Santos, 2020; Beigel *et al*., 2020; Caly *et al*., 2020; Wu *et al*., 2004; Amici *et al*., 2006; Ahn *et al*., 2020; Ye *et al*., 2020).

Dexamethasone has shown improvement in COVID-19 patients who developed Systemic Inflammatory Response Syndrome (SIRS) and pulmonary inflammation (Horby *et al*., 2020).

ALA, due to its antioxidant effects, may help mitigate complications linked to viral oxidative stress (Tibullo *et al*., 2017; Wu *et al*., 2008).

Antithrombotic therapy is not used unless there is a clear indication for either prophylaxis or treatment. Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) are favored for critically ill patients, while Direct Oral Anticoagulants (DOACs) or warfarin are appropriate for stable outpatients when monitoring is feasible (American Society of Hematology, 2020).

For hospitalized, critically ill patients, LMWH or UFH may be preferred because of their shorter half-lives, intravenous or subcutaneous administration, and fewer drug-drug interactions compared with oral anticoagulants. For outpatients, warfarin or DOACs are preferred. In cases where international normalized ratio monitoring is not possible during isolation, DOAC therapy is recommended. Patients with mechanical heart valves, ventricular assist devices, valvular atrial fibrillation, or antiphospholipid antibody syndrome or lactating patients should continue warfarin therapy (American Society of Hematology, 2020).

CONCLUSION

Finally, treating physicians should consider patients' co-morbidities and efficacy of medications used in patient management. Cardiac patients taking antiarrhythmic drugs should avoid medications causing QT-interval prolongation (azithromycin, chloroquine and hydroxychloroquine). Corticosteroids using in hypertensive and diabetic patients require monitoring BP and RBG. Nutritional interventions (ex: vitamin C and zinc) have important role in enhanching immunity against viral infection on long term use.

Medications that show antiviral activity against COVID-19, have proven benefits in SARS-COV2 management (remedisvir, nilfenvir, oseltamvir, azithromycin, ivermectin, niclosamid). Corticosteroids improve SIRS and respiratory symptoms associated with COVID-19 infection.

ALA has antioxidant activity and prevents oxidative stress and neuropathy associated with viral infection.

Anti-thrombotic therapy is used only when there is an indication for its use whether treatment or prophylaxis. Injectable anticoagulants are preferred in hospitalized patients while warfarin and direct oral anticoagulants are preferred in outpatients.

Other medications still do not show benefits in COVID-19 management and their use is limited to clinical trials (Chloroquine, hydroxychloroquine, Lopinavir/ritonavir, anakinra, tocilizumab, Interferons, Baricitinib, ACEIs, ARBs and statins).

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ABBREVIATIONS

ACE2: Angiotensin-Converting Enzyme 2; **ACEIs:** Angiotensin-Converting Enzyme Inhibitors; **AE:** Adverse Effect; **ALA:** α-Lipoic Acid; **ALT and AST:** Alanine Transaminase and Aspartate Aminotransferase; **ARBs:** Angiotensin Receptor Blockers; **AUC:** Area Under the Curve; **AV:** Atrioventricular; **AZM:** Azithromycin; **CBC:** Complete Blood Count; **CoVs:** Coronaviruses; **COVID-19:** Coronavirus Induced Disease 2019; **CQ:** Chloroquine; **CYP:** Cytochrome P; **ECG:** Electrocardiogram; **ECMO:** Extracorporeal Membrane Oxygenation; **EUA:** Emergency Use Authorization; **eGFR:** Estimated Glomerular Filtration Rate; **FDA:** Food and Drug Administration; **G6PD:** Glucose-6-Phosphate Dehydrogenase; **GFR:** Glomerular Filtration Rate; **GSH:** Glutathione; **HCQ:** Hydroxychloroquine; **HIV:** Human Immunodeficiency Virus; **INR:** International Normalized Ratio; **IV:** Intravenous; **LPV:** Lopinavir; **LPV/r:** Lopinavir/Ritonavir; **MERS:** Middle East Respiratory Syndrome; **NSAIDs:** Nonsteroidal Anti-Inflammatory Drugs; **OATP:** Organic Anion Transporter Polypeptide; **P-gp:** P-Glycoprotein; **PI:** Protease Inhibitors; **PM:** Postmenstrual Age; **PO:** Orally; **PT:**

Prothrombin Time; **RDV:** Remdesivir; **RTV:** Ritonavir; **SARS:** Severe Acute Respiratory Syndrome; **SBECD:** Sulfobutylether Beta-Cyclodextrin Sodium; **SCr:** Serum Creatinine; **UGT:** Uridine Diphosphate Glucuronyl Transferase; **ULN:** Upper Limit of Normal; **WHO:** World Health Organization.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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