Clinical update on COVID-19 for the emergency and critical care clinician: Medical management

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ABSTRACT

Introduction: Coronavirus disease of 2019 (COVID-19) has resulted in millions of cases worldwide. As the pandemic has progressed, the understanding of this disease has evolved.
Objective: This is the second part in a series on COVID-19 updates providing a focused overview of the medical management of COVID-19 for emergency and critical care clinicians.
Discussion: COVID-19, caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), has resulted in significant morbidity and mortality worldwide. A variety of medical therapies have been introduced for use, including steroids, antivirals, interleukin-6 antagonists, monoclonal antibodies, and kinase inhibitors. These agents have each demonstrated utility in certain patient subsets. Prophylactic anticoagulation in admitted patients demonstrates improved outcomes. Further randomized data concerning aspirin in outpatients with COVID-19 are needed. Any beneficial impact of other therapies, such as colchicine, convalescent plasma, famotidine, ivermectin, and vitamins and minerals is not present in reliable medical literature. In addition, chloroquine and hydroxychloroquine are not recommended.
Conclusion: This review provides a focused update of the medical management of COVID-19 for emergency and critical care clinicians to help improve care for these patients.

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1. Introduction

Coronavirus disease of 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), is a global pandemic, with the first outbreak in late 2019 in Wuhan, Hubei Province, China [1-4]. The virus spread rapidly around the world and was initially declared a pandemic on March 11, 2020 [1,2]. As of February 27, 2022, over 435 million cases have occurred worldwide, with over 5.9 million deaths [4]. In the United States, there have been over 78.9 million confirmed cases and over 948,000 deaths [4]. This pandemic has resulted in significant challenges worldwide, and our understanding of this disease continues to evolve. This paper is the second in a series that provides a focused update on the medical management of COVID-19 for emergency medicine and critical care physicians. This review will not cover emergent resuscitation or airway interventions including noninvasive ventilation, endotracheal intubation and mechanical ventilation, and proning, but rather current medical treatments for COVID-19 [5-8].

2. Methods

A literature review of PubMed and Google Scholar databases was performed for articles up to February 25, 2022, using the keywords 'COVID' OR 'COVID-19' OR 'SARS-CoV-2' OR 'coronavirus' for this narrative review. The authors included retrospective and prospective studies, systematic reviews and meta-analyses, and other narrative reviews. Guidelines and international/national organization websites were also included. The literature search was restricted to studies published or translated into English. Authors reviewed all relevant articles and

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decided which studies to include for the review by consensus, with focus on emergency medicine-relevant articles, including guidelines. A total of 165 resources were selected for inclusion in this review.

3. Discussion

A variety of therapies have been investigated for use in COVID-19 for the outpatient, emergency department, and critical care settings. These include steroids, antivirals, interleukin-6 (IL-6) antagonists, monoclonal antibodies, kinase inhibitors, chloroquine and hydroxychloroquine, colchicine, convalescent plasma, famotidine, fluvoxamine, ivermectin, and vitamins and minerals [9,10]. The following discussion will provide a description of the current available evidence for each of these treatments in patients with COVID-19. Table 1 lists currently recommended therapies, and Table 2 provides specific details concerning these medications.

3.1. Steroids

The use of steroids in patients with COVID-19 has been extensively evaluated [10–18]. Current evidence suggests steroids can reduce all-cause mortality at 28 days in patients requiring supplemental oxygen, with no association between steroids and serious adverse events [9-12]. A meta-analysis of 7 randomized controlled trials (RCTs) found an odds ratio (OR) of 0.66 (95% confidence interval (CI) 0.53 to 0.82) and a reduction in mortality by 8% (32% from 40%) with use of steroids in critically patients with COVID-19 [11]. This meta-analysis found dexamethasone in particular was associated with reduced mortality (odds ratio [OR] 0.64, 95% confidence interval [CI] 0.50 to 0.82), but methylprednisolone was evaluated in one included RCT with 47 patients and was not associated with reduced mortality (OR 0.91, 95% CI 0.29 to 2.87) [11]. Current guidelines recommend dexamethasone be used in hospitalized patients with either severe or critical disease (defined as oxygen saturation ≤ 94% on room air or on supplemental oxygen, admitted to the intensive care unit [ICU], septic shock, mechanically ventilated, extracorporeal membrane oxygenation [ECMO], end organ dysfunction, or acute respiratory distress syndrome [ARDS]) [9,10]. Steroids should not be used in patients with COVID-19 who do not require oxygen supplementation.

Most recommendations for steroid administration include dexamethasone, which lacks mineralocorticoid activity and likely has minimal effect on sodium and fluid balance [18]. Dexamethasone may be given 6 mg IV or PO for either 10 days or until discharged in those requiring supplemental oxygen [10,18]. The COVID STEROID 2 trial included 982 patients and compared dexamethasone 12 mg versus 6 mg in patients with COVID-19 requiring at least 10 L/min of oxygen or mechanical ventilation. Authors found no difference in median number of days alive without life support (adjusted mean difference 1.3 days, 95% CI 0 to 2.6 days) or mortality at 28 days (27.1% vs. 32.3%, adjusted relative risk 0.86, 95% CI 0.68 to 1.08) [13,14]. However, this study may have been underpowered to detect a difference in delays alive without life support or mortality [14]. A preplanned secondary analysis of the COVID STEROID 2 trial including patients with severe hypoxia (those requiring >10 L of oxygen or on noninvasive ventilation) found that when compared with 6 mg daily, 12 mg daily for up to 10 days increased days alive without life support by 1.3 days, with no difference in adverse events [14]. The CoDEX study found that patients with COVID-19 and moderate to severe ARDS treated with higher dose IV dexamethasone (20 mg once daily for 5 days followed by 10 mg daily for 5 days or until ICU discharge in combination with standard care) had greater ventilator-free days compared to standard care alone (6.6 days vs. 4.0 days; difference 2.26 days, 95% CI 0.2 to 4.38) [15]. One single center retrospective study found methylprednisolone 1 mg/kg/day for ≥3 days was associated with reduced risk of 50-day mortality versus dexamethasone 6 mg/day for ≥7 days in mechanically-ventilated patients only (RR 0.480, 95% CI 0.235 to 0.956) [16]. In patients not requiring

Table 1
National Institutes of Health (NIH) medication recommendations.

Setting	NIH Recommendations
Outpatient	• First line - Paxlovid (nirmatrelvir 300 mg plus ritonavir 100 mg) orally twice daily for 5 day) • Second line - Sotrovimab 500 mg administered as a single IV infusion • Third line - Remdesivir 200 mg IV on Day 1 followed by remdesivir 100 mg IV on Days 2 and 3 • Fourth line - Molnupiravir 800 mg orally twice daily for 5 days
Hospitalized Without Hypoxia	• No steroids • Can consider remdesivir for those at high risk for worsening disease. Dosed 200 mg IV once, then 100 mg IV daily x 4 days or until discharge
Hospitalized – Requiring Supplemental Oxygen	• Dexamethasone 6 mg IV or PO (or methylprednisolone 32 mg or prednisone 40 mg) daily for up to 10 days (or discharge) and remdesivir (especially if increasing oxygen requirement) • Remdesivir 200 mg IV once, then 100 mg IV daily x 4 days or until discharge • Dexamethasone (can be used alone if remdesivir unavailable)
Hospitalized – Requiring High-Flow Nasal Cannula or NIV	• Dexamethasone 6 mg IV or PO (or methylprednisolone 32 mg or prednisone 40 mg) daily for up to 10 days (or discharge) • Dexamethasone and remdesivir 200 mg IV once, then 100 mg IV daily x 4 days or until discharge • If recently hospitalized and increasing oxygen requirement, consider adding: ○ Barcitinib or IV tocilizumab. Tocilizumab is given as single dose, 8 mg/kg actual body weight, up to 800 mg maximum. Baricitinib is renally dosed. Given for up to 14 days or discharge from hospital. ○ eGFR ≥60 mL/min: 4 mg PO daily ○ eGFR 30–59 mL/min: 2 mg PO daily ○ eGFR 15 to-29: 1 mg PO daily ○ eGFR <15: Not recommended. • Alternatives are tofacitinib or IV sarilumab. Tofacitinib is given 10 mg PO BID for up to 14 days or until discharge. For Sarilumab, must use single-dose prefilled syringe for SC administration, then reconstitute 400 mg into 100 cc of 0.9% NaCl, given as an IV infusion for 1 h. • If elevated inflammatory markers, tocilizumab (or sarilumab if unavailable) and steroids should be given. • If steroids are contraindicated, the combination of baricitinib and remdesivir can be considered
Hospitalized - Intubated or ECMO	• Dexamethasone 6 mg IV or PO (or methylprednisolone 32 mg or prednisone 40 mg) daily for up to 10 days (or discharge) • Within 24 h of admission to the ICU, dexamethasone and IV tocilizumab (preferred) (single dose, 8 mg/kg actual body weight, up to 800 mg max dose) or IV sarilumab (must use single-dose prefilled syringe for SQ administration, then reconstitute 400 mg into 100 cc of 0.9% NaCl, given IV infusion for 1 h). • If elevated inflammatory markers, tocilizumab (or sarilumab if unavailable) and steroids should be given.

GFR, glomerular filtration rate; kg, kilograms; IU, international units; IV, intravenous; mg, milligrams; mL, milliliters; PO, per oral; SC, subcutaneous; U, units; QD, once daily; BID, 2 times per day; TID, 3 times a day; ECMO, extracorporeal membrane oxygenation.

mechanical ventilation, both steroids reduced mortality, with no difference in overall mortality between methylprednisolone and dexamethasone (RR 0.635, 95% CI 0.326 to 1.218) [16]. However, a retrospective study including 1379 patients of receiving steroids suggests higher

Table 2
COVID-19 Medication Considerations.

Treatment	Dosage	Consideration
Steroids - Dexamethasone - Prednisone - Methylprednisolone - Hydrocortisone	- Dexamethasone 6 mg IV or PO once daily for 10 days or discharge from hospital in those with hypoxia - Daily equivalents of other agents to dexamethasone 6 mg are hydrocortisone 160 mg methylprednisolone 32 mg, or prednisone 40 mg - Dexamethasone 12 mg IV should be considered for those with severe hypoxia	- Prednisone and methylprednisolone should be given either once daily or as two divided doses - Hydrocortisone should be given in two to four divided doses each day
Antivirals - Remdesivir - Molnupiravir - Paxlovid	- Remdesivir dosed at 200 mg IV x 1, then 100 mg IV daily for 4 days or discharge from hospital (or 200 mg IV on day one followed by 100 mg IV on days 2 and 3 in the outpatient setting) - Paxlovid: Nirmatrelvir 300 mg and ritonavir 100 mg PO twice daily for 5 days (GFR > 60); if moderate renal impairment (GFR 30–59), use nirmatrelvir 150 mg and ritonavir 100 mg PO twice daily for 5 days; not recommended if GFR < 30 - Molnupiravir dosed at 800 mg PO every 12 h for 5 days	- Can extend remdesivir course up to 10 days if no significant improvement by day 5 in inpatients - Remdesivir may be used for high-risk outpatients - Remdesivir not recommended for patients with eGFR <30 mL/min - Remdesivir not recommended for patients on mechanical ventilation or ECMO - Paxlovid is approved for use in those over 12 years and at least 40 kg - Contraindications include hypersensitivity to nirmatrelvir or ritonavir, on contraindicated medication (see below), severe renal impairment (< 30 mL/min), and severe liver impairment (Child-Pugh Class C) - Paxlovid is contraindicated with the following medications: Alfuzosin (Uroxatral), Amiodarone, Apalutamide (Erleada), Carbamazepine (Tegretol), Colchicine, Clozapine (Clozaril), Dihydroergotamine (DHE), Dronedarone (Multaq), Ergotamine (Ergomar), Flecainide (Tambocor), Lovastatin (Altoprev), Lurasidone (Latuda), Methylergonovine (Methergine), Midazolam, Pethidine (Meperidine, Demerol), Phenobarbital (Luminal), Phenytoin (Dilantin), Pimozide (Orap), Piroxicam (Feldene), Propafenone (Rythmol), Propoxyphene, Quinidine, Ranolazine (Ranexa), Rifampin, Sildenafil (Viagra, Revatio), Simvastatin (Zocor), St. John's Wort, Triazolam (Halcion) - May lead to HIV protease inhibitor resistance in patients with untreated and uncontrolled HIV-1 - Molnupiravir is not authorized for those less than 18 years and should only be considered a

Table 2 (*continued*)

Treatment	Dosage	Consideration
		last-line agent when Paxlovid, remdesivir, or sotromivab are unavailable - Molnupiravir has lower efficacy compared to other agents and there is no efficacy data on vaccinated patients. - If no other agent is available and a pregnant patient is at high-risk, molnupiravir may be considered. Early animal studies demonstrate toxicity, however, can be used in pregnant patients after embryogenesis (10+ weeks) with a careful discussion - Patients should not breastfeed while taking the medication until 4 days after conclusion of treatment - Males should use contraception for a minimum of 3 months after last dose of molnupiravir
IL-6 Antagonists - Tocilizumab - Sarilumab	- Tocilizumab dosed at 8 mg/kg of actual body weight (maximum of 800 mg); administered as a single IV dose - Sarilumab is administered using a single-dose, pre-filled pen as a SC injection; can also be administered IV if 400 mg formulation reconstituted in 100 mL of 0.9% NaCl with IV infusion over 1 h	- In clinical trials, some participants received a second dose of tocilizumab 8 h after the first dose if no improvement was seen - Sarilumab is an alternative if tocilizumab is unavailable - Sarilumab only approved via SC route; IV formulation studied in REMAP-CAP trial
Kinase Inhibitors - Baricitinib - Tofacitinib	- Baricitinib dosage depends on eGFR; administered for up to 14 days or discharge from hospital: - eGFR ≥60 mL/min: 4 mg PO daily - eGFR 30–59 mL/min: 2 mg PO daily - eGFR 15 to-29: 1 mg PO daily - eGFR <15: Not recommended - Tofacitinib is administered for up to 14 days or until discharge from hospital: - eGFR >60: 10 mg PO BID - eGFR <60 mL/min: 5 mg PO BID - Alternative if baricitinib unavailable	- Baricitinib can be administered in combination with remdesivir for patients requiring supplemental oxygen, but not critical disease - Baricitinib and tofacitinib should not be administered in combination with tocilizumab or other IL-6 inhibitors - Can combine baricitinib with remdesivir and steroids - Baricitinib has the most benefit for patients on HFNC or NIV at baseline; limited/unclear benefit for those with greater oxygen requirements - Tofacitinib has the greatest benefit for those on supplemental oxygen or HFNC - Prophylactic anticoagulant should be administered if tofacitinib is provided
Monoclonal Antibodies - Bamlanivimab/ Etesevimab - Casirvimab/ imdevimab - Sotrovimab	- Casirivimab 600 mg and imdevimab 600 mg IV or SQ - Sotrovimab is given 500 mg as a single dose -Bamlanivimab/ etesevimab given in combination, with 700 mg of bamlanivimab	- Sotrovimab is the only monoclonal antibody demonstrating efficacy against the Omicron variant - Sotrovimab recommended starting as soon as possible within 10 days of symptom

Table 2 (*continued*)

Treatment	Dosage	Consideration
	700 mg and etesevimab 1400 mg IV or SC once	onset if in an area with high Omicron prevalence.
		- Antibody therapy should be tailored based on local availability and susceptibility; recommended for patients in the ambulatory setting with mild-to-moderate disease who are not hospitalized - If located in area with high Delta prevalence and no alternatives available, can consider using bamlanivimab/etesevimab or casirivimab and imdevimab with the caveat these treatments are ineffective against the Omicron variant - Can consider giving to patients who are at high risk for worsening disease admitted to the hospital for reasons unrelated to COVID-19 infection
Pre-exposure prophylaxis - Tixagevimab/ cilgavimab	- Tixagevimab 150 mg and cilgavimab 150 mg IM administered as two consecutive injections	- For use in those with no current infection or known recent exposure and moderately to severely immunocompromised who may not have an immune response to vaccination or if vaccination is not recommended
Post-exposure Prophylaxis - Casirivimab/ imdevimab	- Casirivimab 600 mg and imdevimab 600 mg IV or SC one time	- Casirivimab/imdevimab does not demonstrate efficacy against the Omicron variant

CrCl, creatinine clearance (depicted as mL/min); GFR, glomerular filtration rate; kg, kilograms; IU, international units; IV, intravenous; IM, intramuscular; mg, milligrams; mL, milliliters; PO, per oral; SC, subcutaneous; U, units; QD, once daily; BID, 2 times per day; TID, 3 times a day; ECMO, extracorporeal membrane oxygenation.

doses (≥ 40 mg daily methylprednisolone equivalent dosing) are associated with a greater odds of in-hospital mortality (OR 2.14, 95% CI 1.45 to 3.14) and decreased odds of requiring dialysis (OR 0.33, 95% CI 0.18 to 0.63), with no difference in hospital-associated infections (OR 1.00, 95% CI 0.59 to 1.68), need for invasive mechanical ventilation (OR 0.77, 95% CI 0.40 to 1.46), or hospital readmissions (OR 1.14, 95% CI 0.74 to 1.76) [17]. However, this study was retrospective and included admitted patients with varying degrees of illness severity.

Based on the available data, patients with critical illness such as ARDS or those requiring mechanical ventilation may benefit from higher doses of steroids (dexamethasone 20 mg IV) although this is controversial [15]. If dexamethasone is unavailable, an equivalent alternative steroid may be used such as methylprednisolone 32 mg, prednisone 40 mg, or hydrocortisone 160 mg [10,18–21]. Patients who are hospitalized with COVID-19 classified as non-severe and thus not requiring supplemental oxygen should not receive steroids; similar recommendations exist for non-hospitalized patients [10,18].

Inhaled steroids have been evaluated, specifically inhaled budesonide and inhaled and intranasal ciclesonide. The non-placebo-controlled steroids in COVID-19 (STOIC) trial included 139 patients within 7 days of onset of mild COVID-19 symptoms randomized to budesonide (two inhalations, twice daily, 400 μg per actuation) versus usual care until symptom resolution [22]. Fewer patients required medical evaluation or admission compared with those assigned to usual care

(intention to treat analysis 3% vs. 15%, difference in proportions 0.123, 95% CI 0.033 to 0.213), with a number needed to treat (NNT) of 8 [22]. In the budesonide group, clinical recovery time was 1 day shorter (median 7 days, 95% CI 6 to 9) compared to usual care (8 days, 95% CI 7 to 11) [22]. However, this trial was unblinded and stopped early with no prespecified criteria. The PRINCIPLE trial compared usual care (antipyretics and oral hydration), usual care with inhaled budesonide 800 μg twice per day for 14 days, and usual care in combination with "other therapies" (azithromycin, colchicine, doxycycline, and hydroxychloroquine) in patients ≥65 years or those ≥55 years with comorbidities who were symptomatic for up to 14 days with suspected COVID-19 but not admitted [23]. Authors included 2530 patients with COVID-19 and found 2.94 day shorter recovery time in patients receiving inhaled budesonide (95% Bayesian credible interval 1.19–5.11, hazard ratio [HR] 1.21 (95%CI Bayesian credible interval 1.08 to 1.36), but no statistically significant reduction in hospital admission or death at 28 days (OR 0.75, 95% Bayesian confidence interval 0.55 to 1.03) [23].

A multicenter double blind RCT evaluated ciclesonide 320 micrograms twice per day versus placebo in 400 outpatients 12 years and older with symptomatic confirmed COVID-19 [24]. Time to symptom alleviation was similar (19 days in both groups), and there was no difference in hospital admissions. Authors state there was a difference in the combined secondary outcome of ED visits or hospitalization (1.0% vs. 5.4%, $p = 0.03$), but there was no difference in hospitalizations alone [24]. Another RCT evaluated inhaled ciclesonide 600 micrograms twice per day and intranasal ciclesonide 200 micrograms daily versus placebo [25]. Authors included 203 symptomatic patients 18 years and older with COVID-19 within 6 days of symptom onset. There was no difference in self-reported resolution of symptoms by day 7 (adjusted risk difference 5.5%, 95% CI -7.8% to 18.8%) or day 14. The RCT was also stopped early with no prespecified endpoint [25]. Currently, there is not clear evidence that inhaled or intranasal steroids significantly improve patient outcomes, and further RCTs are needed.

3.2. Antiviral treatments

A variety of antiviral therapies have been developed and evaluated for use in COVID-19. Remdesivir is the only currently recommended antiviral for hospitalized patients, and it may also be used in the outpatient setting as a 3-day regimen [9,10,26–35]. It inhibits viral RNA polymerase and may speed recovery [9,10]. ACTT-1 was a double-blind RCT including 1059 hospitalized patients with COVID-19 and found patients receiving remdesivir had a median recovery of 10 days, compared to 15 days in those not receiving the medication (rate ratio for recovery 1.29, 95% CI 1.12 to 1.49) [28]. This benefit was predominantly observed in those requiring low flow supplemental oxygen but not other airway treatments (e.g., NIPPV, HFNC, mechanical ventilation) [28]. A second study including 584 hospitalized patients with moderate COVID-19 found that a 5-day course of remdesivir was associated with improved clinical status based on a 7-point ordinal scale (ranging from death to discharged) compared to placebo (OR 1.65, 95% CI 1.09 to -2.48), while 10-day course demonstrated no difference when compared with placebo [29]. The WHO Solidarity trial including 11,330 adults in 30 countries found no difference in mortality, duration of ventilation, or hospital length of stay in patients randomized to one of five arms: remdesivir for 10 days, hydroxychloroquine for 10 days, lopinavir for 14 days, interferon regimens over 6 days, or standard of care [30]. The DisCoVeRy trial, a phase 3 open-label RCT including 857 patients across 48 European sites, found no benefit in clinical status at 15 days in hospitalized patients with confirmed COVID-19, illness of any duration, and evidence of hypoxic pneumonia or need for oxygen supplementation receiving remdesivir for 10 days plus standard of care versus standard of care [31]. In those patients with severe COVID-19 or those requiring supplemental oxygen, the Infectious Diseases Society of America (IDSA) conditionally recommends a 5-day course of remdesivir [10]. Shorter courses have also been evaluated. A double-blind RCT

(PINETREE) including 562 outpatients with COVID-19 and symptom onset within 7 days at high risk for disease progression (≥60 years, obesity, certain coexisting medical conditions) evaluated 3 days of remdesivir (200 mg on day 1 followed by 100 mg on days 2 and 3) compared with placebo. Authors found reduced rates of hospitalization and death by day 28 in patients receiving remdesivir (0.7% versus 5.3%, HR 0.13, 95% CI 0.03 to 0.59) [32]. Four patients in the remdesivir group (1.6%) and 21 patients receiving placebo (8.3%) had a COVID-19 medically attended visit within 28 days (HR 0.19, 95% CI 0.07 to 0.56) [32]. There were no mortality events in either group. IDSA guidelines conditionally recommend the use of remdesivir in patients (outpatient or hospitalized) with mild-to-moderate COVID-19 who are at risk for progression to severe disease, regardless of the need for supplemental oxygen [10]. The NIH recommends remdesivir in admitted patients requiring supplemental oxygen. The NIH also recommends it as the third line therapy in the outpatient setting (Table 2) [33-35]. The WHO does not recommend treatment with remdesivir [36,37]. Of note, remdesivir may be active against the Omicron variant, but in vitro and in vivo evidence is limited [33-35,38].

Novel oral antivirals include nirmatrelvir/ritonavir and molnupiravir [33,34,37-44]. As of February 15, 2022, both medications have US FDA emergency use authorization (EUA) approval [33,34,37-44]. Paxlovid is a combination of two protease inhibitors: nirmatrelvir, a protease inhibitor, and ritonavir, a pharmacokinetic booster [33,34,37-41]. It is approved for use in those over 12 years and at least 40 kg, and based on NIH guidelines as of February 15, 2022, is the current first line recommended therapy for outpatients who meet criteria for treatment [33,34]. An interim analysis of phase 2/3 of the randomized Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) trial included 2246 unvaccinated adult outpatients with COVID-19 with symptom onset no more than 5 days before randomization and at least one risk factor for severe disease [39,40]. Patients were randomized to receive 300 mg of nirmatrelvir and 100 mg of ritonavir versus placebo twice daily for 5 days. Patients were excluded if there was an anticipated need for hospitalization within 48 h after randomization and prior receipt of convalescent plasma or SARS-CoV-2 vaccine. Patients receiving nirmatrelvir/ritonavir within 3 days of symptom onset were found to have a reduced risk of hospitalization and death compared to those who received placebo by 6.32 percentage points (95% CI -9.04 to −3.59, relative risk reduction 89.1%), with 0 deaths in the treatment groups compared to 7 deaths in the placebo group. Viral load was lower in the treatment groups when treatment was initiated within 3 days of symptom onset (0.8% versus 7%, $p < 0.0001$) [39,40]. The incidence of adverse events was similar between the groups. Patients with no high risk features also demonstrated reduced rates of hospitalization and decreased viral loads with Paxlovid [39,40]. Paxlovid interacts with over 28 other medications, with several contraindications including renal impairment, liver impairment, and hypersensitivity to nirmatrelivr or ritonavir (Table 2). Based on limited in vitro evidence and structural properties, Paxlovid is expected to be effective against Omicron [33,34,38,39].

Molnupiravir is a nucleoside analogue which inhibits SARS-CoV-2 replication, approved for use in those over age 18 years. Indications include positive test for SARS-CoV-2, symptomatic for 5 days or fewer, high risk for progression to severe disease, and the patient does not require hospitalization (Table 2) [33,34,42-44]. An international phase 3 randomized control trial reported interim results with 775 patients demonstrating a reduced risk of hospital admission or death with molnupiravir (7.3% versus 14.1%, $p = 0.0012$), with no deaths in the group receiving molnupiravir [42]. A phase 3, double-blind RCT evaluated molnupiravir in 1433 unvaccinated outpatients within 5 days of onset of signs or symptoms of COVID-19 and at least one risk factor for severe illness [43]. Patients were randomized to molnupiravir 800 mg or identical placebo twice daily for 5 days. Patients were excluded if there was an anticipated need for hospitalization within the next 48 h, dialysis or glomerular filtration rate < 30 mL/min/1.73 m2,

pregnancy, severe neutropenia, platelets <100,000/mL, SARS-CoV-2 vaccination, and unwilling to use contraceptives during the intervention period and for at least 4 days after regimen completion. Authors found reduced hospitalization and death through 29 days in the molnupiravir group compared to placebo (6.8% versus 9.7%; difference − 3.0 percentage points; 95% CI −5.9 to −0.1) [43]. Molnupiravir should be avoided in pregnancy, breastfeeding is not recommended until 4 days after course conclusion, and men should use contraception for 3 months after use [33,34,44]. Limited in vitro data suggest molnupiravir is effective against Omicron [33,34,38,44].

3.3. Interleukin-6 antagonists

IL-6 antagonists include tocilizumab and sarilumab. These are humanized monoclonal antibodies approved by the United States Food and Drug Administration (FDA) for use in rheumatoid arthritis, giant cell arteritis, and cytokine release syndrome [9,10,45,46]. Multiple trials have evaluated IL-6 antagonists for treatment of COVID-19, finding an overall reduction in 28-day mortality [45-51]. The REMAP-CAP study evaluated tocilizumab or sarilumab versus standard of care within the first 24 h of ICU admission for COVID-19 patients requiring either respiratory support (invasive and non-invasive mechanical ventilation including HFNC >30 L/min and FiO2 > 0.4) or cardiovascular support (vasopressor or inotrope infusion) [51]. Patients receiving IL-6 antagonists had more organ support-free days (median 10 days for tocilizumab, 11 days for sarilumab, and 0 days in the control group) and lower hospital mortality (tocilizumab OR 1.64, 95% CI 1.14 to 2.35; sarilumab OR 2.01, 95% CI 1.18 to 4.71) [51]. A meta-analysis of 27 randomized controlled trials found the 28-day all-cause mortality was lower with IL-6 antagonists compared to placebo or standard care (OR 0.86, 95% CI 0.79 to 0.95) [50]. Tocilizumab was associated with reduced mortality (OR 0.83, 95% CI, 0.74 to 0.92), but the OR for sarilumab was 1.08 (95% CI, 0.86 to 1.36) [50]. The benefit was enhanced further when patients also received steroids simultaneously (OR 0.78, 95% CI 0.69 to 0.88 with steroids vs. OR 1.09, 95% CI 0.91 to 1.30 without steroids) [50]. Amongst those requiring supplemental oxygen or high flow nasal cannula (HFNC), there was lower 28-day all-cause mortality (supplemental oxygen OR 0.81, 95% 0.67 to 0.98; NIV or HFNC OR 0.83, 95% CI 0.72 to 0.96), but there was no difference for those on mechanical ventilation or ECMO (OR 0.95, 95% CI 0.78 to 1.16) [50]. When subgroup analysis was performed by C-reactive protein (CRP), results varied by level of CRP elevation and outcome, specifically progression to mechanical ventilation, ECMO, or death by 28 days (<75 μg/mL OR 0.74, 95% CI 0.51 to 1.09; 75 μg/mL to <150 μg/mL OR 0.76, 95% CI 0.65 to 0.89; ≥ 150 μg/mL OR 0.78, 95% CI 0.67 to 0.92) and 28 day mortality (<75 μg/mL OR 0.84, 95% CI 0.56 to 1.26; 75 μg/mL to <150 μg/mL OR 0.79, 95% CI 0.67 to 0.92; ≥150 μg/mL OR 0.96, 95% CI 0.83 to 1.11). Additional analysis by other inflammatory markers in this study was not provided (ferritin, lactate dehydrogenase [LDH], D-dimer) [50]. The EMPACTA trial evaluated tocilizumab in 377 high-risk and minority patients admitted with COVID-19 not receiving mechanical ventilation, with combined primary outcome of mechanical ventilation or 28-day mortality [52]. The authors found that tocilizumab was associated with reduced mechanical ventilation or death (HR 0.56, 95% CI 0.33 to 0.97) but not the secondary outcome of mortality alone (HR 1.14, 95% CI 0.92 to 1.42) compared to the placebo group [52]. CRP elevation was not an inclusion criterion in the EMPACTA trial (Tocilizumab 124.50 mg/L, placebo 143.40 mg/L, overall 136.10 mg/L) [52]. In the RECOVERY trial, hospitalized patients with hypoxia or on supplemental oxygen with CRP ≥ 75 mg/L were randomized to either standard care or standard care with an initial weight-based dose of tocilizumab [49]. A second dose was given 12–24 h if the patient had not improved clinically. Although most patients were given systemic steroids (3385/4116; 82%), patients given tocilizumab were more likely to be discharged from the hospital by 28 days (57% versus 50%, rate ratio 1.22, 95% CI 1.22 to 1.33). For patients not requiring mechanical ventilation at baseline, those in the tocilizumab group were less

likely to progress to death or invasive mechanical ventilation (35% compared to 42%, risk ratio 0.84, 95% CI 0.77 to- 0.92) [49].

There are concerns of superinfection, hepatotoxicity, thrombocytopenia, and leukopenia with IL-6 antagonists, but current data suggest no significant difference in adverse events when compared with placebo or standard care [9,10,45-52]. The WHO recommends patients with severe or critical COVID-19 infections should be given both steroids and IL-6 antagonists simultaneously [9]. NIH guidelines recommend tocilizumab or sarilumab only in combination with dexamethasone (or other steroid equivalent) for select admitted patients with COVID-19 and respiratory decompensation (defined as patients admitted to the ICU in the previous 24 h requiring HFNC >40% FiO2, non-invasive ventilation [NIV], or mechanical ventilation), as well as recently admitted patients requiring HFNC or NIV with significantly elevated inflammatory markers [45].

3.4. Monoclonal antibodies

Monoclonal antibodies are manufactured antibodies that can provide a transient but immediate effect against SARS-CoV-2 [9,10,33,34,39, 40,53-67]. These antibodies include bamlanivimab, etesevimab, casirivimab, imdevimab, sotrovimab, tixagevimab, and cilgavimab [9,10,33,34,39,40,53-67]. Although in vitro data suggest this class of drugs continues to be effective against the Delta variant, emerging evidence suggests limited efficacy against newer variants, such as Omicron [33,34,54]. Furthermore, if monoclonal antibody treatment is given before vaccination for either prophylaxis or treatment, vaccination should be delayed 30 or 90 days, respectively, as it may adversely impact the developing immune response [54,68]. In patients who are vaccinated, this does not apply and should not affect timing of or decision to use monoclonal antibody treatment [54-56]. Bamlanivimab is an antibody treatment used in combination with etesevimab, but due to reduced efficacy against variants, is no longer recommended by the NIH [54]. The combination of casirivimab and imdevimab (also known as REGN-COV2 or REGEN-COV™) has demonstrated activity against the SARS-CoV-2 spike protein prior to the Omicron variant and may be used in non-hospitalized adults with mild to moderate COVID-19 at risk of decompensation [9,54,57-59]. In a systematic review and network meta-analysis, casirivimab-imdevimab was the only monoclonal antibody that lowered the risk of hospitalization in patients with non-severe disease with moderate certainty data [57].

Monoclonal antibodies may be more effective in patients with non-severe rather than severe disease and may also be used to prevent infection in high-risk patients, with a meta-analysis of 47 trials which evaluated several COVID therapies finding lower risk of hospitalization when compared with placebo for casirivimab-imdevimab (OR 0.29, 95% CI 0.17 to 0.47; risk difference (RD) −4.2%; moderate certainty), bamlanivimab (OR 0.24, 95% CI 0.06 to 0.86; RD −4.1%; low certainty), bamlanivimab-etesevimab (OR 0.31, 95% CI 0.11 to 0.81; RD −3.8%; low certainty), and sotrovimab (OR 0.17, 95% CI 0.04 to 0.57; RD −4.8%; low certainty) [57]. However, this meta-analysis found no further impact on other outcomes and is comprised of studies conducted prior to the Omicron variant [33,34,57]. A combined phase 1–3 trial of 275 outpatients with COVID-19 and symptoms <7 days were randomized to receive REGN-COV2 at 2.4 g versus 8 g versus placebo [58]. Authors found reduced viral load with no difference in adverse effects between the groups [58]. In March 2021, Regeneron released a report including 4567 outpatients, which demonstrated a risk reduction in hospitalization or death by 70% (1.0% vs. 3.2%, *p* = 0.0024) with 1.2 g and 71% with 2.4 g (1.3% vs. 4.6%, *p* < 0.0001) in non-hospitalized patients and a reduction in symptoms by 4 days (10 days vs. 14 days) with both 1.2 g and 2.4 g [59]. A report including 409 patients also announced efficacy in reducing overall rates of COVID-19 infection by 50% (23/223 placebo vs. 10/186 receiving intervention) in unvaccinated patients with household contacts, with a reduction of symptomatic infection by 100% (8/223 placebo vs. 0/186 receiving intervention) [60].

However, this combination has not demonstrated efficacy against the Omicron variant [33,34].

Sotrovimab was studied in the COMET-ICE trial, which included 583 high-risk outpatients with COVID-19 within 5 days of symptom onset [61]. High risk was defined as age > 55 years, diabetes, body mass index >30, chronic kidney disease, heart failure, chronic obstructive pulmonary disease, and moderate-to-severe asthma. There was a lower rate of disease progression leading to death or hospitalization at 29 days in the sotrovimab group compared to the placebo group (1% vs 7%, RR reduction 85%, *p* = 0.002) [61]. Sotrovimab retains activity against the Omicron variant spike protein based on a single pre-print in vitro study, but further data are needed [33,34,62]. The NIH recommends sotrovimab as the second line treatment for patients in the outpatient setting who meet treatment criteria (Table 2) [33,34,54].

Evusheld is a long-acting antibody combination by AstraZeneca consisting of tixagevimab and cilgavimab (Table 2) [63]. As of January 2022, the US FDA has issued an emergency use authorization for this combination for patients without COVID-19 and no recent known exposure pre-exposure prophylaxis who are severely immunocompromised and may not develop an immune response to vaccination or if vaccination is not recommended [64]. It is not recommended for post exposure prophylaxis. This is primarily based on two trials, PROVENT and STORM CHASER. PROVENT included 5197 patients who had an increased risk of inadequate response to active immunization or increased risk of COVID-19 [65,66]. Authors found a reduced relative risk of symptomatic infections by 77% with use of this combination for pre-exposure prophylaxis (95% CI 46 to 90%, *P* < 0.001) [64-67]. However, the STORM CHASER trial, which included 1121 unvaccinated patients with confirmed exposure to COVID1–19, found no reduction in symptomatic infection with use as post-exposure prophylaxis (RR reduction −33%, 95% CI -26 to 65%) [67]. There are limited data evaluating the efficacy of Evusheld against the Omicron variant [33,34].

3.5. Kinase inhibitors

Kinase inhibitors include baricitinib, imatinib, ruxolitinib, and tofacitinib [9,33,34]. These medications inhibit JAK 1, JAK 2, and intracellular kinase, reducing inflammation. The ACTT-2 trial compared baricitinib and remdesivir versus remdesivir alone in 1033 hospitalized patients across 8 countries, finding more rapid recovery in the baricitinib and remdesivir group (7 days vs. 8 days, rate ratio for recovery 1.16, 95% CI 1.01 to 1.32) and higher likelihood or clinical improvement at 15 days (OR 1.3, 95% CI 1.0 to 1.6), which was predominantly seen in patients receiving high flow oxygen or noninvasive ventilation (rate ratio for recovery 1.51, 95% CI 1.10 to 2.08) [69]. This trial, however, did not evaluate these medications in combination with dexamethasone. The COV-BARRIER trial evaluated baricitinib versus placebo in 1525 hospitalized adult patients with confirmed COVID-19, evidence of pneumonia or active and symptomatic COVID-19, and at least one elevated inflammatory marker greater than the upper limit of normal (CRP, D-dimer, LDH, or ferritin) [70]. Patients requiring mechanical ventilation; receiving immunosuppressants; had received convalescent plasma or intravenous immunoglobulin for COVID-19; or had neutropenia, lymphopenia, estimated glomerular filtration rate < 30 mL/min/1.73 m2, or alanine aminotransferase (ALT) or aspartate aminotransferase concentration greater than five times the upper limit of normal. All patients received standard care including steroids such as dexamethasone and antivirals including remdesivir. Authors found no difference in the composite primary endpoint of progression to HFNC, NIV, mechanical ventilation, or death at 28 days (odds ratio 0.85, 95% CI 0.67 to 1.08). Authors found a reduction in the secondary endpoint of all-cause mortality at 28 days (8% vs. 13%, HR 0.57, 95% CI 0.41 to 0.78) and all-cause mortality at 60 days (10% vs. 15%, HR 0.62, 95% CI 0.47 to 0.83) [70]. Adverse events were similar between groups. A RCT including 385 admitted patients with confirmed COVID-19 requiring oxygen supplementation randomized to receive oral imatinib versus

placebo found imatinib did not reduce the primary outcome of time to discontinuation of ventilation and supplemental oxygen for more than 48 consecutive hours (unadjusted hazard ratio HR 0.95, 95% CI 0.76 to 1.20), though the secondary outcome of mortality was reduced with imatinib (unadjusted HR 0.51, 95% CI 0.27 to 0.95) [71]. A 2021 RCT evaluated the use of tofacitinib versus placebo in 289 hospitalized patients with confirmed COVID-19 for less than 72 h from 15 different sites in Brazil with COVID-19 and found the medication was associated with reduced incidence of death or respiratory failure at 28 days (18.1% vs. 29%, RR 0.63, 95% CI 0.41 to 0.97) [72]. NIH guidelines recommend baricitinib with steroids for patients with escalating oxygen requirements and increased inflammatory markers [73]. Baricitinib can be used with a steroid instead of tocilizumab, but baricitinib and tocilizumab should not be used together [73].

3.6. Antibiotics

In the setting of treating COVID-19 infections, controversies persist regarding the concurrent administration of antibiotics. A meta-analysis of 24 studies composed of 3338 patients diagnosed with COVID-19 found most COVID-19 patients received antibiotics (71.9%, 95% CI 56.1 to 87.7%) [74]. However, 6.9% (95% CI 4.3 to 9.5%) of patients also had a bacterial infection. Patients who were critically ill were more likely to have a bacterial infection (8.1%, 95% CI 2.3 to 13.8%) [74]. Another review found similar rates of antibiotic prescribing (74.0%), with 17.6% of patients diagnosed with secondary bacterial infection [75]. Finally, a systematic analysis and meta-analysis of 3834 patients determined 7% (95% CI 3 to 12%) of patients hospitalized with COVID-19 had a bacterial co-infection, compared to 14% (95% CI 5 to 26%) of ICU patients [76].

Based on the available literature and the current IDSA guidelines, routine use of empiric antibiotics in patients with confirmed COVID-19 is not recommended, unless evidence of bacterial superinfection is present [10]. Objective findings suggestive of an increased risk of superinfection with bacteria include an increased leukocyte count, return of fever after an initial defervescence, lobar consolidation, or findings consistent with necrotizing infection on imaging [10]. Antibiotics in these patients should be considered. The Dutch Working Party on Antibiotic Policy recommends utilizing sputum cultures, blood cultures, and pneumococcal urinary antigen testing to identify those who may benefit from antibiotics [77]. If these tests are negative after 48 h, discontinuation of empiric antibiotics initiated on admission can be considered [77].

Clinicians should consider fungal coverage for patients who are those on mechanical ventilation for an extended period of time, have invasive catheters, or are receiving steroids [10]. Patients who develop secondary bacterial respiratory infections should be started on antibiotics as dictated by current guidelines for either hospital-acquired or ventilator associated pneumonia [77].

3.7. Venous thromboembolic (VTE) prophylaxis

3.7.1. Anticoagulation agents

Non-hospitalized patients with COVID-19 should not receive prophylactic anticoagulants or antiplatelet therapy without a specific indication or participation in a clinical trial [78-80]. While the NIH recommends anticoagulation in all hospitalized nonpregnant adults with COVID-19, the American Society of Hematology recommends consideration of prophylactic-dose anticoagulation on admission for critically-ill patients, and there is variation between several society recommendations based on illness severity of COVID-19 disease and presence of VTE risk factors (Tables 3, 4) [78-85].

Patients admitted to the ICU without confirmed or suspected VTE should be started on prophylactic-dose anticoagulation [78-85]. Evidence from the ACTIV4a, ATTACC, and REMAP-CAP trials demonstrate that therapeutic-level anticoagulation dosing compared to prophylactic dosing regimens in critically-ill COVID-19 patients does not reduce in-hospital mortality rates (62.7% vs. 64.5%, OR 0.84, 95% CI 0.64–1.11) or the need for organ support (OR 0.83, 95% CI 0.67–1.03) [86]. A meta-analysis comparing higher-dose (either intermediate- or therapeutic-dose regimens) to standard-dose prophylactic anticoagulation amongst seven RCTs found a reduction in VTE (2.5% vs. 4.7%, RR 0.55, 95% CI 0.41–0.74, NNT 45) but without a significant reduction in all-cause mortality (17.8% vs. 18.6%, RR 0.96, 95% CI 0.78–1.18) [85]. Potential benefit must be weighed in this context against increased risk of major bleeding (2.4% vs. 1.4%, RR 1.73, 95% CI 1.15–2.60) [85]. Therefore, high-dose thromboprophylaxis should not be started outside of clinical trials [88]. Of note, a variety of medications and regimens have been evaluated for use in prophylaxis and as treatment for confirmed VTE (Table 3) [85-89].

Patients receiving ECMO, continuous renal replacement therapy (CRRT), or have thrombosis of these systems should be treated per individual institutional protocols as non-COVID-19 patients (Table 4) [78]. Additionally, hospitalized pregnant patients should be started on prophylactic-dose anticoagulation [78].

3.7.2. Antiplatelet therapy

Recent data suggest that aspirin use is associated with improved COVID-19 patient outcomes, including decreased risk of thromboembolism, mechanical ventilation, ICU admission, and mortality [90-96]. Aspirin has been proposed to act on the intracellular signaling pathway

Table 3
COVID-19 anticoagulation regimens [78-85].

Medication	Dosing Regimen		
	Prophylactic	Intermediate	Therapeutic
Apixaban	2.5 mg PO BID	No recommendation given	5 mg, PO BID 10 mg, PO BID
Enoxaparin	30 mg (3000 U) SC QD (for GFR 15–30) 30-40 mg (3000–4000 U) SC BID (for BMI ≥ 40) 40 mg (4000 U), SC QD (for GFR > 30)	0.5 mg/kg (50 U/kg), SC BID (CrCl >30) 0.5 mg/kg (50 U/kg), SC QD (CrCl <30) 30 mg (3000 U), SC BID (BMI < 40) 40 mg (4000 U), SC BID (CrCl >30 and BMI < 40) 60 mg (6000 U), SC BID (CrCl >30 and BMI > 40)	0.8 mg/kg, SC BID (BMI > 40 and CrCl >30) 1 mg/kg (100 U/kg), SC BID (for CrCl >30) 1.5 mg/kg (150 U/kg) SC QD (for CrCl >30) 1 mg/kg (100 U/kg), SC QD (CrCl <30)
Rivaroxaban	10 mg, PO QD	No recommendation given	15 mg, PO QD (GFR 15–50 in AF patients) 15 mg, PO BID 20 mg, PO QD
UFH	5000 U, SC BID-TID 7500 U, SC BID (for BMI ≥ 40)	7500 U, SC TID	250 U/kg, SC q12h IV to target aPTT therapeutic range as per institutional guidelines, or anti-Xa activity 0.3–0.7 IU/mL

AF, atrial fibrillation; aPTT, activated partial thromboplastin time; BID, twice daily; BMI, body mass index (depicted as kg/m^2); CrCl, creatinine clearance (depicted as mL/min); GFR, glomerular filtration rate; kg, kilograms; IU, international units; IV, intravenous; mg, milligrams; mL, milliliters; PO, per oral; SC, subcutaneous; QD, once daily; BID, 2 times per day; TID, 3 times a day; U, units.

Table 4
Society recommendations on VTE prophylaxis in COVID-19 patients [78-85].

Patient Population	Organization			
	NIH	American Society of Hematology	International Society on Thrombosis, Hemostasis	CHEST
Outpatient	Do not initiate thromboprophylaxis unless otherwise indicated Continue chronic thromboprophylactic therapy	Recommend against anticoagulant thromboprophylaxis	No recommendation	No recommendation
Inpatient, non-pregnant, not critically-ill	Prophylactic dosing Therapeutic dosing if D-dimer above upper limit of normal in patients receiving supplemental oxygen and low risk of bleeding	Prophylactic dosing	Prophylactic dosing (LMWH preferred over UFH) Intermediate dosing may be considered	Prophylactic dosing
Inpatient, non-pregnant, critically-ill	Prophylactic dosing ECMO/CRR patients per institution protocols	Prophylactic dosing	Prophylactic or intermediate dosing Multimodal thromboprophylaxis with mechanical devices can be considered	Prophylactic dosing Suggest against the additional of mechanical prophylaxis to pharmacological thromboprophylaxis
Inpatient, pregnant, not critically-ill	Continue thromboprophylaxis if already on No initiation recommendations	No recommendation for initiating LMWH preferred over UFH	Prophylactic dosing	No recommendation
Inpatient, pregnant, critically-ill	Prophylactic dosing	No recommendation	Multidisciplinary discussion on dosing regimen	No recommendation
Inpatient children	Indications same as those without COVID-19	No recommendation	No recommendation	No recommendation

CRR, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; LMWH, low-molecular weight heparin; NIH, National Institutes of Health; UFH, unfractionated heparin.

involved with viral replication and reduction in systemic inflammation, cytokine release, platelet activity, and hypercoagulability. A 2021 retrospective study including 412 admitted patients with COVID-19 found aspirin was associated with risk of mechanical ventilation (adjusted HR 0.56, 95% CI, 0.37 to 0.85), ICU admission (adjusted HR 0.57, 95% CI 0.38 to 0.85), and in-hospital mortality (adjusted HR 0.53, 95% CI 0.31 to 0.90) [90]. Most patients received aspirin 81 mg daily. A single retrospective cohort study evaluated confirmed COVID-19 patients divided into four treatment groups: control (who did not receive aspirin, enoxaparin, or other antiplatelet or anticoagulation agents), aspirin alone, enoxaparin alone, or concomitant use of aspirin and enoxaparin [91]. Aspirin use included dosing of 81–162 mg daily within 7 days prior to or within 24 h following COVID-19 diagnosis. Odds of VTE compared to control were significantly lower in those on aspirin alone (OR 0.163, 95% CI 0.035 to 0.752), but were even lower in enoxaparin alone (OR 0.071, 95% CI 0.018 to 0.280), or simultaneous aspirin and enoxaparin use (OR 0.010, 95% CI 0.001 to 0.078). Need for mechanical ventilation was reduced in only the combination group compared to control (OR 0.032, 95% CI 0.004 to 0.226) [91]. A study of patients on aspirin prior to COVID-19 found a decrease in overall mortality at 14 days (35,370 patients, OR 0.38, 95% CI 0.32 to 0.46) and 30 days (32,836 patients, OR 0.38, 95% CI 0.33 to 0.45) [92]. However, these studies were limited by their retrospective nature and included both patients initiating aspirin on admission and those taking it prior to hospitalization [90-92]. A propensity score-matched study of 638 hospitalized patients with COVID-19 found reduced in-hospital mortality with aspirin (HR 0.52, 95% CI 0.34 to 0.81) [93]. A meta-analysis of 6 studies with 13,993 patients with COVID-19 and an active prescription for low-dose aspirin found reduced mortality (RR 0.46, 95% CI 0.35 to 0.61) [94], and a second meta-analysis including 7 RCTs with 34,415 patients found aspirin was associated with reduced risk of mortality (RR 0.56, 95% CI 0.38 to 0.81) [95]. One of the highest quality studies is the RECOVERY Trial, an RCT that included 14,892 patients randomized to aspirin 150 mg daily by mouth or rectum compared to usual care alone [96]. Patients receiving aspirin had a shorter duration of hospital stay (median 8 days versus 9 days) and greater likelihood of discharge from the hospital alive within 28 days (RR 1.06, 95% CI 1.02 to 1.10). Aspirin was associated with reduced thrombotic events (absolute reduction 0.6%, standard error 0.4%) but also increase in major bleeding events (1.6% versus 1.0%, absolute increase 0.6%, standard error 0.2%). There was no reduction in progression to invasive mechanical ventilation or death (RR 0.96, 95% CI 0.90 to 1.03) [96].

Investigations of antiplatelet therapies outside of aspirin alone do not consistently demonstrate improved patient outcomes and were nevertheless largely dominated by aspirin therapy. A large study of nearly 35,000 patients ≥50 years old demonstrated improved benefits for those taking antiplatelet therapy prehospital to those who did not for in-hospital mortality (18.9% vs. 21.5%, *p* < 0.001) and a 2.6% absolute reduction in mortality (HR 0.81, 95% CI 0.76–0.87, *p* < 0.005) [97]. However, most patients were taking aspirin (83.9%), with less on clopidogrel (8.2%), dual antiplatelet therapy (7.4%), or ticagrelor or prasugrel, and the authors did not break down differences between therapies. The ACTIV-4a multicenter RCT compared heparin anticoagulation alone to added P2Y12 inhibitor administration (ticagrelor or clopidogrel) and found no significant benefit amongst 2219 non-critically ill patients, including no difference in days free of respiratory or cardiovascular support and major thrombotic events [98]. Similar trials with much smaller populations of less than 100 patients on antiplatelet therapy, most on aspirin, found no significant mortality benefit compared to controls [99,100].

3.8. Controversial and experimental treatments

In the initial period of the pandemic, several medications were theorized to be effective against COVID-19. These include chloroquine (CLQ) and hydroxychloroquine (HCQ), colchicine, convalescent plasma, famotidine, fluvoxamine, ivermectin, and vitamin and mineral supplements. Most of these were based largely on perceived successes in initial case reports and case series, but subsequent trials found inconsistent efficacy and concerns for increased risk of adverse events.

3.8.1. Chloroquine and hydroxychloroquine

CLQ and HCQ were initially theorized to improve patient outcomes in COVID-19 through an antiviral effect, but multiple studies found no benefit and even increased risk of mortality with their use [101-111]. These medications have significant risk of toxicity, most notably electrolyte derangements and cardiovascular complications, including potentially fatal QTc prolongation [103-105,112]. Lack of efficacy and

increased mortality led to the revocation of the FDA EUA in June 2020 [113] and the discontinuation of the HCQ arm in the WHO SOLIDARITY trial the following month [104,114]. Currently, IDSA and NIH strongly recommend against the use of CLQ and HCQ for treating COVID-19 given the level of risk without significant benefit in COVID-19 [10,115]. This extends to prophylactic use in healthcare workers, as clinical trials demonstrated no significant benefit in preventing viral illness [10,116,117].

3.8.2. Colchicine

As an anti-inflammatory agent, colchicine is theorized to reduce the diffuse hyperinflammatory state of COVID-19 and improve patient recovery [118-121]. Several RCTs demonstrated decreased duration of supplemental oxygen and lower rates of pneumonia development with use of colchicine in COVID-19. However, colchicine was associated with increased risk of gastrointestinal side effects and rates of pulmonary embolism and no significant differences in mortality [118,119,122]. Despite enthusiasm from a small initial Italian study showing mortality benefit in patients receiving colchicine compared to standard care, the majority of evidence to-date, including several larger trials and meta-analyses, have found no significant mortality benefit for colchicine [118,120-126]. At this time, there is insufficient evidence to support the use of colchicine in COVID-19 patients. The NIH specifically recommends against colchicine use in admitted patients and states that there is insufficient evidence for outpatient use [126].

3.8.3. Convalescent plasma

Convalescent plasma has been utilized in prior viral pandemics including SARS, H_1N_1 influenza, and Ebola Virus Disease [57,101,127, 128]. Convalescent plasma has a theoretical benefit in COVID-19, as this is plasma obtained from donors who have recovered from COVID-19 and may contain antibodies that can suppress viral replication [101,127-132]. An initial report described 5 critically-ill patients in China with improvement in ARDS following initiation of convalescent plasma, and other similarly small case series demonstrated patient improvement [101,130,131]. Larger trials showed significant improvement in those treated with high-titer plasma compared to low-titer groups, driving enthusiasm further and prompting an initial FDA EUA [10,57,128,129,132,133]. However, these early studies demonstrate significant issues with confounders, and more recent high-quality trials and meta-analyses have found no significant benefit for the use of convalescent plasma in the treatment of COVID-19 [10,57,127-129,134,135]. Much of this lack of benefit may come from the period of infection the patient is admitted to the hospital and treated. The majority of patients will be admitted later in the disease course after they have started creating antibodies and are clearing the virus, and thus convalescent plasma will not benefit. At this time, both the IDSA and NIH recommend against convalescent plasma use in general patient populations [10,129].

3.8.4. Famotidine

The proposed mechanism of action for famotidine centers on competitive inhibition of two essential SARS-CoV-2 protease enzymes that allow for viral docking [136,137]. However, in-vitro studies are inconsistent, and this theory has been disputed [136,137]. Retrospective analyses early in the COVID-19 pandemic found that small populations given famotidine had a reduced risk of intubation and death [136-140]. Several of these analyses were limited by significant heterogeneity in formulations and dosing of famotidine, including some patients already taking the medication prior to hospitalization [136,138]. Additionally, several studies employed famotidine at more than double the standard dose or simultaneously used intravenous and oral formulations, prompting concerns for increased side effect risks [137,139]. Subsequent larger trials and meta-analyses demonstrated no reduction in mortality [141-143]. Current IDSA guidelines state that famotidine should not be used solely to treat COVID-19 disease [10].

3.8.5. Fluvoxamine

Fluvoxamine is an antidepressant that may reduce inflammation and progression to severe disease in those with mild COVID-19 through activity at the sigma-1 receptor. An RCT conducted in Brazil including 1497 unvaccinated outpatients with COVID-19 diagnosed within 7 days and at least 1 risk factor for severe disease found fluvoxamine 100 mg twice per day for 10 days reduced rates of hospitalization at 28 days (11% versus 16%, RR 0.68, 95% CI 0.52–0.88) [144]. However, the definition of hospitalization included an ED length of stay for at least 6 h, and most of the reductions in hospitalization were due to decrease in ED visits [144]. There was no change in mortality, viral clearance at day 7, need for mechanical ventilation, length of mechanical ventilation, or days hospitalized [144]. A double-blind RCT evaluated 15 days of fluvoxamine compared to placebo in patients with confirmed COVID-19 within 7 days of symptoms [145]. Of the 152 enrolled patients, 115 completed the trial. Authors found fluvoxamine reduced clinical deterioration compared with placebo (0% versus 8.3%, 95% CI 1.8%–16.4%), but the study was stopped early [145]. Current trials suffer from significant methodological issues, and thus clear recommendations for fluvoxamine cannot be made at this time.

3.8.6. Ivermectin

Ivermectin is an effective antiparasitic with multiple proposed mechanisms of action against SARS-CoV-2, including inhibition of viral transfer and replication in vitro and anti-inflammatory effects based on prior studies of other viruses (e.g., Zika, Dengue) [146-150]. Current evidence based on higher quality data suggests no benefit [151-153]. While several early studies suggested reduced mortality, shortened recovery time, and decreased transmissibility benefits with ivermectin in the treatment of COVID-19 patients, these studies suffered from major limitations, including wide heterogeneity, poor subject allocation, limited or no blinding, and inadequate controls with risk of confounding [10,146-153]. Additionally, many studies employed dosing regimens larger than those previously approved for parasitic infections, increasing the risks of side effects [10,148,152]. A meta-analysis released in 2021 including 10 RCTs found no improvement in all-cause mortality, length of stay, or viral clearance in patients with mild COVID-19 [151]. An RCT including 490 patients 50 years and older with mild-to-moderate COVID-19 within 7 days of symptom onset found no change in progression to severe disease (RR 1.25, 95% CI 0.87 to 1.80), as well as no difference in ICU admission, mechanical ventilation, and 28-day in-hospital death with ivermectin [153]. Furthermore, the IDSA and NIH recommend against its use in both inpatient and outpatient settings for COVID-19 [10,154].

3.8.7. Vitamin and mineral supplements

Vitamin C has been evaluated for its theorized immunomodulation and free radical scavenging benefits in systemic illness. However, a limited number of recent small trials and meta-analyses provide low-quality data suggesting no benefits in mortality, mechanical ventilation metrics, or hospital stay in COVID-19 patients [155-158]. Similarly, there are sparse studies available on vitamin D treatment in COVID-19 and insufficient evidence for recommendation in treatment of COVID-19 [159-161]. An RCT published in 2021 found no reduction in hospital length of stay in 237 admitted patients with COVID-19 from 2 sites in Brazil who received 200,000 IU of vitamin D3 [162]. Earlier studies demonstrated concerns of worse patient outcomes in COVID-19 patients with zinc deficiency, prompting examination of zinc supplementation in COVID-19 treatment regimens [163,164]. However, recent trials find no significant benefits in symptom duration, recovery time, hospitalization, or mortality [157]. Currently the NIH recommends against zinc supplementation above the recommended dietary allowance in COVID-19 patients outside of clinical trials, and the NIH states there is insufficient evidence for or against the use of vitamin C or D [147,152,161,165].

4. Conclusions

The COVID-19 pandemic has led to over 5.9 million deaths. A variety of therapies have been investigated for the medical management of COVID-19. Steroids, antivirals, IL-6 antagonists, monoclonal antibodies, and kinase inhibitors have demonstrated utility in certain patient subsets. Prophylactic anticoagulation in admitted patients demonstrates improved outcomes. Aspirin in outpatients may also be associated with improved outcomes, but data are controversial. Other therapies including CLQ and HCQ, colchicine, convalescent plasma, famotidine, ivermectin, and vitamins and minerals are controversial, with no evidence in rational medical literature to support their use.

Credit authorship contribution statement

Brit Long: Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Summer Chavez:** Writing – review & editing, Writing – original draft, Conceptualization. **Brandon M. Carius:** Writing – review & editing, Writing – original draft. **Stephen Y. Liang:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **William J. Brady:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Alex Koyfman:** Conceptualization, Supervision. **Michael Gottlieb:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of Competing Interest

None.

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