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ONLINE EXCLUSIVE

COVID-19 therapy: What works? What doesn't? And what's on the horizon?

Here is the latest evidence on the efficacy and safety of treatments that are FDA approved or authorized, in clinical trials, or *not* recommended to combat COVID-19.

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PRACTICE RECOMMENDATIONS

› *Use antivirals (eg, molnupiravir, nirmatrelvir packaged with ritonavir [Paxlovid], and remdesivir) and monoclonal antibody agents (eg, bebtelovimab) effective against the circulating Omicron variant, to treat symptoms of mild-to-moderate COVID-19 illness.* (C)

› *Treat severely ill hospitalized COVID-19 patients who require supplemental oxygen with dexamethasone, alone or in combination with remdesivir, to produce better outcomes.* (B)

› *Consider administering baricitinib or tocilizumab, in addition to dexamethasone with or without remdesivir, to COVID-19 patients with rapidly increasing oxygen requirements.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

The ongoing COVID-19 pandemic has caused more than 1 million deaths in the United States and continues to be a major public health challenge. Cases can be asymptomatic, or symptoms can range from a mild respiratory tract infection to acute respiratory distress and multiorgan failure.

Three strategies can successfully contain the pandemic and its consequences:

- Public health measures, such as masking and social distancing
- Prophylactic vaccines to reduce transmission
- Safe and effective drugs for reducing morbidity and mortality among infected patients.

Optimal treatment strategies for patients in ambulatory and hospital settings continue to evolve as new studies are reported and new strains of the virus arise. Many medical and scientific organizations, including the National Institutes of Health (NIH) COVID-19 treatment panel,[1] Infectious Diseases Society of America (IDSA),[2] World Health Organization (WHO),[3] and Centers for Disease Control and Prevention,[4] provide recommendations for managing patients with COVID-19. Their guidance is based on the strongest research available and is updated intermittently; nevertheless, a plethora of new data emerges weekly and controversies surround several treatments.

In this article, we summarize evidence for the efficacy of treatments for COVID-19. We present data based on the severity of illness, and review special considerations for some patient populations, including pregnant women and children. We focus on practical therapeutic information for primary care providers practicing in a variety of settings, including outpatient and inpatient care.

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When planning treatment, consider the availability of medications; the local COVID-19 situation; patient factors and preferences; and evolving evidence about treatments.

We encourage clinicians, in planning treatment, to consider:

- The availability of medications (ie, use the COVID-19 Public Therapeutic Locator[a])
- The local COVID-19 situation
- Patient factors and preferences
- Evolving evidence regarding new and existing treatments.

Most evidence about the treatment of COVID-19 comes from studies conducted when the Omicron variant of SARS-CoV-2 was not the dominant variant, as it is today in the United States. As such, drugs authorized or approved by the US Food and Drug Administration (FDA) to treat COVID-19 or used off-label for that purpose might not be as efficacious today as they were almost a year ago. Furthermore, many trials of potential therapies against new viral variants are ongoing; if your patient is interested in enrolling in a clinical trial of an investigational COVID-19 treatment, refer them to www.clinicaltrials.gov.

General management of COVID-19

Patients with COVID-19 experience a range of illness severity—from asymptomatic to mild symptoms, such as fever and myalgia, to critical illness requiring intensive care (**TABLE 1**[1,2]). Patients with COVID-19 should therefore be monitored for progression, remotely or in person, until full recovery is achieved. Key concepts of general management include:

Assess and monitor patients' oxygenation status by pulse oximetry; identify those with low or declining oxygen saturation before further clinical deterioration.

Consider the patient's age and general health. Patients are at higher risk of severe disease if they are > 65 years or have an underlying comorbidity.[4]

Emphasize self-isolation and supportive care, including rest, hydration, and over-the-counter medications to relieve cough, reduce fever, and alleviate other symptoms.

[a] https://healthdata.gov/Health/COVID-19-Public-Therapeutic-Locator/rxn6-qnx8/data

Drugs: Few approved, some under study

The antiviral remdesivir is the only drug fully approved for clinical use by the FDA to treat COVID-19 in patients > 12 years.[5,6]

In addition, the FDA has issued an emergency use authorization (EUA) for several monoclonal antibodies as prophylaxis and treatment: tixagevimab packaged with cilgavimab (Evusheld) is the first antibody combination for pre-exposure prophylaxis (PrEP) against COVID-19; the separately packaged injectables are recommended for patients who have a history of severe allergy that prevents them from being vaccinated or those with moderate or severe immune-compromising disorders.[7]

In the pipeline. Several treatments are being tested in clinical trials to evaluate their effectiveness and safety in combating COVID-19, including:

- Antivirals, which prevent viruses from multiplying
- Immunomodulators, which reduce the body's immune reaction to the virus
- Antibody therapies, which are manufactured antibodies against the virus
- Anti-inflammatory drugs, which reduce systemic inflammation and prevent organ dysfunction
- Cell therapies and gene therapies, which alter the expression of cells and genes.

Outpatient treatment

Several assessment tools that take into account patients' age, respiratory status, and comorbidities are available for triage of patients infected with COVID-19.[8]

Most (> 80%) patients with COVID-19 have mild infection and are safely managed as outpatients or at home.[9,10] For patients at high risk of severe disease, a few options are recommended for patients who do not require hospitalization or supplemental oxygen; guidelines on treatment of COVID-19 in outpatient settings that have been developed by various organizations are summarized in **TABLE 2**.[7,11-25]

Antiviral drugs target different stages of the SARS-CoV-2 replication cycle. They should be used early in the course of infection, particularly in patients at high risk of severe disease.

TABLE 1

Severity classification of coronavirus disease 2019[1,2]

Severity of disease	Signs and symptoms	Setting	Treatment options[1,2]
Asymptomatic infection[a]	None	Home monitoring	—
Mild illness	Fever, myalgia, cough, sore throat, nausea, vomiting, diarrhea, loss of smell and taste	Home or outpatient (tele)monitoring	Bebtelovimab Molnupiravir Nirmatrelvir + ritonavir Remdesivir Sotrovimab
Moderate Illness	Shortness of breath and associated symptoms but oxygen saturation ≥ 94% at rest *or* Abnormal chest imaging consistent with lower respiratory tract disease	Urgent care or referral to emergency department	Bebtelovimab Molnupiravir Nirmatrelvir + ritonavir Remdesivir Sotrovimab
Severe illness	Severe respiratory distress, with signs such as: • chest wall in-drawing • grunting • oxygen saturation < 94% • respiratory rate > 30 breaths/min • ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg • lung infiltrates > 50%	Inpatient hospitalization	Bebtelovimab Molnupiravir Nirmatrelvir + ritonavir Remdesivir Sotrovimab
Critical illness	Respiratory failure that requires mechanical ventilation or vasopressor therapy, including: • acute respiratory distress syndrome • septic shock • multiple organ dysfunction	Intensive care unit	Remdesivir Tocilizumab Baricitinib

[a] Tested positive for SARS-CoV-2 using an antigen test or a nucleic acid amplification test.

IDSA recommends antiviral therapy with molnupiravir, nirmatrelvir + ritonavir packaged together (Paxlovid), or remdesivir.[11,12,26,27] Remdesivir requires intravenous (IV) infusion on 3 consecutive days, which can be difficult in some clinic settings.[13,28] Nirmatrelvir + ritonavir should be initiated within 5 days after symptom onset. Overall, for most patients, nirmatrelvir + ritonavir is preferred because of oral dosing and higher efficacy in comparison to other antivirals. With nirmatrelvir + ritonavir, carefully consider drug–drug interactions and the need to adjust dosing in the presence of renal disease.[28,29] There are no data on the efficacy of any combination treatments with these agents (other than co-packaged Paxlovid).

Monoclonal antibodies for COVID-19 are given primarily intravenously. They bind to the viral spike protein, thus preventing SARS-CoV-2 from attaching to and entering cells. Bamlanivimab + etesevimab and bebtelovimab are available under an EUA for outpatient treatment.[14b] Treatment should be initiated as early as possible in the course of

[b] Sotrovimab was effective against the Omicron variant of SARS-CoV-2—the dominant variant in early 2022—but is currently not FDA authorized in any region of the United States because of the prevalence of the Omicron BA.2 subvariant.[30]

TABLE 2

Outpatient therapies for COVID-19[7,11-25]

Medication	Indication, disease severity	EUA or FDA approval status	SOR	Recommendations, comments	Estimated effectiveness
Pre-exposure and postexposure prophylaxis					
Tixagevimab + cilgavimab 300 mg + 300 mg as 2 separate but consecutive intramuscular injections Pediatric use: Indicated only for children ≥ 12 y and ≥ 40 kg, at the adult dosing (above)	Pre-exposure prophylaxis for moderately to severely immunocompromised patients who are at increased risk of inadequate immune response to vaccine or for whom vaccine is not recommended	EUA, December 2021	B	Should be administered 2 wk after COVID-19 vaccination Not authorized for use in unvaccinated patients unless full vaccination is not possible Reportedly offers as long as 12 months of protection Cilgavimab component might retain activity against Omicron variant of SARS-CoV-2 Patients who initially received 150 mg + 150 mg dosing should receive an additional dose of 150 mg + 150 mg if their initial dose was ≤ 3 mo earlier. If the initial dose was > 3 mo earlier, they should receive full dosing (300 mg + 300 mg)	*As pre-exposure prophylaxis:* Absolute risk reduction of developing symptomatic disease in unvaccinated patients compared to placebo = 0.8%[7] (median follow-up was 83 d) NNT = 13 *As postexposure prophylaxis:* Absolute risk reduction of developing symptomatic disease = 1.5%[7] NNT = 37
Treatment					
Bebtelovimab 175 mg IV push over ≥ 30 sec	Mild-to-moderate infection in outpatients at high risk of progressing to severe COVID-19	EUA, February 2022	B	Should be administered within 7 d of symptom onset Expected to retain activity against Omicron variant of SARS-CoV-2 and its subvariants	Efficacy is based on in vitro data showing activity against circulating Omicron subvariants, including BA.1, BA.1.1, and BA.2. Clinical efficacy data are from a small, Phase 2 clinical trial in subjects with mild-to-moderate COVID-19 who had low risk of progression; those who received bebtelovimab had more rapid viral decay than those who received placebo. Phase 3 clinical data are pending.[25] NNT = 17
Molnupiravir 800 mg PO q12h for 5 d	Mild-to-moderate infection in outpatients	EUA, December 2021	B	Studied in unvaccinated patients who had ≥ 1 risk factor for poor disease outcome and symptom onset ≤ 5 d before randomization	Absolute risk reduction of hospitalization or death through Day 29 compared to placebo = 2.9%[11] NNT = 35

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infection—ideally, within 7 to 10 days after onset of symptoms.

Bebtelovimab was recently given an EUA. It is a next-generation antibody that neutralizes all currently known variants and is the most potent monoclonal antibody against the Omicron variant, including its BA.2 subvariant.[31] However, data about its activity against the BA.2 subvariant are based on laboratory testing and have not been confirmed in clinical trials. Clinical data were similar for this agent alone and for its use in combination

TABLE 2

Outpatient therapies for COVID-19[7,11-25] (*cont'd*)

Medication	Indication, disease severity	EUA or FDA approval status	SOR	Recommendations, comments	Estimated effectiveness
			Treatment		
Nirmatrelvir + ritonavir (Paxlovid) 300 mg + 100 mg PO q12h for 5 d	Mild-to-moderate infection in outpatients at high risk of progressing to severe COVID-19	EUA, December 2021	B	Recommended initiation in ≤ 5 d of symptom onset in ambulatory patients with mild-to-moderate COVID-19 at high risk of progression to severe disease Significant drug interactions can occur with ritonavir component in many high-risk patients (eg, solid-organ transplant recipients) Requires dosage adjustment in the setting of moderate renal impairment	Absolute risk reduction of hospitalization or death at Day 28 compared to placebo = 6.2%[12] NNT = 17
Remdesivir 1 200-mg IV dose followed by 100-mg IV dose daily for 2 d Pediatric use (body weight, 3.5 to < 40 kg): 5 mg/kg IV dose on Day 1; then 2.5 mg/kg/dose once daily	Mild-to-moderate infection in outpatients at high risk of progressing to severe COVID-19	EUA, January 2022	A	Expected to retain activity against Omicron variant of SARS-CoV-2 Can be administered to outpatients as a 3-d course within 7 d of symptom onset in areas where Omicron variant of SARS-CoV-2 represents > 80% of infections; however, limited by logistical issues with administration	Absolute risk reduction of hospitalization or death at Day 28, compared to placebo = 4.6%[13] NNT = 22
Sotrovimab 1-time IV dose of 500 mg	Mild-to-moderate infection in outpatients at high risk of progressing to severe COVID-19	EUA, May 2021	B	Should be administered within 10 d of symptom onset Remains active against all current variants and subvariants of SARS-CoV-2	Absolute risk reduction of hospitalization or death at Day 28 compared to placebo = 6.0%[14] NNT = 17
			Supportive care		
NSAIDs	Supportive care	No	C	Systematic review and meta-analysis found that theoretical risks of NSAIDs or ibuprofen in COVID-19 infection are not confirmed by observational data. In COVID-19-positive patients, exposure to NSAIDs was not associated with excess risk of hospital admission (OR = 0.90; 95% CI, 0.80-1.17), death (OR = 0.88; 95% CI, 0.80-0.98), or severe outcomes (OR = 1.14; 95% CI, 0.90-1.44); with ibuprofen, there was no increased risk of death during study period (OR = 0.94; 95% CI, 0.78-1.13)[17]	
Acetaminophen	Supportive care	No	C	No systematic reviews or meta-analyses undertaken on the use of acetaminophen in COVID-19	

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TABLE 2

Outpatient therapies for COVID-19[7,11-25] (*cont'd*)

Medication	Indication, disease severity	EUA or FDA approval status	SOR	Recommendations, comments	Estimated effectiveness
Supportive care					
Nebulized medications	Supportive care	No	C	There is concern that use of nebulized medication might aerosolize SARS-CoV-2 and expose others Systematic review found that evidence is inconclusive that nebulizer therapy increases the risk of transmission of coronaviruses that are similar to COVID-19[23]	
Inhaled corticosteroids	Treatment	No	C	No recommendation for or against use Recent trials are promising but overall evidence of efficacy is unclear; in patients with chronic obstructive pulmonary disease or asthma, inhaled corticosteroids were associated with worse outcomes[18,19,24]	
Famotidine	Treatment	No	C	No recommendation for or against use	
Vitamin C	Treatment	No	C		
Vitamin D	Prophylaxis or treatment	No	C		
Zinc	Prophylaxis or treatment	No	C	No recommendation for or against use Adverse effects include nausea, vomiting, and changes in taste	
Not recommended for treating COVID-19 outside a clinical trial					
Angiotensin-converting enzyme inhibitors	Hypothetical harm or benefit, or both	No		Should be continued if indicated for treatment unrelated to COVID-19	
Bamlanivimab + etesevimab 1 IV dose of 700-1400 mg	Mild-to-moderate infection in outpatients at high risk of progressing to severe COVID-19	EUA, February 2021		Not recommended because of lack of benefit for Omicron variant of SARS-CoV-2	Absolute risk reduction for hospitalization or death by Day 29 compared to placebo = 4.9%[15] NNT = 21
Colchicine		No		Medication for gout; adverse effects range from diarrhea to myelosuppression	—
Convalescent plasma		EUA, August 2020		FDA previously issued an EUA for convalescent plasma in patients hospitalized with COVID-19 but narrowed the EUA to immunocompromised patients	—
Fluvoxamine (selective serotonin reuptake inhibitor)	Ambulatory patients with COVID-19	No		Risk of adverse effects range from headache to extrapyramidal symptoms	—

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TABLE 2

Outpatient therapies for COVID-19[7,11-25] (*cont'd*)

Medication	Indication, disease severity	EUA or FDA approval status	SOR	Recommendations, comments	Estimated effectiveness
Not recommended for treating COVID-19 outside a clinical trial					
Chloroquine, hydroxychloroquine		No		Risk of gastrointestinal symptoms and adverse cardiac events, such as QT prolongation	—
Ivermectin		No		Antiparasitic with risk of hypotension, tachycardia, seizures, and hepatitis	—
Lopinavir + ritonavir		No		Not recommended outside a clinical trial	—
Prednisone	Recommended only for hospitalized patients who meet certain criteria when dexamethasone is unavailable	No		Recommended only for hospitalized patients when dexamethasone is unavailable	—
Statin agents	Hypothetical harm or benefit, or both	No		Meta-analysis of observational studies found no significant reduction in in-hospital mortality or COVID-19 severity when comparing statin users and nonusers[16] Second meta-analysis determined that available evidence of moderate to high–intensity statin therapy might be effective but more data, from prospective studies, are needed[17]	—

EUA, emergency use authorization; FDA, US Food and Drug Administration; IV, intravenous; NNT, number needed to treat; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; SOR, strength of recommendation.

with other monoclonal antibodies, but those trials were conducted before the emergence of Omicron.

In your decision-making about the most appropriate therapy, consider (1) the requirement that monoclonal antibodies be administered parenterally and (2) the susceptibility of the locally predominating viral variant.

Other monoclonal antibody agents are in the investigative pipeline; however, data about them have been largely presented through press releases or selectively reported in applications to the FDA for EUA. For example, preliminary reports show cilgavimab coverage against the Omicron variant[14]; so far, cilgavimab is not approved for treatment but is used in combination with tixagevimab for PreP—reportedly providing as long as 12 months of protection for patients who are less likely to respond to a vaccine.[32]

Corticosteroids. Guidelines recommend against dexamethasone and other systemic corticosteroids in outpatient settings. For patients with moderate-to-severe symptoms but for whom hospitalization is not possible (eg, beds are unavailable), the NIH panel recommends dexamethasone, 6 mg/d, for the duration of supplemental oxygen, not to exceed 10 days of treatment.[1]

Patients who were recently discharged after COVID-19 hospitalization should not continue remdesivir, dexamethasone, or baricitinib at home, even if they still require supplemental oxygen.

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Because patients with COVID-19 experience a range of illness severity, they should be monitored for progression, remotely or in person, until fully recovered.

Some treatments should not be in your COVID-19 toolbox

High-quality studies are lacking for several other potential COVID-19 treatments. Some of these drugs are under investigation, with unclear benefit and with the potential risk of toxicity—and therefore should not be prescribed or used outside a clinical trial. See "Treatments *not* recommended for COVID-19," page E14.[1-4,15-19,33-41]

Treatment during hospitalization

The NIH COVID-19 treatment panel recommends hospitalization for patients who have any of the following findings[1]:

- Oxygen saturation < 94% while breathing room air
- Respiratory rate > 30 breaths/min
- A ratio of partial pressure of arterial O_2 to fraction of inspired O_2 (PaO_2/FiO_2) < 300 mm Hg
- Lung infiltrates > 50%.

General guidance for the care of hospitalized patients:

- Treatments that target the virus have the greatest efficacy when given early in the course of disease.
- Anti-inflammatory and immunosuppressive agents help prevent tissue damage from a dysregulated immune system. (See **TABLE 3**[26,42-46])
- The NIH panel,[1] IDSA,[2] and WHO[3] recommend against dexamethasone and other corticosteroids for hospitalized patients who do not require supplemental oxygen.
- Prone positioning distributes oxygen more evenly in the lungs and improves overall oxygenation, thus reducing the need for mechanical ventilation.

Remdesivir. Once a hospitalized patient does require supplemental oxygen, the NIH panel,[1] IDSA,[2] and WHO[3] recommend remdesivir; however, remdesivir is not recommended in many other countries because WHO has noted its limited efficacy.[42] Dexamethasone is recommended alone, or in combination with remdesivir for patients who require increasing supplemental oxygen and those on mechanical ventilation.

Baricitinib. For patients with rapidly increasing oxygen requirements, invasive mechanical ventilation, and systemic inflammation, baricitinib, a Janus kinase inhibitor, can be administered, in addition to dexamethasone, with or without remdesivir.[47]

Tocilizumab. A monoclonal antibody and interleukin (IL)-6 inhibitor, tocilizumab is also recommended in addition to dexamethasone, with or without remdesivir.[48] Tocilizumab should be given only in combination with dexamethasone.[49] Patients should receive baricitinib or tocilizumab—not both. IDSA recommends tofacitinib, with a prophylactic dose of an anticoagulant, for patients who are hospitalized with severe COVID-19 but who are not on any form of ventilation.[50]

Care of special populations

Special patient populations often seek primary care. Although many questions remain regarding the appropriate care of these populations, it is useful to summarize existing evidence and recommendations from current guidelines.

Children. COVID-19 is generally milder in children than in adults; many infected children are asymptomatic. However, infants and children who have an underlying medical condition are at risk of severe disease, including multisystem inflammatory syndrome.[51]

The NIH panel recommends supportive care alone for most children with mild-to-moderate disease.[1] Remdesivir is recommended for hospitalized children ≥ 12 years who weigh ≥ 40 kg, have risk factors for severe disease, and have an emergent or increasing need for supplemental oxygen. Dexamethasone is recommended for hospitalized children requiring high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation. Molnupiravir is *not* authorized for patients < 18 years because it can impede bone and cartilage growth.

There is insufficient evidence for or against the use of monoclonal antibody products for children with COVID-19 in an ambulatory setting. For hospitalized children, there

TABLE 3

Inpatient treatment of COVID-19[26,42-46]

Medication	Indication, disease severity	EUA or FDA approval status for COVID-19	SOR	Recommendations, comments	Estimated effectiveness
			Treatment		
Baricitinib 4 mg/d PO for 14 d or until discharge Pediatric use: • children 2 to < 9 y: 2 mg/d po • children ≥ 9 y to adolescence: 4 mg/d po	Severe or critically ill hospitalized patients	EUA, November 2020	B	Also used to treat rheumatoid arthritis Baricitinib (*or* tocilizumab) should be used in recently hospitalized patients who have a high oxygen requirement with either evidence of clinical progression or elevated levels of inflammatory markers Ideally, utilized in addition to remdesivir and dexamethasone Do not use in patients who have received tocilizumab Available in a crushable and renal dose-adjusted oral formulation Avoid in patients with: • a history of clot (previous 12 wk) • absolute neutrophil count < 500/μL • absolute lymphocyte count < 200/μL Contraindicated in: • active tuberculosis • uncontrolled systemic infection • liver injury > 10 times the upper limit of normal • creatinine clearance ≦ 15 mL/min without continuous renal replacement therapy • anticipated death within 48 h Tofacitinib, similar to baricitinib and studied in a randomized controlled clinical trial, is an alternative treatment that can be used in patients with severe COVID-19 who are not on any form of mechanical ventilation (invasive or noninvasive)	Baricitinib + remdesivir decreased time to recovery by a median of 1 d[43] Absolute risk of all-cause mortality by Day 28 in hospitalized patients = 4.5%[43] All-cause mortality over trial period = 12.5% in controls, compared to 8.0% in treated patients[43] NNT = 23

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is insufficient evidence for or against use of baricitinib and tocilizumab.

Patients who are pregnant are at increased risk of severe COVID-19.[52,53] The NIH states that, in general, treatment and vaccination of pregnant patients with COVID-19 should be the same as for nonpregnant patients.[1]

Pregnant subjects were excluded from several trials of COVID-19 treatments.[54] Because Janus kinase inhibitors, such as baricitinib, are associated with an increased risk of thromboembolism, they are not recommended in pregnant patients who are already at risk of thromboembolic complications. Molnupiravir is not recommended for pregnant patients because of its potential for teratogenic effects.

The Society for Maternal-Fetal Medicine states that there are no absolute contraindications to the use of monoclonal antibodies in appropriate pregnant patients with

TABLE 3

Inpatient treatment of COVID-19[26,42-46] (*cont'd*)

Medication	Indication, disease severity	EUA or FDA approval status for COVID-19	SOR	Recommendations, comments	Estimated effectiveness
			Treatment		
Dexamethasone 6 mg/d IV or po for ≤ 10 d Children: 0.15 mg/kg once daily for ≤ 10 d; maximum dose, 6 mg	Severe or critically ill hospitalized patients	No	A	Do not use in hospitalized patients if (1) COVID-19 is not severe and (2) they do not require supplemental oxygen for hypoxemia Adverse effects include hyperglycemia and mood disturbances	Decreased mortality at Day 28 in patients who are mechanically ventilated or require oxygen—but not in hospitalized patients who do not require oxygen[44] NNT: • overall, for recovery = 36 • with invasive mechanical ventilation = 9 • with oxygen but without invasive mechanical ventilation = 35
Remdesivir 1 dose of 200 mg IV, followed by 100 mg/d IV for 4 d	Hospitalized patients with COVID-19	EUA, May 2020	B	Can be discontinued upon discharge if course has not been completed Generally well-tolerated Can be considered for hospitalized patients who: • do not require supplemental oxygen • require supplemental oxygen, but do *not* require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation • require high-flow oxygen or noninvasive ventilation (in addition to receiving baricitinib + dexamethasone *or* tocilizumab + dexamethasone)	Outcomes data are in conflict: • Adaptive COVID-19 Treatment Trial found faster recovery (11 d, compared to 15 d) and lower mortality (NNT = 21)[26] • WHO Solidarity Trial reported a trend toward benefit among nonventilated patients (RR = 0.80; 95% CI, 0.63-1.01) and a trend toward harm (RR = 1.16; 95% CI, 0.85-1.60) among patients on mechanical ventilation[42]

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COVID-19.[55] Remdesivir has no known fetal toxicity and is recommended as a treatment that can be offered to pregnant patients. Dexamethasone can also be administered to pregnant patients who require oxygen; however, if dexamethasone is also being used to

TABLE 3

Inpatient treatment of COVID-19[26,42-46] (*cont'd*)

Medication	Indication, disease severity	EUA or FDA approval status for COVID-19	SOR	Recommendations, comments	Estimated effectiveness
			Treatment		
Tocilizumab 1 dose of 8 mg/kg IV; maximum dose, 800 mg Pediatric use: • < 30 kg: One 12 mg/kg IV dose • ≥ 30 kg: One 8 mg/kg IV dose Maximum dose, 800 mg	Severe disease in combination with dexamethasone for patients who have rapid respiratory decompensation	EUA, June 2021	A	Systematic review found a lower risk (1) of death and (2) mechanical ventilatlion requirement during duration of trials[46] Tocilizumab (*or* baricitinib) should be used in recently hospitalized patients who have a high oxygen requirement with either evidence of clinical progression or increased levels of inflammatory markers Sarilumab is an alternative if tocilizumab is unavailable	Decreased 28-d mortality (22.3%, compared to 27.3%)[45]; NNT = 21 (but only in patients also being treated with a corticosteroid) Decreased duration of progression to invasive mechanical ventilation or death (26.6% compared to 33.8%)[45]; NNT = 14
			Not recommended		
Convalescent plasma	Not recommended	EUA, August 2020		Not recommended outside a clinical trial	—

EUA, emergency use authorization; FDA, US Food and Drug Administration; IV, intravenous; NNT, number needed to treat; RR, relative risk; SOR, strength of recommendation.

accelerate fetal lung maturity, more frequent initial dosing is needed.

Older people. COVID-19 treatments for older patients are the same as for the general adult population. However, because older people are more likely to have impaired renal function, renal function should be monitored when an older patient is being treated with COVID-19 medications that are eliminated renally (eg, remdesivir, baricitinib). Furthermore, drug–drug interactions have been reported in older patients treated with nirmatrelvir + ritonavir, primarily because of the effects of ritonavir. Review all of a patient's medications, including over-the-counter drugs and herbal supplements, when prescribing treatment for COVID-19, and adjust the dosage by following guidance in FDA-approved prescribing information—ideally, in consultation with a pharmacist.

Immunocompromised patients. The combination product tixagevimab + cilgavimab [Evusheld] is FDA approved for COVID-19 PrEP, under an EUA, in patients who are not infected with SARS-CoV-2 who have an immune-compromising condition, who are unlikely to mount an adequate immune response to the COVID-19 vaccine, or those in whom vaccination is not recommended because of their history of a severe adverse reaction to a COVID-19 vaccine or one of its components.[7]

Summing up

With a growing need for effective and readily available COVID-19 treatments, there are an unprecedented number of clinical trials in process. Besides antivirals, immunomodulators, and antibody therapies, some novel mechanisms being tested include Janus kinase inhibitors, IL-6-receptor blockers, and drugs that target adult respiratory distress syndrome and cytokine release.

Once larger trials are completed, we can expect stronger evidence of potential treatment options and of safety and efficacy in children, pregnant women, and vulnerable populations. During the pandemic, the FDA's EUA program has brought emerging treatments rapidly to clinicians; nevertheless,

Treatments not recommended for COVID-19[1-4,15-19,33-41]

Fluvoxamine. A few studies suggest that the selective serotonin reuptake inhibitor fluvoxamine reduces progression to severe disease; however, those studies have methodologic challenges.[33] The drug is *not* FDA approved for treating COVID.[33]

Convalescent plasma, given to high-risk outpatients early in the course of disease, can reduce progression to severe disease,[34,35] but it remains investigational for COVID-19 because trials have yielded mixed results.[34-36]

Ivermectin. The effect of ivermectin in patients with COVID-19 is unclear because high-quality studies do not exist and cases of ivermectin toxicity have occurred with incorrect administration.[39]

Hydroxychloroquine showed potential in a few observational studies, but randomized clinical trials have not shown any benefit.[15]

Azithromycin likewise showed potential in a few observational studies; randomized clinical trials have not shown any benefit, however.[15]

Statins. A few meta-analyses, based on observational studies, reported benefit from statins, but recent studies have shown that this class of drugs does not provide clinical benefit in alleviating COVID-19 symptoms.[16,17,37]

Inhaled corticosteroids. A systematic review reported no benefit or harm from using an inhaled corticosteroid.[18] More recent studies show that the inhaled corticosteroid budesonide used in early COVID-19 might reduce the need for urgent care[38] and, in patients who are at higher risk of COVID-19-related complications, shorten time to recovery.[19]

Vitamins and minerals. Limited observational studies suggest an association between vitamin and mineral deficiency (eg, vitamin C, zinc, and vitamin D) and risk of severe disease, but high-quality data about this finding do not exist.[40,41]

Casirivimab + imdevimab [REGEN-COV2]. This unapproved investigational combination treatment was granted an EUA in 2020 for postexposure prophylaxis. The EUA was withdrawn in January 2022 because of the limited efficacy of casirivimab + imdevimab against the Omicron variant of SARS-CoV-2.

Postexposure prophylaxis. National guidelines[1-4] recommend against postexposure prophylaxis with hydroxychloroquine, colchicine, inhaled corticosteroids, or azithromycin.

TABLE 2[7,11-25] and **TABLE 3**[26,42-46] provide additional information on treatments not recommended outside trials, or not recommended at all, for COVID-19.

high-quality evidence, with thorough peer review, remains critical to inform COVID-19 treatment guidelines. JFP

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