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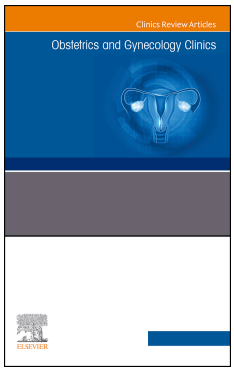


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# COVID-19 Therapeutics and Considerations for Pregnancy

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## Synopsis

The COVID-19 pandemic has generated an unprecedented amount of novel and repurposed vaccines and therapeutics which have been rapidly developed and implemented into clinical use. Unfortunately, pregnant persons have been excluded from most phase III clinical studies; therefore, our understanding regarding their safety for use in this population stems from understanding of theoretical risks and observational data. In this review, we discuss pregnancy-specific considerations for COVID-19 therapeutics.

## Key Points

- COVID-19 is associated with heightened risk for worsened disease severity and poor obstetric outcomes.

- Although COVID-19 therapeutics have not been adequately studied in pregnancy, safe options exist for the pharmacologic treatment of mild, moderate, or severe disease in pregnancy.
- Vaccination in pregnancy is safe and associated with both maternal and neonatal protection against severe disease.

## Introduction

The unprecedented impact of the novel Coronavirus Disease 2019 (COVID-19) pandemic has been met with equally unprecedented scientific innovation. Over 3,000 vaccine and drug clinical trials are underway or completed,[1] yet 80% excluded pregnant patients,[2] resulting in administration to pregnant patients without research protocol safeguards or delay in the receipt of life-saving interventions. Considerations for the clinical management of COVID-19 disease in pregnancy have been published and basic tenets remain mostly unchanged.[3,4] However, the data supporting the use of vaccines and therapeutics have evolved and warrant pregnancy-specific consideration.

## Perinatal Implications

Multiple studies demonstrate that pregnancy is associated with a higher risk for severe COVID-19 disease, defined by intensive care unit (ICU) admission, mechanical ventilation, extracorporeal membrane oxygenation (ECMO) and death, compared to nonpregnant persons.[5,6] Compared to unaffected pregnancies, COVID-19 disease in pregnancy is associated with increased risk for preeclampsia,[7,8] cesarean delivery, and severe maternal morbidity from direct obstetric causes.[8] A systematic review including 42 studies comparing fetal and neonatal outcomes in pregnant patients with and without confirmed SARS-CoV-2 infection demonstrated 2-fold increased risk for stillbirth, low birth weight and prematurity.[7] Whether there is increased risk for other neonatal complications, such as neonatal ICU admission, respiratory disorders and hyperbilirubinemia is controversial, and may be

mediated by disease severity.[9] Congenital infection does occur in 1-3%.[10–12] There is insufficient data to describe a congenital viral syndrome or to clarify disease severity in infants born with infection. There is a global registry to better understand long term childhood and adult outcomes following prenatal exposure to SARS-CoV-2 infection.[13]

**COVID-19 Drug Treatments**

COVID-19 therapeutics impact the two main pathophysiologic processes implicated in disease progression. The early phase is driven by SARS-CoV-2 viral replication, while progression to multi-organ involvement in the later phase is driven by cytokine release syndrome. Therefore, therapies that directly target and limit viral replication have the greatest efficacy early in the disease course, while immunosuppressive/anti-inflammatory therapies are more beneficial in later stages of the disease.

Outpatient Treatments

High-risk, non-hospitalized patients with mild or moderate COVID-19[29] may be offered secondary preventive therapeutics to reduce the risk of severe disease and death. Pregnant or recently pregnant individuals are included in the “high-risk” criteria, which also includes age ≥ 65 years, Hispanic, non-Hispanic Black, American Indian or Alaska Natives race/ethnicity, and certain medical conditions (*e.g.*, active malignancy, chronic lung, liver, or kidney disease, cystic fibrosis, insulin dependent diabetes mellitus, cardiac conditions, disabilities, primary and secondary immunodeficiency, use of corticosteroids or other immunosuppressive medications). Available antivirals include bebtelovimab, remdesivir, nirmatrelvir/ritonavir, and molnupiravir (Table 1).

*Bebtelovimab*

Bebtelovimab is a monoclonal antibody (MAb) targetting the highly antigenic and immunogenic surface spike glycoprotein of the SARS-CoV-2 virus. As a drug class, MAbs have low potential for adverse effects (hypersensitivity reaction in < 1%) or significant drug interactions (not metabolized by cytochrome P450 enzymes). MAbs readily cross the placenta; the degree of fetal transfer is variable and depends on specific drug structure, drug half-life, dose, and the timing of the last dose in relation to the gestational age.[14] Transfer is minimal during the first trimester and occurs by simple diffusion. By 20 weeks, MAbs are actively transferred in increasing amounts across the placenta, with the highest rate occurring after 36 weeks. Although not empirically studied, this may have added benefit of protecting infants younger than 6 months from severe COVID-19. Nonclinical and observational data have not demonstrated increased risk for birth defects in exposed infants.[15]

Bebtelovimab is currently recommended because it retains activity against Omicron. Although not studied in phase 3 clinical trials, MAbs used prior to widespread circulation of Omicron were associated with 70% relative reduction in COVID-19 related hospitalization or death from any cause, including in pregnant patients.[16–18] It may be offered to high risk patients who present more than five days from symptom onset or positive viral test when first line antivirals are not available.[19]

Tixagevimab/cilgavimab reduces the risk of symptomatic COVID-19 by 77% and is the only currently available antiviral for pre-exposure prophylaxis. It can offered to uninfected individuals with moderate to severe immune compromise who are unlikely to mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccine is not recommended.[20,21] Pregnancy-specific effectiveness data are not available.

*Ritonavir-boosted nirmatrelvir*

Nirmatrelvir, which is metabolized by CYP3A enzyme, inhibits viral replication through direct inhibition of the SARS-CoV-2 main protease. Ritonavir is an HIV-1 protease inhibitor, has no activity against SARS-CoV-2, but functions to boost nirmatrelvir plasma levels by inhibition of the CYP3A enzyme. These medications are co-packaged and sold under the commercial name Paxlovid™. Paxlovid is 89.1% effective in reducing the incidence of COVID-19–related hospitalization or death in patients treated within five days of symptom onset.[22] Preliminary data suggests it retains effectiveness in vaccinated individuals.[23]

Paxlovid is currently the preferred treatment of mild COVID-19 in high-risk individuals and ideally is administered within 5 days of positive test or symptom onset. There are no available human data on the use of nirmatrelvir during pregnancy to evaluate drug-associated risks of major birth defects, miscarriage, adverse maternal or fetal outcomes, or its pharmacokinetics, given the known increase in CYP3A activity in pregnancy. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects.[24] While placental transfer of ritonavir occurs, fetal ritonavir concentrations are low.

*Remdesivir*

Remdesivir is an antiviral initially indicated for treatment in hospitalized patients until the PINETREE trial demonstrated that the highest mortality benefit occurred in patients whose treatment was initiated early in the disease course.[25] It is administered as a 3-day infusion and is resource intensive, which limits its use. Remdesivir has not been approved specifically for use in pregnancy. Data suggest a low (16%) rate of serious adverse events and high tolerablity,[26] yet efficacy, and pharmacokinetic data are lacking. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network is currently comparing remdesivir pharmacokinetics in pregnant and non-pregnant women of reproductive age who are hospitalized with COVID-19 to assess pregnancy-specific adverse events.[27]

*Molnupiravir*

Molnupiravir is a nucleoside analogue (NA) antiviral that acts by causing chain termination of nascent viral DNA. NAs are currently used to treat viral infections, rheumatologic disorders, and cancer.[28] Despite being named after Mjölnir, the hammer of the god Thor, the observed effect showed that it was only 30% effective in reducing the risk of hospitalization of death, compared to untreated patients.[29] In addition to its reduced efficacy, there are several concerns which limit use in pregnancy. First, the greatest benefit was observed in patients who initiated therapy within 72 hours of symptom onset, however a readily available diagnostic test is unavailable. Second, mutagenic and carcinogenic toxicity have been demonstrated in mammalian hamster models, but in vivo risk is under debate.[30,31] Finally, although there are no human pregnancy data, animal data reported in the Food and Drug Administration's Emergency Use Authorization suggested risk for embryo toxicity, lethality, mutagenicity, and low birthweight.[32] Nonetheless, as one of two orally bioavailable therapies for COVID-19 it retains a role in the arsenal. Molnupiravir is recommended when nirmatrelvir or remdesivir are not available or not appropriate, often because of potential drug interactions with ritonavir, and should only be offered to pregnant individuals after consideration of alternative therapies, risk for severe disease, and fetal risk.

Inpatient Treatments

Therapeutic management of adults hospitalized for COVID-19 is based on disease severity and includes the use systemic corticosteroids, antiviral and immunomodulatory therapy (Table 2).[33]

*Corticosteroids*

Corticosteroids are currently standard of care in the treatment of severe disease for both pregnant and nonpregnant people. Dexamethasone was the first trial-proven beneficial treatment for COVID-19. In the RECOVERY randomized controlled trial, dexamethasone reduced the risk of all-cause mortality in patients requiring invasive mechanical ventilation by 36% compared to placebo.[34] It is administered as a once daily oral or intravenous dose of 6mg for up to 10 days.

Dexamethasone (and betamethasone) is preferentially administered to women at high risk for preterm birth within seven days. Unlike other steroids, which are extensively metabolized by placental 11-b-hydroxlase steroid dehydrogenase-2, dexamethasone and betamethasone have high rates of placental transfer and have been shown to reduce the rates of pulmonary, neurologic, and infectious morbidity and mortality associated with prematurity. However, repeated courses have been associated with deleterious effects, such as decreased fetal head circumference, fetal growth restriction, and impaired neurodevelopment. [35] After the RECOVERY trial was published, debate ensued regarding how to manage critically ill pregnant patients, as dexamethasone was the only proven treatment with mortality benefit, yet repeated doses were associated with significant fetal or neonatal adverse outcomes. [36] However, a landmark meta-analysis evaluating dexamethasone, hydrocortisone, and methylprednisolone demonstrated the mortality benefit as a class effect of corticosteroids. [37] Given concerns regarding impact of repeated prenatal steroid exposure on long-term neurodevelopment and the presence of reassuring effectiveness data for other steroids, hydrocortisone or methylprednisolone, rather than dexamethasone, should be administered to pregnant patients with severe COVID-19 meeting criteria. If there is a high likelihood of preterm delivery, clinicians should first administer IV dexamethasone or betamethasone, dosed for fetal lung maturity, then complete the steroid course using hydrocortisone or methylprednisolone.

*Remdesivir*

The effectiveness of remdesivir for inpatient adults with severe COVID-19 has been mixed.[38,39] The Adaptive Covid-19 Treatment Trial showed that remdesivir led to a shorter median time from randomization to recovery (10 days, vs. 15 days with placebo) and may have reduced the time to hospital discharge (12 days vs. 17 days), yet no mortality benefit in mechanically ventilated patients.[40] However, the Solidarity Trial meta-analysis showed a modest mortality benefit (remdesivir 14.6% vs control 16.3%; RR 0.87, 95% CI 0.76–0.99, p=0.03) and a reduction in need for mechanical ventilation. (23.7% vs 27.1%; RR 0.83, 95%CI 0.75–0.93, p =0.001).[41] Remdesivir is recommended for hospitalized patients with moderate or severe disease, not requiring invasive ventilation or ECMO. An intravenous 200mg loading dose is administered on day 1, followed by 100mg intravenous from day 2. For patients who require minimal oxygen supplementation, the recommended treatment duration is 5 days. For patients requiring escalating oxygen support, the recommended treatment duration is 10 days.[41] Although efficacy data in pregnant patients are lacking, remdesivir should be offered to pregnant patients who meet clinical criteria.

*IL-6 Inhibitors*

Hyperactivation of the immune response, including release of pro-inflammatory cytokines such as interleukin-6 (IL-6) is implicated in pathophysiology of severe illness. Tocilizumab is a recombinant humanized monoclonal antibody that inhibits binding of IL-6 to its receptors.[42]
Tocilizumab has been associated with a 15% - 44% reduction in need for mechanical ventilation and a 15% reduction in all-cause mortality, when given in combination with steroids or remdesivir.[43,44] It is currently recommended as adjunctive treatment of severe or critically ill patients. The available pregnancy data for tocilizumab are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage with exposure. The Developmental and Reproductive Toxicity Data (DART) shows embryo-fetal lethality at concentrations 1.25 times higher than the maximum

recommended human dose.[45] IL-6 inhibition may theoretically delay parturition through interference with cervical ripening and dilation.

*Janus Kinase (JAK) inhibitors*

JAK inhibitors reduce cytokine and growth factor stimulation leading to reduced immune cell function. Baricitinib is currently available on a case-by-case basis in patients with rapidly increasing oxygen requirements and evidence of systemic inflammation. It is orally administered and only given in combination with dexamethasone or another corticosteroid.[46]

The data on effectiveness of JAK inhibitors are inconclusive. The COV-BARRIER trial did not find a statistically significant benefit for baricitinib in patients on low-flow oxygen; however, patients were also receiving remdesivir and steroids.[47]

An increased risk of serious infection (e.g., *Strongyloides*, herpes zoster, tuberculosis, protozoal), gastrointestinal perforations and venous thromboembolism have been described in patients receiving either JAK or IL-6 inhibitors. Embryo-fetal toxicities including skeletal anomalies have been observed in animal studies; however, the limited data on use of baricitinib in pregnancy are not sufficient to inform a drug-associated risk for major birth defects or miscarriage.[48]

*Anticoagulation*

Severe and critical COVID-19 is associated with an inflammatory and hypercoagulable state characterized by increased D-dimers, fibrin, fibrin degradation products and fibrinogen. Yet trials evaluating the efficacy and safety of different antithrombotic regimens in patients with COVID-19 have found little benefit of therapeutic anticoagulation in the treatment of mild, moderate, or severe disease.

Additionally, a clinically significant increased risk of major bleeding events in patients receiving therapeutic dose anticoagulation has been consistent across all trials.[49–52] In mild disease, neither aspirin, prophylactic or therapeutic coagulation has demonstrated any benefit against risk for symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause.[53]

The failure of anticoagulation to demonstrate a benefit suggests that COVID-19 thrombosis is immunologically mediated, rather than through the conventional VTE pathway.

Pregnant patients were excluded from these trials and pregnancy is known to confer additional increased risk for VTE. The only available data evaluating the combined risks of COVID-19, pregnancy and venous or arterial thromboembolisms are limited by their retrospective nature and lack of appropriate controls.[54] Based on the available data, there does not appear to be a role for prophylactic anticoagulation in the outpatient setting. Prophylactic anticoagulation should be administered to all hospitalized pregnant patients. The choice to use intermediate dosing should be guided by disease severity, patient mobility, and patient risk factors (i.e., BMI > 30 kg/m2, multifetal gestation, personal history of thrombophilia disorder). Therapeutic anticoagulation should be reserved for patients with active VTE.

**Vaccination**

Vaccination is the primary mode of protection against SARS-CoV-2. It is currently recommended that pregnant people receive either of the two available mRNA vaccines (Pfizer-BioNTech's BNT162b2[55] or Moderna/NIAID's mRNA-1273[56]). Both vaccines instruct cells to make large amounts of spike protein antigen, mimicking natural infection, but induce a rapid, robust humoral immune response.[57] Other COVID-19 vaccines are available in the US; however, the COVID-19 protein-subunit and adenovirus vector vaccines are not preferred for use in pregnancy.

Initial vaccine data for use in pregnancy was derived from inadvertent inclusion of pregnant persons in clinical trials which demonstrated no increased rates of adverse effects.[58] Subsequently, a report of 3,958 participants enrolled the CDC's V-safe Surveillance System and Pregnancy Registry demonstrated pregnancy outcomes such as miscarriage, stillbirth, congenital anomalies, small for gestational age, and preterm birth did not differ significantly in vaccinated patients when compared against historic controls.[59] Additionally, reactogenicity and immunogenicity data were reassuring. The most common events, injection-site pain, fatigue, headache, myalgia, and fever, were more prevalent following the second dose, and occurred much less frequently in pregnant, compared to non-pregnant women.[60] Multiple other epidemiologic studies have failed to identify an association of COVID-19 vaccination with adverse fetal/neonatal outcomes such a stillbirth, prematurity, or congenital anomalies.[59,61,62]

COVID-19 mRNA vaccines elicit similar immune responses in pregnant and non-pregnant adults. A prospective study enrolled 103 women, 30 of whom were pregnant and 16 lactating. Binding, neutralizing, and functional non-neutralizing antibody responses as well as CD4 and CD8 T cell responses in pregnant, lactating, and non-pregnant women following vaccination were present in equal amounts, and higher than immune response following natural infection.[63,64] Binding and neutralizing antibodies were also observed in infant cord blood and breast milk.

Vaccination is equally effective in protection against severe disease and averting COVID-19 related pregnancy complications. An observational cohort of 10,861 vaccinated pregnant patients matched to 10,861 unvaccinated pregnant without prior history of infection showed 89% effectiveness against hospitalization and severe disease 7 to 77 days after the second dose.[65] Another study demonstrating protection from adverse pregnancy outcomes included 1,332 vaccinated patients and 8,760

incompletely vaccinated or unvaccinated patients, and found a higher association with stillbirth in unvaccinated patients with infection *vs*. vaccinated patients with breakthrough infection.[66]

Finally, maternal vaccination is associated with neonatal benefit through passive immunity. Infants younger than 6 months are especially vulnerable given dampened immunity. Transplacental antibody transfer is an important source of protection from COVID-19 in this group. Studies have demonstrated that infant concentrations are increased and more persistent following maternal vaccination compared to maternal infection, especially when delivery occurs at least one week following the second mRNA dose.[63,67,68] A large, multicenter, case-controlled of 1000 mother-infant pairs, half of whom had received COVID-19 vaccination during pregnancy demonstrated that maternal vaccine effectiveness against COVID-19-associated hospitalization among infants was 52% and against ICU admission for infants at 70%.[69] These data support current recommendations for COVID-19 vaccination for all persons who are pregnant or considering pregnancy, or lactating.[2,70]

The current immunization schedule for persons 18 years of age or older include a two-dose primary series with either monovalent mRNA COVID-19 vaccine or the monovalent protein subunit vaccine, given 4 – 8 weeks or 3 weeks apart, respectively. A single dose mRNA bivalent booster vaccine should be given 8 weeks following.[71] Vaccination is also recommended in previously infected individuals.[72]

## Conclusions

Despite substantial research and therapeutic developments arising out of necessity during the global pandemic, there are still many unanswered questions. Data on how pregnancy affects the pharmacokinetics or effectiveness of current interventions are limited. It is unclear how in utero exposure to SARS-CoV-2 *versus* treatments affect long-term child development.

Clinicians must therefore be prepared to discuss the evidence for safety, effectiveness, maternal and fetal risks with non-treatment, and potential for harms with treatment options during pregnancy. In addition, clinicians should be empowered to advocate for inclusion and access to live-saving interventions for their pregnant patients.

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513

514 **TABLES**

515

516 Table 1. Outpatient Therapeutics and Considerations in Pregnancy

517

| Agent | **Remdesivir** | **Nirmatrelvir/ritonavir** | **Molnupiravir** | **Bebtelovimab** | **Tixagevimab/cilgavimab** |
|---|---|---|---|---|---|
| Drug Class | Antiviral agent<br>RNA polymerase inhibitor | Antiviral agent<br>SARS-CoV-2 main protease inhibitor (Mpro)<br>HIV-1 protease inhibitor and Mpro concentration booster | Antiviral agent<br>nucleoside inhibitor | Antiviral agent<br>monoclonal antibody | Antiviral agent<br>monoclonal antibody |
| Dose | Day 1: 200mg<br>Day 2 and 3: 100mg | Nirmatrelvir 300mg (two 150mg tablets) with ritonavir 100mg TWICE daily for five days | 800 mg twice daily for 5 days (four 200mg capsules) | 175 mg once | Tixagevimab 150mg and cilgavimab 150 mg administered every 6 months while SARS-CoV-2 in circulation |
| Route of Administration | Intravenous infusion over 30 – 120 minutes | Oral (Do not crush) | Oral (Do not crush) | Intravenous infusion over 30 seconds | 2 separate intramuscular injections in separate sites |
| Dose Adjustments | Renal:<br>○ eGFR < 30 mL/min: Theoretical risk SBECD accumulation in kidneys, manufacturer labeling does not recommend, however significant toxicity with 5-10 days treatment unlikely, multiple studies have not shown adverse events. Discuss risk/benefit with patient<br>Hepatic:<br>○ ALT >10 times upper limit, consider discontinuation | Renal:<br>○ eGFR ≥ 30 to < 60 mL/min nirmatrelvir 150mg with ritonavir 100mg TWICE daily for five days<br>○ eGFR < 30 mL/min: Not recommended<br>Hepatic:<br>○ Child-Pugh C: Not recommended | None | None | None |
| Drug-Drug Interactions | Chloroquine, hydroxychloroquine, CYP3A inducers | Significant CYP3A interactions; review patient's other medications for possible temporary discontinuation | Cladribine | None | None |
| Indication | Mild to moderate COVID-19 or positive direct SARS-CoV-2 viral test and at high risk for progression to severe disease | | | | Pre-exposure prophylaxis |

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| Time Frame from Symptom Onset | ≤ 7 days | ≤ 5 days | ≤ 3-5 days | ≤ 7 days | |
| Contraindications and Considerations | ○ Hypersensitivity<br>○ Chloroquine or Hydroxychloroquine may diminish therapeutic effect of RDV<br>○ CYP3A inducers may decrease serum concentration RDV | ○ eGFR < 30 mL/min<br>○ Severe hepatic impairment (Child-Pugh Class C)<br>○ CYP3A inducers may reduce nirmatrelvir or ritonavir plasma concentrations leading to loss of virologic response and resistance<br>○ CYP3A substrates where elevated concentrations are associated with serious/ life-threatening reactions (i.e., methergine, statins)<br>○ HIV screening if untested and resistance testing among untreated or non-virally suppressed patients<br>○ Hypersensitivity<br>○ Switch to nonhormonal contraceptive | ○ May diminish therapeutic effect of cladribine<br>○ Evaluate and verify pregnancy status<br>○ Use when preferred treatment options unavailable | ○ Consider local prevalence of SARS-CoV-2 variants and available susceptibility data<br>○ Use when preferred treatment options unavailable | ○ May diminish effect of COVID-19 vaccines.<br>○ Suggest at least 2 weeks interval from receipt of COVID-19 vaccine before administration |
| EUA Documentation Requirement | No | Yes | Yes | Yes | Yes |
| | Patient Fact Sheet[73] | Patient EUA Form[74] | Patient Fact Sheet[32] | Patient Fact Sheet[75] | Patient Fact Sheet[21] |
| | Submit FDA Form 3500 to report adverse events[76] | | | | |
| Evidence | | | | | |
| Primary Trial | PINETREE[25] | EPIC-HR[22] | MOVE-OUT[29] | | PROVENT[77] |
| Population Studied | Double blind, randomized, placebo- controlled trial in symptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe disease (n=562) | Phase 2-3 double blind, randomized, placebo- controlled trial in symptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe disease (n=1379) | Phase 3 double blind, randomized, placebo-controlled trial in symptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe disease (n=1433) | No Phase 3 clinical efficacy data, based on *in vitro* data showing activity against all circulating Omicron subvariants and clinical efficacy data from Phase 2 clinical trial in an era when Omicron was not dominant.[39] | Phase 3 randomized, placebo controlled trial in adults with increased risk of inadequate response to vaccination followed to 6-7 months (n=5197) |
| Relative Risk reduction (RRR) | 87% | 88.9% | 31% (HR 0.69, 95%CI 0.48, 1.01) | Not known for bebtelovimab, 85% for sotrovimab | 77% (Hazard Ratio (HR) 0.23, 95% CI 0.10-0.54) |
| Number Needed to Prevent Hospitalization or Death | 21.7 | 16 | 14.7 | Not known for bebtelovimab. 17 for sotrovimab | 66.7 |

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| Adverse Events | Any 42.3%, serious 5% (*vs*. 46.3% and 5% in placebo, respectively); nausea, headache, cough, ↑ALT, ↓creatinine clearance, severe bradycardia, heart failure, acute liver failure | Any 22.6%, serious 2.1% (*vs.* 23.9% and 4.1% in placebo, respectively); treatment discontinuation, dysgeusia, diarrhea, hypertension, ↑ALT, ↓creatinine clearance, angioedema | 30.4% *vs*. 33.0% in placebo; diarrhea, nausea, dizziness, urticaria, anaphylaxis, angioedema | 22% *vs*. 23% in placebo; diarrhea, headache, nausea, pruritis, rash, vasovagal reaction, hypersensitivity | Any 35.3%, serious 1.4% in both groups; injection site reaction, |
| Inpatient Use | Can continue in the inpatient setting to complete 5 consecutive days of treatment if admitted for reasons other than COVID-19 | Continuation of outpatient therapy allowed if admitted for reasons other than COVID-19 without severe or critical illness | If hospitalization required, complete at provider discretion | Discontinue if hospitalization for disease progression required | N/A |
| Pregnancy data | | | | | |
| DART | No adverse effect on embryo/fetal development | Nirmatrelvir: reduced fetal body weights<br>Ritonavir: no adverse developmental outcomes | Increased risk of miscarriage, malformation of eye, kidney, axial skeleton, and ribs, delayed ossification, decreased fetal birthweight | None | None |
| Human Data | Observational study of 67 pregnant people: no adverse pregnancy outcomes. Insufficient data to identify drug associated risk of birth defects or miscarriage[26] | Nirmatrelvir: None<br>Ritonavir: observational studies have not identified an increase in risk of major birth defects and are insufficient to identify a drug-associated risk of miscarriage | None | None | None |

*Abbreviations: ALT, alanine tranaminase; CYP, cytochrome P450; DART, Development and Reproductive Toxicity; eGFR, estimated Glomerular Filtration rate; EUA, emergency use authorization; FDA, Food and Drug Administration, RDV, remdesivir; SARS-CoV-2,* severe acute respiratory syndrome coronavirus- 2; *SBECD sulfobutylether-beta-cyclodextrin.*

*High risk factors include age > 60, obesity (BMI > 30 kg/m$^2$), patient with immunocompromising conditions (B cell depleting therapies, i.e. rituximab, patients receiving tyrosine kinase inhibitors, chimeric antigen receptor T cell recipients, post-hematopoietic cell transplant recipients, active*

*malignancy, lung and solid organ transplant recipients, patients with severe combined primary immunodeficiencies, patients with untreated HIV and CD4 T lymphocyte cell counts < 500 cells /mm$^3$), unvaccinated individuals, cardiovascular conditions (e.g. hypertension, myocardial infarct, stroke), diabetes, liver disease, kidney disease.*

*Therapeutics can be located at* https://healthdata.gov/Health/COVID-19-Public-Therapeutic-Locator/rxn6-qnx8/data

*Clinicians are encouraged to refer to https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/ for most recent recommendations*

530 Table 2. Inpatient Therapeutics and Considerations in Pregnancy

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| Agent | **Dexamethasone** | **Remdesivir** | **Tocilizumab** | **Baricitinib** |
|---|---|---|---|---|
| Drug Class | Systemic corticosteroid, anti-inflammatory | Antiviral, RNA polymerase inhibitor | Recombinant human monoclonal antibody Interleukin-6 Receptor antagonist | Janus Kinase 1 and 2 inhibitors, reduces cytokine and growth factor stimulation |
| Dose | 6mg daily for 7 days or until discharge | Day 1: 200mg<br>Day 2 -10: 100mg | Weight > 30kg: 8 mg/kg<br>Weight < 30kg: 12 mg/kg<br><br>Max dose 800mg/infusion<br><br>Single dose, 2nd dose administered if clinical symptoms worsen or do not improve | 4mg daily for 14 days |
| Route of Administration | Intravenous or oral | Intravenous | Intravenous | Oral<br>Oral Dispersion |
| Dose Adjustments | None | None, monitor transaminase levels | Renal:<br>○ None<br>Hepatic:<br>○ Not recommended for patients with ALT or AST >10 times upper limit | Renal:<br>○ eGFR < 15 mL/min: not recommended<br>Hepatic:<br>○ Treatment interruption if rising LFTs to exclude diagnosis of Drug Induced Liver Injury |

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| Drug-Drug Interactions | Multiple considerations CYA3A4 substrate and weak inducer | See Table 1 | Uncertain CYP450 metabolism in the setting of severe disease and pregnancy, therefore close drug monitoring recommended<br><br>Should not be used with other immunomodulators | Increased levels when co-administered with strong OAT3 inhibitors (*i.e.*, probenecid)<br><br>Should not be used with other immunomodulators |
| Indication | Hospitalized patients with severe or critical COVID-19 disease requiring oxygen support | Hospitalized patients who require noninvasive oxygen support.<br><br>○ Given alone in patients requiring supplemental oxygen.<br>○ Given with dexamethasone in patients requiring noninvasive oxygen therapy | Severe or critical COVID-19 receiving systemic corticosteroids and requiring supplemental oxygen, mechanical ventilation and/or ECMO | Severe or critical COVID-19 receiving systemic corticosteroids and requiring supplemental oxygen, mechanical ventilation and/or ECMO<br><br>Considered case by case basis in patients with rapidly increasing oxygen requirements and evidence of systemic inflammation |
| Contraindications and Considerations | Monitor adverse effects including hyperglycemia, fungal, bacterial, or | See Table 1 | ○ Known hypersensitivity | ○ None known<br>○ Consider treatment interruption if |

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| | *Strongyloides* infections (especially if using with baricitinib or tocilizumab), and diffuse multi-organ toxicity | | ○ Any non-COVID concurrent active infection, including localized infection<br>○ Absolute neutrophil count < 1000 per $mm^3$, platelet count < 50,000 per $mm^3$, or ALT/AST > 10x upper limit | absolute lymphocyte count < 200 cells/ per $mm^3$ or absolute neutrophil count < 500 per $mm^3$ |
| Adverse Events | ○ Multiple cardiac, dermatologic, endorine, metabolic, gastrointestinal, hepatic and psychiatric effects<br>○ Hyperglycemia, pulmonary edema, poor wound healing frequent | See Table 1 | ○ Adverse effects (3%): constipation, anxiety, diarrhea, insomnia, hypertension, nausea<br>○ High risk for serious and fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens<br>○ GI perforation<br>○ Hepatotoxicity | ○ Transaminitis (18%)<br>○ Neutropenia (2.2%)<br>○ Venous thromboembolism (1.5%)<br>○ Serious opportunistic infections (0.9%) |
| Evidence | | | | |

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| Effectiveness in general population | Reduction in all cause 28-day mortality[36] | ○ Modest mortality benefit in non-mechanically ventilated patients<br>○ Shorter median time to recovery<br>○ Reduced need for mechanical ventilation | ○ Reduced all-cause mortality at 28 days<br>○ Reduced risk of progression to mechanical ventilation or death<br>○ Reduced risk of hemodialysis or hemofiltration<br>○ Greater probability of discharge alive at 28 days | ○ Reduced progression to mechanical ventilation or death<br>○ Most pronounced in patients receiving high flow oxygen or noninvasive ventilation |
| Pregnancy considerations | | | | |
| | Concern for small head circumference, lowbirthweight, long term mental and neurocognitive disorders<br>Alternates:<br>○ IV or oral hydrocortisone 5160 mg in divided doses for 7 days or until discharge<br>○ IV or oral methylprednisolone 32 mg daily in divided doses for 7 | See Table 1<br><br>Report of 67 pregnant women treated demonstrated similar recovery rates to non-pregnant and low rate of adverse events[26] | Human data insufficient to determine drug associated risk for major birth defects and miscarriages.<br><br>Risk for miscarriage at 1.25 times maximum recommended human dose in animal studies<br><br>May interfere with parturition | Human data insufficient to determine drug associated risk for major birth defects and miscarriages<br><br>Increased risk of skeletal anomalies and pregnancy loss in animal data |

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|---|---|---|---|---|
| | days or until discharge | | | |

*Abbreviations: ALT, alanine tranaminase; AST, aspartate transaminase; CYP, cytochrome P450; DART, Development and Reproductive Toxicity; eGFR, estimated Glomerular Filtration rate; ECMO, extracorporeal membrane oxygenation; EUA, emergency use authorization; FDA, Food and Drug Administration; OAT, ornithine aminotransferase; RDV, remdesivir; SARS-CoV-2,* severe acute respiratory syndrome coronavirus- 2;