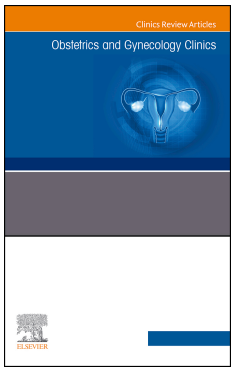

COVID-19 Therapeutics and Considerations for Pregnancy

Naima T. Joseph, MD, MPH, Ai-ris Y. Collier, MD

PII: S0889-8545(22)00109-7

DOI: https://doi.org/10.1016/j.ogc.2022.10.018

Reference: OGC 1191

To appear in: *OBSTETRICS AND GYNECOLOGY CLINICS OF NORTH AMERICA*

Please cite this article as: Joseph N.T. & Collier A.-r.Y., COVID-19 Therapeutics and Considerations for Pregnancy, *OBSTETRICS AND GYNECOLOGY CLINICS OF NORTH AMERICA* (2022), doi: https://doi.org/10.1016/j.ogc.2022.10.018.

COVID-19 Therapeutics and Considerations for Pregnancy

Naima T. Joseph, MD, MPH, Ai-ris Y. Collier, MD

Both from the Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology at Beth Israel Deaconess Medical Center and Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, Boston, MA, USA.

Corresponding author:
Naima T. Joseph
330 Brookline Ave
Kirstein, 3rd Floor
Boston, MA, 02215
Njoseph5@bidmc.harvard.edu

Keywords: COVID-19, Pregnancy, Therapeutics, Vaccines

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.

References

1. COVID-19 Views - ClinicalTrials.gov. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/covid_view

2. COVID Clinical | SMFM.org - The Society of Maternal-Fetal Medicine. Accessed October 5, 2022. https://www.smfm.org/covidclinical

3. Joseph NT, Miller ES. Obstetric Outpatient Management During the COVID-19 Pandemic: Prevention, Treatment of Mild Disease, and Vaccination. *Clin Obstet Gynecol*. 2022;65(1):161-178.

4. Vaught AJ. Inpatient Management and OBICU Care for Pregnant Patients With Severe COVID-19 Disease. *Clin Obstet Gynecol*. 2022;65(1):189-194.

5. Zambrano LD, Ellington S, Strid P, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(44):1641-1647.

6. Galang RR, Newton SM, Woodworth KR, et al. Risk Factors for Illness Severity Among Pregnant Women With Confirmed Severe Acute Respiratory Syndrome Coronavirus 2 Infection-Surveillance for Emerging Threats to Mothers and Babies Network, 22 State, Local, and Territorial Health Departments, 29 March 2020-5 March 2021. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2021;73(Suppl 1):S17-S23.

7. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. *CMAJ*. 2021;193(16):E540-E548.

8. Metz TD, Clifton RG, Hughes BL, et al. Association of SARS-CoV-2 Infection With Serious Maternal Morbidity and Mortality From Obstetric Complications. *JAMA*. 2022;327(8):748-759.

9. Norman M, Navér L, Söderling J, et al. Association of Maternal SARS-CoV-2 Infection in Pregnancy With Neonatal Outcomes. *JAMA*. 2021;325(20):2076-2086.

10. Zhang H, Zhang H. Entry, egress and vertical transmission of SARS-CoV-2. *J Mol Cell Biol*. 2021;13(3):168-174.

11. Gale C, Quigley MA, Placzek A, et al. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. *Lancet Child Adolesc Health*. 2021;5(2):113-121.

12. Shook LL, Collier AY, Goldfarb IT, et al. Vertical transmission of SARS-CoV-2: consider the denominator. *Am J Obstet Gynecol MFM*. 2021;3(4):100386.

13. Banerjee J, Mullins E, Townson J, et al. Pregnancy and neonatal outcomes in COVID-19: study protocol for a global registry of women with suspected or confirmed SARS-CoV-2 infection in pregnancy and their neonates, understanding natural history to guide treatment and prevention. *BMJ Open*. 2021;11(1):e041247.

14. Pham-Huy A, Sadarangani M, Huang V, et al. From mother to baby: antenatal exposure to monoclonal antibody biologics. *Expert Rev Clin Immunol*. 2019;15(3):221-229.

15. Pham-Huy A, Top KA, Constantinescu C, Seow CH, El-Chaâr D. The use and impact of monoclonal antibody biologics during pregnancy. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2021;193(29):E1129-E1136.

16. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. *N Engl J Med*. 2021;384(3):229-237.

17. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *N Engl J Med*. 2021;384(3):238-251.

18. Gottlieb RL, Nirula A, Chen P, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2021;325(7):632-644.

19. Westendorf K, Žentelis S, Wang L, et al. LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. *Cell Rep*. 2022;39(7):110812.

20. Tixagevimab and Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis of COVID-19. *JAMA*. 2022;327(4):384-385.

21. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Evusheld. Accessed October 5, 2022. https://www.fda.gov/media/154701/download

22. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N Engl J Med*. 2022;386(15):1397-1408.

23. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study. *Lancet Infect Dis*. Published online August 24, 2022:S1473-3099(22)00507-2.

24. Roberts SS, Martinez M, Covington DL, Rode RA, Pasley MV, Woodward WC. Lopinavir/ritonavir in pregnancy. *J Acquir Immune Defic Syndr 1999*. 2009;51(4):456-461.

25. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med*. 2022;386(4):305-315.

26. Burwick RM, Yawetz S, Stephenson KE, et al. Compassionate Use of Remdesivir in Pregnant Women With Severe Coronavirus Disease 2019. *Clin Infect Dis*. Published online October 2020.

27. National Institute of Allergy and Infectious Diseases (NIAID). *Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States*. clinicaltrials.gov; 2022. Accessed October 4, 2022. https://clinicaltrials.gov/ct2/show/NCT04582266

28. Nucleoside Analogues. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Accessed October 5, 2022. http://www.ncbi.nlm.nih.gov/books/NBK548938/

29. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med*. 2022;386(6):509-520.

30. Zhou S, Hill CS, Sarkar S, et al. β-d-N4-hydroxycytidine Inhibits SARS-CoV-2 Through Lethal Mutagenesis But Is Also Mutagenic To Mammalian Cells. *J Infect Dis*. 2021;224(3):415-419.

31. Troth S, Butterton J, DeAnda CS, et al. Letter to the Editor in Response to Zhou et al. *J Infect Dis*. 2021;224(8):1442-1443.

32. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO (molnupiravir) CAPSULES. Accessed October 5, 2022. https://www.fda.gov/media/155054/download

33. Hospitalized Adults: Therapeutic Management. COVID-19 Treatment Guidelines. Accessed October 5, 2022. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/hospitalized-adults--therapeutic-management/

34. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704.

35. Ninan K, Liyanage SK, Murphy KE, Asztalos EV, McDonald SD. Evaluation of Long-term Outcomes Associated With Preterm Exposure to Antenatal Corticosteroids: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2022;176(6):e220483..

36. Saad AF, Chappell L, Saade GR, Pacheco LD. Corticosteroids in the Management of Pregnant Patients With Coronavirus Disease (COVID-19). *Obstet Gynecol*. 2020;136(4):823-826.

37. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA*. 2020;324(13):1330-1341.

38. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet Lond Engl*. 2020;395(10236):1569-1578.

39. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(11):1048-1057.

40. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med*. 2020;383(19):1813-1826.

41. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *The Lancet*. 2022;399(10339):1941-1953.

42. Gupta S, Leaf DE. Tocilizumab in COVID-19: some clarity amid controversy. *Lancet Lond Engl*. 2021;397(10285):1599-1601.

43. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med*. 2021;384(1):20-30.

44. Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Lond Engl*. 2021;397(10285):1637-1645.

45. Jorgensen SCJ, Lapinsky SE. Tocilizumab for coronavirus disease 2019 in pregnancy and lactation: a narrative review. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2022;28(1):51-57.

46. FACT SHEET FOR HEALTHCARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BARICITINIB. Accessed October 6, 2022. https://www.fda.gov/media/143823/download

47. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407-1418.

48. Jorgensen SCJ, Lapinsky SE. Tocilizumab for coronavirus disease 2019 in pregnancy and lactation: a narrative review. Clin Microbiol Infect. 2022; 28(1): 51 - 7.

49. Lopes RD, de Barros e Silva PGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet Lond Engl*. 2021;397(10291):2253-2263.

50. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med*. 2021;385(9):790-802.

51. Talasaz AH, Sadeghipour P, Kakavand H, et al. Recent Randomized Trials of Antithrombotic Therapy for Patients With COVID-19: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2021;77(15):1903-1921.

52. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med*. 2021;385(9):777-789.

53. Connors JM, Brooks MM, Sciurba FC, et al. Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19: The ACTIV-4B Randomized Clinical Trial. *JAMA*. 2021;326(17):1703-1712.

54. Servante J, Swallow G, Thornton JG, et al. Haemostatic and thrombo-embolic complications in pregnant women with COVID-19: a systematic review and critical analysis. *BMC Pregnancy Childbirth*. 2021;21(1):108.

55. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. Published online December 2020:NEJMoa2034577.

56. Baden LR, Sahly HME, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-416.

57. Collier A ris Y, Yu J, McMahan K, et al. Differential Kinetics of Immune Responses Elicited by Covid-19 Vaccines. *N Engl J Med*. 2021;385(21):2010-2012.

58. Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Announcement - 12/17/2020. FDA. Published September 27, 2022. Accessed October 6, 2022. https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-17-2020-meeting-announcement

59. Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion. *N Engl J Med*. 2021;385(16):1533-1535.

60. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *N Engl J Med*. Published online April 2021.

61. COVID-19 vaccine weekly surveillance reports (weeks 39 to 40, 2021 to 2022). GOV.UK. Accessed October 6, 2022. https://www.gov.uk/government/publications/covid-19-vaccine-weekly-surveillance-reports

62. Goldshtein I, Nevo D, Steinberg DM, et al. Association between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women. *JAMA - J Am Med Assoc*. 2021;326(8):728-735.

63. Collier A ris Y, McMahan K, Yu J, et al. Immunogenicity of COVID-19 mRNA Vaccines in Pregnant and Lactating Women. *JAMA*. Published online 2021.

64. Gray KJ, Bordt EA, Atyeo C, et al. COVID-19 vaccine response in pregnant and lactating women: a cohort study. *Am J Obstet Gynecol*. Published online 2021.

65. Dagan N, Barda N, Biron-Shental T, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. *Nat Med*. Published online September 2021:1-3.

66. Morgan JA, Biggio JR, Martin JK, et al. Maternal Outcomes After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Vaccinated Compared With Unvaccinated Pregnant Patients. *Obstet Gynecol*. 2022;139(1):107-109.

67. Prabhu M, Murphy EA, Sukhu AC, et al. Antibody Response to Coronavirus Disease 2019 (COVID-19) Messenger RNA Vaccination in Pregnant Women and Transplacental Passage Into Cord Blood. *Obstet Gynecol*. Published online April 2021.

68. Shook LL, Atyeo CG, Yonker LM, et al. Durability of Anti-Spike Antibodies in Infants After Maternal COVID-19 Vaccination or Natural Infection. *JAMA*. 2022;327(11):1087-1089.

69. Halasa NB, Olson SM, Staat MA, et al. Maternal Vaccination and Risk of Hospitalization for Covid-19 among Infants. *N Engl J Med*. 2022;387(2):109-119.

70. Maternal Immunization Task Force and Partners Urge That COVID-19 Vaccine be Available to Pregnant Individuals. Accessed October 6, 2022. https://www.acog.org/en/news/news-releases/2021/02/maternal-immunization-task-force-and-partners-urge-that-covid-19-vaccine-be-available-to-pregnant-individuals

71. Clinical Guidance for COVID-19 Vaccination | CDC. Published September 28, 2022. Accessed October 6, 2022. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

72. Plumb ID, Feldstein LR, Barkley E, et al. Effectiveness of COVID-19 mRNA Vaccination in Preventing COVID-19-Associated Hospitalization Among Adults with Previous SARS-CoV-2 Infection - United States, June 2021-February 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(15):549-555.

73. VEKLURY® (remdesivir) | Approved Treatment for COVID-19. Accessed October 8, 2022. https://www.veklury.com/

74. FDA Paxlovid Fact Sheet for Patients. Accessed October 8, 2022. https://www.fda.gov/media/155051/download

75. Fact Sheet for Patients, Parents, and Caregivers Emergency Use Authorization (EUA) of Bebtelovimab. Accessed October 8, 2022. https://www.fda.gov/media/156153/download

76. MedWatch Online Voluntary Reporting Form. Accessed October 8, 2022. https://www.accessdata.fda.gov/scripts/medwatch/index.cfm

77. Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19. *N Engl J Med*. 2022;386(23):2188-2200.

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 RNA polymerase inhibitor	Antiviral agent SARS-CoV-2 main protease inhibitor (Mpro) HIV-1 protease inhibitor and Mpro concentration booster	Antiviral agent nucleoside inhibitor	Antiviral agent monoclonal antibody	Antiviral agent monoclonal antibody
Dose	Day 1: 200mg 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: ○ 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 Hepatic: ○ ALT >10 times upper limit, consider discontinuation	Renal: ○ eGFR ≥ 30 to < 60 mL/min nirmatrelvir 150mg with ritonavir 100mg TWICE daily for five days ○ eGFR < 30 mL/min: Not recommended Hepatic: ○ 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

Time Frame from Symptom Onset	≤ 7 days	≤ 5 days	≤ 3-5 days	≤ 7 days	
Contraindications and Considerations	○ Hypersensitivity ○ Chloroquine or Hydroxychloroquine may diminish therapeutic effect of RDV ○ CYP3A inducers may decrease serum concentration RDV	○ eGFR < 30 mL/min ○ Severe hepatic impairment (Child-Pugh Class C) ○ CYP3A inducers may reduce nirmatrelvir or ritonavir plasma concentrations leading to loss of virologic response and resistance ○ CYP3A substrates where elevated concentrations are associated with serious/ life-threatening reactions (i.e., methergine, statins) ○ HIV screening if untested and resistance testing among untreated or non-virally suppressed patients ○ Hypersensitivity ○ Switch to nonhormonal contraceptive	○ May diminish therapeutic effect of cladribine ○ Evaluate and verify pregnancy status ○ Use when preferred treatment options unavailable	○ Consider local prevalence of SARS-CoV-2 variants and available susceptibility data ○ Use when preferred treatment options unavailable	○ May diminish effect of COVID-19 vaccines. ○ 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

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 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 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

531

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 Day 2 -10: 100mg	Weight > 30kg: 8 mg/kg Weight < 30kg: 12 mg/kg Max dose 800mg/infusion 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 Oral Dispersion
Dose Adjustments	None	None, monitor transaminase levels	Renal: ○ None Hepatic: ○ Not recommended for patients with ALT or AST >10 times upper limit	Renal: ○ eGFR < 15 mL/min: not recommended Hepatic: ○ Treatment interruption if rising LFTs to exclude diagnosis of Drug Induced Liver Injury

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 Should not be used with other immunomodulators	Increased levels when co-administered with strong OAT3 inhibitors (*i.e.*, probenecid) 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. ○ Given alone in patients requiring supplemental oxygen. ○ 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 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 ○ Consider treatment interruption if

	Strongyloides infections (especially if using with baricitinib or tocilizumab), and diffuse multi-organ toxicity		○ Any non-COVID concurrent active infection, including localized infection ○ 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 ○ Hyperglycemia, pulmonary edema, poor wound healing frequent	See Table 1	○ Adverse effects (3%): constipation, anxiety, diarrhea, insomnia, hypertension, nausea ○ High risk for serious and fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens ○ GI perforation ○ Hepatotoxicity	○ Transaminitis (18%) ○ Neutropenia (2.2%) ○ Venous thromboembolism (1.5%) ○ Serious opportunistic infections (0.9%)
Evidence				

Effectiveness in general population	Reduction in all cause 28-day mortality[36]	○ Modest mortality benefit in non-mechanically ventilated patients ○ Shorter median time to recovery ○ Reduced need for mechanical ventilation	○ Reduced all-cause mortality at 28 days ○ Reduced risk of progression to mechanical ventilation or death ○ Reduced risk of hemodialysis or hemofiltration ○ Greater probability of discharge alive at 28 days	○ Reduced progression to mechanical ventilation or death ○ 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 Alternates: ○ IV or oral hydrocortisone 5160 mg in divided doses for 7 days or until discharge ○ IV or oral methylprednisolone 32 mg daily in divided doses for 7	See Table 1 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. Risk for miscarriage at 1.25 times maximum recommended human dose in animal studies May interfere with parturition	Human data insufficient to determine drug associated risk for major birth defects and miscarriages Increased risk of skeletal anomalies and pregnancy loss in animal data

	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;