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GUIDANCE FOR TREATMENT OF COVID-19 IN HOSPITALIZED ADULTS AND CHILDREN

NOTE: Details regarding testing, isolation/precautions, personal protective equipment, patient movement, family/visitor policy, and cleaning/disinfection can be found here.

Treatment:

NOTE: In patients with confirmed COVID-19 pneumonia, community-onset bacterial co-infection is uncommon, even in critically ill patients, and elevated procalcitonin levels are not reliably associated with bacterial infection, especially in the setting of concomitant renal dysfunction (Vaughn VM et al, Clin Infect Dis 2021). Furthermore, no unique association with specific and/or resistant pathogens, including MRSA or Pseudomonas, has been made in patients with COVID-19 pneumonia. Empiric antibiotic therapy may be indicated in patients with signs concerning for bacterial co-infection and/or severe pneumonia such as hemodynamic instability. De-escalation/discontinuation of antibiotics should be considered based on clinical and microbiological data.

Pneumonia treatment guidelines are available in their entirety at:

- Pneumonia Treatment (Adult)
- Pneumonia Treatment (Pediatrics)

Table 1. **Potential Treatment Recommendations by Severity of Disease**

Patients who are receiving outpatient oral antiviral therapy for COVID-19 (molnupiravir or ritonavir-boosted nirmatrelvir (Paxlovid)) and admitted should complete their course using their own supply (Michigan Medicine does not have these medications). Consult Infectious Diseases for patients admitted for worsening COVID-19 infection who started oral antivirals as an outpatient.

Disease severity	**Potential Treatment Recommendations** (per ID consult discretion based on details in Table 2)
Multisystem Inflammatory Syndrome in Adults (MIS-A)	• MIS-A therapeutic management considerations are available here
Multisystem Inflammatory Syndrome in Children (MIS-C)	• MIS-C management considerations are available here
No supplemental oxygen	• **Supportive care** • **Remdesivir (3 days)** may be an option in certain high-risk patients (see eligibility criteria in Table 2) who have mild to moderate symptoms of COVID-19.
Low flow supplemental oxygen	• **Supportive care** • **Dexamethasone** (Exceptions: Minimal supplemental oxygen (1-2 L) with < 7 days of symptoms or pediatric bronchiolitis—uncertain benefit) • **Remdesivir (5 days)**
High flow supplemental oxygen or non-invasive mechanical ventilation	• **Supportive Care** • **Dexamethasone** (Uncertain benefit for pediatric bronchiolitis) • Baricitinib (**Tocilizumab for patients where enteral administration is not possible or reliable OR if eGFR ≤15 or IHD)** • **Remdesivir (5 days)**
Mechanical ventilation or ECMO	• **Supportive care** • **Dexamethasone** (Uncertain benefit for pediatric bronchiolitis) • Baricitinib (**Tocilizumab for patients where enteral administration is not possible or reliable OR if eGFR ≤ 15 or IHD)**

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Table 2: Therapeutic agents dosing, duration, and details for treatment of COVID-19

Therapeutic Agents	Dosing & Duration	Comments
Remdesivir *(3-day regimen)* **Note** the eligibility criteria below. This 3-day regimen is indicated for patients **with mild-moderate COVID-19 (not hypoxic)** Eligibility Criteria Patients with **mild or moderate** COVID-19 who meet criteria #1-3 **AND** consideration of criteria #4 1. No requirement for supplemental oxygen (or no increase from baseline supplemental oxygen) 2. Symptoms ≤ 7 days 3. Patient ≥ 28 days of age AND ≥ 3 kg 4. PINETREE (study (doi: 10.1056/nejmoa2116846), the clinical trial supporting 3-day remdesivir, was conducted in immune-naïve *outpatients* with additional characteristics or conditions placing them at high risk of hospitalization or death. However, the results of this study are not directly applicable to present-day patients, as > 90% of the elderly population has received at least a primary vaccination series, virtually the entire population has evidence of immunity from prior infection and/or vaccination, and a different, less virulent, variant (Omicron) predominates. As such, it is unknown what patient populations remain at high risk of progression. Patients at highest risk include those > 75 years old and those with moderate-severe immunocompromise, as defined below. In other patients, a decision on whether to treat should consider totality of risk, including age, severity and number of comorbidities, and time since last vaccination and/or infection Moderate-to-Severe immunocompromise defined by: a. Solid organ transplant b. Bone marrow transplant c. Hematologic malignancy d. On B-cell depleting therapy e. Primary immunodeficiency f. Active malignancy and receiving chemotherapy g. Autoimmune diseases requiring immunosuppressive therapy (hydroxychloroquine or sulfasalazine alone is not sufficient) h. Advanced or untreated HIV infection	Adult dosing: 200 mg IV load, then 100 mg IV q24h Pediatric dosing (≥28 days of age): *3 kg to < 40 kg:* 5 mg/kg IV load, then 2.5 mg/kg q24h *≥ 40 kg:* 200 mg IV load, then 100 mg IV q24h Duration: **3 days** or until hospital discharge whichever comes first. Some patients with significant immunocompromise (especially those receiving B-cell depleting agents) may warrant a prolonged course of therapy. Such cases require consultation with Infectious Diseases.	• Patients < 28 days or < 3 kg: Remdesivir is not FDA approved in this population. Consult Pediatric Infectious Diseases to discuss use. • **TO ORDER: Choose the 'New Starts' Remdesivir order panel but change duration of the maintenance (100 mg) dose to 2 days.** • CrCl < 30 mL/min is not a contraindication to remdesivir. The risk of cyclodextrin accumulation to a toxic level with 5 days of therapy is small & benefit likely outweighs risk • Increased LFTs: daily monitoring of hepatic function is recommended. The risk of hepatotoxicity with a baseline AST/ALT > 5x ULN is not known due to patient exclusion from clinical trials; weigh benefit versus risk

Therapeutic Agents	Dosing & Duration	Comments
Remdesivir *(5-day regimen, this regimen is recommended for patients with severe COVID-19 (hypoxic). Refer to above 3-day regimen recommendations for consideration of remdesivir in patients who are not hypoxic)* **Data has not demonstrated that remdesivir therapy confers a benefit in patients with critical COVID-19, i.e. those requiring mechanical ventilation or ECMO. There may be a role for remdesivir therapy in some patients, such as in immunocompromised patients. Exceptions to these criteria may be considered on an individualized basis.* <u>Patients < 28 days or < 3 kg</u> Remdesivir is not FDA approved in this population. Consult Pediatric Infectious Diseases to discuss use.	<u>Adult dosing:</u> 200 mg IV load, then 100 mg IV q24h <u>Pediatric dosing ≥28 days of age:</u> *3 kg to < 40 kg:* 5 mg/kg IV load, then 2.5 mg/kg q24h *≥ 40 kg:* 200 mg IV load, then 100 mg IV q24h <u>Duration:</u> 5 days or until hospital discharge whichever comes first. Patients started on remdesivir and progress to requiring higher level of oxygen support (i.e., mechanical ventilation) should still complete a course of remdesivir. Some patients with significant immunocompromise (especially those receiving B-cell depleting agents) may warrant a prolonged course of therapy. Such cases require consultation with Infectious Diseases.	• ID consult is recommended for the following reasons: ○ To discuss remdesivir use in pediatric patients < 28 days or < 3 kg with severe COVID-19 ○ Question about whether remdesivir should be initiated/ continued ○ Patient does not meet criteria for remdesivir but unique clinical circumstances warrant ID evaluation for treatment • CrCl < 30 mL/min is not a contraindication to remdesivir. The risk of cyclodextrin accumulation to a toxic level with 5 days of therapy is small & benefit likely outweighs risk • Increased LFTs: daily monitoring of hepatic function is recommended. The risk of hepatotoxicity with a baseline AST/ALT > 5x ULN is not known due to patient exclusion from clinical trials; weigh benefit versus risk • Pregnancy: Use of remdesivir should not be withheld in pregnant patients if otherwise indicated per criteria on this page.

Therapeutic Agents	Dosing & Duration	Comments
Dexamethasone Patients 18 years and older: 1. *Recommended in patients with COVID-19 who require mechanical ventilation or ECMO* 2. *Recommended for patients on supplemental oxygen. The benefit of dexamethasone is uncertain in adults on minimal levels of supplemental oxygen (1-2L) with <7 days of symptoms. Decisions should be individualized in such patients with consideration of disease severity in conjunction with risks and benefits of glucocorticoid therapy.* Patients < 18 years: *Corticosteroids are not recommended for treatment of children with viral bronchiolitis. For children with asthma or croup triggered by SARS-CoV-2 infection, corticosteroids should be used per the usual standards of care for those indications.* *For other pediatric patients requiring mechanical ventilation or high levels of oxygen support (e.g., high flow oxygen or noninvasive ventilation), NIH guidelines now endorse use of corticosteroids for COVID-19. However, patients < 18 years were not represented in the RECOVERY RCT. It is not known if the benefit of dexamethasone will extend to children with COVID-19 who require oxygen, or if there is even the potential for harm, as seen in adults who did not require oxygen. Recommend consultation with Pediatric Infectious Diseases.*	Adult dosing: 6 mg PO or IV q24h Pediatric dosing*: 0.15 mg/kg/dose IV q24h (max: 6 mg/dose) Duration: Maximum 10 days, or until discharge *Shorter duration is reasonable to consider in patients who have improved rapidly or are experiencing adverse events from steroids. The median duration of therapy in the RECOVERY trial was 6 days.* **Pediatric dosing is based on extrapolation from the adult dose and the RECOVERY protocol but has not been established for COVID-19*	Weigh risks/benefits of use on a case-by-case basis in patients with: • Active bacterial or fungal infection • Diabetic ketoacidosis • Baseline immunosuppression Not recommended in the following patients: • Not requiring supplemental oxygen. (In RECOVERY, those had a trend towards worse outcomes). • No longer COVID-19 PCR positive, but remain intubated. (In RECOVERY, patients were randomized after admission; the risk/benefit of alternative approaches later in the disease course is unknown). Pregnancy, breastfeeding: • Consult OB for gestational age of viability. Alternatives may be prednisone 40 mg PO daily or hydrocortisone 80 mg IV BID. Dexamethasone is a CYP3A4 substrate, as such drug interactions should be assessed prior to use. Alternatives less prone to interactions are prednisone 40 mg PO daily, methylprednisolone 32 mg IV daily, or hydrocortisone 80 mg IV BID. Potential adverse events: • Increased risk for infection • Hyperglycemia • Peripheral edema • Increased appetite • Insomnia, irritability, delirium In the setting of a dexamethasone shortage, an equivalent total daily dose of an alternative glucocorticoid to dexamethasone 6 mg daily can be used (e.g., methylprednisolone 32 mg (< 40 kg: 0.8 mg/kg) daily or prednisone 40 mg (< 40 kg: 1 mg/kg) daily)

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Baricitinib • *Clinical trials have identified that patients with COVID-19 requiring high-flow supplemental oxygen, noninvasive mechanical ventilation, mechanical ventilation or ECMO benefit from combination therapy of dexamethasone and a secondary immunomodulatory agent. Baricitinib is the preferred agent given the consistency and totality of evidence.* • *ID APPROVAL NEEDED, ID consult is recommended for all patients with critical COVID* Recommend **Baricitinib** (*in addition to **dexamethasone***) in patients: 1. Newly on mechanical ventilation (< 48 hours) 2. On high flow supplemental oxygen or noninvasive mechanical ventilation **Baricitinib** is NOT recommended in the following scenarios: 1. Enteral administration is not possible/reliable (use Tocilizumab) 2. Baricitinib is contraindicated if eGFR ≤ 15 or IHD (use Tocilizumab) 3. Patients requiring lower levels of respiratory support than high flow support, noninvasive ventilation, or mechanical ventilation. 4. High concern for systemic bacterial or fungal co-infection 5. Receiving mechanical ventilation for longer than 48 hours 6. Patients who significantly improve with the initiation of enhanced oxygen support or corticosteroids; monitoring such patients for 12-24 hours is reasonable 7. Unlikely to survive > 48 hours 8. Receiving tocilizumab* (see comment) **Baricitinib in Patients < 18 years:** *Safety and effectiveness in younger children with COVID-19 is limited to case reports. In contrast to the strong recommendation for its use for adults, baricitinib is not considered the standard of care for all children who require high-flow oxygen or NIV because of the low mortality in children with*	**Baricitinib Adult Dosing** (NOTE: renal dosing uses MDRD equation, which is not available in MiChart. MDRD calculator is available here:) eGFR ≥ 60 mL/min/1.73 m^2: 4 mg PO q24h eGFR 30 to < 60 mL/min/1.73 m^2: 2 mg PO q24h eGFR 15 to < 30 mL/min/1.73 m^2 or CRRT: 1 mg PO q24h eGFR ≤ 15 mL/min/1.73 m^2 or HD: Not recommended, use Tocilizumab instead Duration: Maximum 14 days, or until discharge **Baricitinib Pediatric Dosing** Children 2 to < 9 years old eGFR ≥ 60 mL/min/1.73 m^2: 2 mg PO q24h Children ≥ 9 years old: eGFR ≥ 60 mL/min/1.73 m^2: 4 mg PO q24h Children 2 to < 9 years old eGFR 30 to < 60 mL/min/1.73 m^2: 1 mg PO q24h Children ≥ 9 years old: eGFR 30 - < 60 mL/min/1.73 m^2: 2 mg PO q24h	*The combination of tocilizumab + baricitinib has not been studied and both the safety and efficacy of this combination is unclear. Cases in which patients are initiated on baricitinib but develop contraindications for use prior to completion of treatment course may arise, and case-by-case considerations for tocilizumab should be discussed with Infectious Diseases. **Baricitinib Considerations:** Pregnancy and Nursing Mothers: • See full NIH recommendations here • Baricitinib is recommended if indicated. However, pregnant patients and healthcare providers should jointly decide whether to use baricitinib based on a discussion of the potential risks and benefits. • Mothers should not breastfeed if receiving baricitinib. Breastfeeding may resume 5 days after baricitinib discontinuation. Potential adverse events: • Thromboembolic events: VTE, PE • Increased risk for infection • Transaminitis • Neutropenia, lymphopenia, and anemia. Baricitinib is FDA approved for patients ≥ 18 years old but remains under Emergency Use Authorization for patients 2 to < 18 years of age. For those patients, Healthcare Providers must review FDA Fact Sheet for Health Care Providers. In addition, Healthcare Providers must provide recipients with the Fact Sheet for Patients/Caregivers and communicate the following information to the recipients: • FDA has authorized emergency use of Baricitinib for patients 2 to 18 years of age with COVID-19, which is not an FDA-approved

Therapeutic Agents	Dosing & Duration	Comments
COVID-19. It is not known if the benefit will extend to children with COVID-19. However, it is reasonable to consider baricitinib or tocilizumab for children who require ECMO, mechanical ventilation or high levels of oxygen support (e.g., high-flow oxygen or noninvasive ventilation) who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone. Recommend consultation with Pediatric Infectious Diseases	<u>Children 2 to < 9 years old eGFR ≤ 30 mL/min/1.73 m^2:</u> Not recommended, use Tocilizumab instead <u>Children ≥ 9 years old: eGFR 15 to < 30 mL/min/1.73 m^2:</u> 1 mg PO q24h <u>Children 2 to 17 years old: eGFR ≤ 15 mL/min/1.73 m^2, PD, or HD:</u> Not recommended, use Tocilizumab instead <u>Duration:</u> Maximum 14 days, or until discharge	indication for use in pediatric patients • The patient or caregiver has the option to accept or refuse administration of Baricitinib • The significant known and potential risks and benefits of Baricitinib and the extent to which such risks and benefits are unknown • Information on available alternative treatments and the risks and benefits of those alternatives.

Therapeutic Agents	Dosing & Duration	Comments
Tocilizumab • *ID APPROVAL NEEDED, ID consult is recommended for all patients with critical COVID* Recommend **Tocilizumab** (*in addition to **dexamethasone***) in patients: 1. With contraindications to using baricitinib (see above) 2. Newly on mechanical ventilation (< 48 hours) 3. On high flow supplemental oxygen or noninvasive mechanical ventilation **Tocilizumab** is <u>NOT</u> recommended in the following scenarios: 1. Patients requiring lower levels of respiratory support than high flow support, noninvasive ventilation, or mechanical ventilation. 2. High concern for systemic bacterial or fungal co-infection 3. Receiving mechanical ventilation for longer than 48 hours 4. Patients who significantly improve with the initiation of enhanced oxygen support or corticosteroids; monitoring such patients for 12-24 hours is reasonable 5. Unlikely to survive > 48 hours 6. Receiving baricitinib* (see comment) <u>Patients <18 years:</u> *Recommendations are primarily based on preliminary findings from the REMAP-CAP trial (see reference 6). Pediatric patients were not represented in these trials. It is not known if the benefit will extend to children with COVID-19. However, it is reasonable to consider tocilizumab for children who require mechanical ventilation or high levels of oxygen support (e.g., high-flow oxygen or noninvasive ventilation) who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone. Recommend consultation with Pediatric Infectious Diseases.*	** Dose rounding currently built into Epic order. Doses should be rounded to nearest available full vial (80 mg, 200 mg, 400 mg vials)** <u>Adult Dosing (≥ 18 years):</u> 8 mg/kg (max: 800 mg/dose) <u>Pediatric Dosing (2 to 17 years):</u> *< 30 kg:* 12 mg/kg *≥ 30 kg:* 8 mg/kg (max: 800 mg/dose) <u>Duration:</u> One dose *There are no data to inform risk vs. benefit of a second dose. Based on local experience a second dose is <u>NOT</u> recommended.*	*Tocilizumab benefit has been shown in studies with concomitant corticosteroid therapy. The combination of tocilizumab + baricitinib has not been rigorously studied and both the safety and efficacy of this combination is unclear. Thus, when tocilizumab is administered, it should be in combination with dexamethasone or an equivalent corticosteroid. Prior use of baricitinib is not a contraindication to using tocilizumab <u>Pregnancy and Nursing Mothers:</u> • See full NIH recommendations here • Tocilizumab is recommended if indicated. However, pregnant patients and healthcare providers should jointly decide whether to use tocilizumab based on a discussion of the potential risks and benefits. • Breastfeeding may continue while a patient receives tocilizumab. <u>Potential adverse events:</u> • Gastrointestinal perforation • Anemia, Neutropenia • Hepatitis • Infusion reaction • Infection Tocilizumab is FDA approved for patients ≥ 18 years old but remains under Emergency Use Authorization for patients 2 to <18 years of age. For those patients, healthcare providers must review FDA Fact Sheet for Health Care Providers. In addition, healthcare providers must provide recipients with the Fact Sheet for Patients/Caregivers and communicate the following information to the recipients: 1. FDA has authorized emergency use of Tocilizumab for patients 2 years to < 18 years of age with COVID-19, which is not an FDA-approved indication for use in pediatric patients 2. The patient or caregiver has the option to accept or refuse administration of Tocilizumab 3. The significant known and potential risks and benefits of Tocilizumab and the extent to which such risks and benefits are unknown 4. Information on available alternative treatments and the risks and benefits of those alternatives.

References:

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4. IDSA COVID-19 Treatment Guidelines, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
5. Vaughn VM, Gandhi T, et al. Empiric Antibacterial Therapy and Community-onset Bacterial Co-infections in Patients Hospitalized with COVID-19: A Multihospital Cohort Study. Clin Infect Dis. 2020 Aug 21;ciaa1239.
6. The REMAP-CAP Investigators.Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 2021.
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8. Gottleib RL et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med 2022.

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Revision History:

3/16/20: Removed testing recommendations - added link to testing document
3/17/20: Added tocilizumab, adjusted pediatric hydroxychloroquine dosing
3/19/20: Revised tocilizumab criteria, added pneumonia guidance
3/20/20: Revised tocilizumab dosing to weight based due to changes in Epic dose rounding capabilities, added limited data for corticosteroids in ARDS
3/24/20: Added guidance on azithromycin, revised tocilizumab dosing, added clinical study enrollment appendix
3/25/20: Revised criteria for HCQ use.
3/26/20: Revised tocilizumab criteria & included sarilumab study caveat
3/27/20: Removed study flow diagram
3/31/20: Removed recommendation for routine HCQ, removed nitazoxanide and lopinavir/ritonavir options, revised ACE/ARB/NSAID recommendations, recommendations re: combination HCQ/Azithromycin, revised pregnancy/breastfeeding recommendations and Remdesivir compassionate use criteria, deleted Tocilizumab re-dosing
4/2/20: Added suggested labs, revised remdesivir clinical trial information
4/3/20: Added hyperlink to Appendix A - review of HCQ data
4/6/20: Revised testing guidance hyperlink
4/7/20: Revised tocilizumab criteria
4/10/20: Revised tocilizumab criteria
4/15/20: Revised tocilizumab criteria
5/15/20: Revised tocilizumab criteria, revised remdesivir comments
6/3/20: Revised secondary infection information, revised remdesivir obtainment information
7/10/20: Added dexamethasone section
8/3/20: Added remdesivir criteria
9/15/20: Added convalescent plasma section
10/5/20: Removed tocilizumab, updated remdesivir comments, updated convalescent plasma comments
10/14/20: Revised remdesivir criteria
10/28/20: Revised Table 1, revised remdesivir section
11/19/20: Revised remdesivir comments
12/3/20: Revised remdesivir criteria
12/8/20: Added neutralizing antibodies section, revised remdesivir criteria.
12/17/20: Revised neutralizing antibodies criteria
12/23/20: Revised neutralizing antibodies criteria
1/5/21: Revised neutralizing antibodies criteria
1/13/21: Revised neutralizing antibodies criteria
1/17/21: Added tocilizumab section
1/27/21: Updated convalescent plasma criteria
2/25/21: Revised tocilizumab criteria, added new reference
3/15/21: Added bamlanivimab + etesevimab to mAb section
3/22/21: Added criteria and comments for tocilizumab, updated vancomycin nomogram hyperlink
4/7/21: Removed bamlanivimab monotherapy from mAb section
5/26/21: Revised mAb criteria
6/9/21: Revised casirivimab + imdevimab dosing and provider fact sheet
6/29/21: Revised mAb product availability
8/10/21: Added Post-exposure Prophylaxis hyperlink
8/25/21: Removed convalescent plasma section, revised tocilizumab section, revised alternative to tocilizumab section, updated pneumonia treatment recommendation
10/14/21: Revised tocilizumab section, removed alternatives to tocilizumab section, revised mAb product availability
12/13/21 Revised bamlanivimab + etesevimab dosing and criteria
12/24/21: Removed bamlanivimab + etesevimab & casirivimab + imdevimab, revised mAb criteria
1/4/22: Revised remdesivir 3-day and 5-day sections, revised mAb criteria
1/10/22: Revised remdesivir 3-day section
1/13/22: Removed serostatus criteria for mAb
2/28/22: Revised remdesivir 3-day criteria, revised mAb criteria
3/15/22: Added MIS-A and MIS-C hyperlinks, updated mAb and remdesivir criteria
3/21/22: Removed sotrovimab, added bebtelovimab
5/13/22: Revised mAb criteria
5/16/22: Revised mAb and remdesivir 3-day criteria
5/24/22: Revised pediatric recommendations
10/31/22: Removed mAb criteria, adjusted remdesivir 3-day criteria
12/6/22: Revised pediatric recommendations
3/20/23: Added baricitinib as preferred 2nd immunomodulator, revised remdesivir 3-day criteria, updated EUA language, updated pregnancy/lactation wording.