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

Patient population:
Adult and pediatric patients with COVID-19 infection, who are admitted on an inpatient floor or to the intensive care unit.

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

Clinical symptoms:
Range from asymptomatic, uncomplicated upper respiratory tract viral infection to pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock (Table 1)

Diagnosis:
See current COVID-19 testing recommendations.

Treatment:
Based on studies with preliminary data reported, the NIH and the IDSA have updated treatment guideline recommendations to include Remdesivir and dexamethasone for select patients with severe COVID-19. We are in agreement with this approach based on available data. Supply is limited, so decisions regarding treatment may need to be made based on availability and the individual patient. See details regarding patient populations in table 2 below.

Table 1. Potential Treatment Recommendations by Severity of Disease

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Potential Treatment Recommendations (per ID consult discretion based on details in Table 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplemental oxygen</td>
<td>• Supportive care</td>
</tr>
<tr>
<td>Supplemental oxygen (low flow)</td>
<td>• Supportive care • Dexamethasone • Remdesivir</td>
</tr>
<tr>
<td>Supplemental oxygen (high flow, mechanical ventilation)</td>
<td>• Supportive care • Dexamethasone • Remdesivir</td>
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Convalescent plasma may also be added per compassionate use trial as available.
Table 2: Therapeutic agents dosing, duration, and details for treatment of COVID-19

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Dosing &amp; Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td></td>
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<tr>
<td></td>
<td>Adult dosing:</td>
<td>• UM has a very limited supply of Remdesivir through the FDA issued Emergency Use Authorization. ID consult and approval is required to prescribe Remdesivir under the EUA.</td>
</tr>
<tr>
<td></td>
<td>200 mg IV load, then 100 mg IV q24h</td>
<td>• Remdesivir is also available for children and pregnant women with moderate-severe COVID-19 infection through Gilead sponsored Expanded Access Program which requires an investigational new drug (IND) application. To start the request for remdesivir through Gilead’s expanded access program, please send an email to the UMHS Expanded Access Group at <a href="mailto:UM-Expanded-Access-Request@med.umich.edu">UM-Expanded-Access-Request@med.umich.edu</a>. Email this group regardless of hour, but the expanded access program typically responds M-F during daytime hours. For urgent weekend and evening/overnight requests, please contact the research pharmacy on-call pager at 2944. After contacting the expanded access program, a request can be initiated via this portal: <a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a>.</td>
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<tr>
<td></td>
<td>Pediatric dosing*:</td>
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<tr>
<td></td>
<td>&lt;40 kg:</td>
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<tr>
<td></td>
<td>5 mg/kg IV load, then 2.5 mg/kg q24h</td>
<td></td>
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<tr>
<td></td>
<td>≥40 kg:</td>
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<tr>
<td></td>
<td>200 mg IV load, then 100 mg IV q24h</td>
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<td></td>
<td>Duration:</td>
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<td></td>
<td>Per ID consult recommendations</td>
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<td></td>
<td>Adverse events:</td>
<td></td>
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<tr>
<td></td>
<td>• Increased liver enzymes and daily monitoring of hepatic function is recommended</td>
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</tbody>
</table>

*pediatric dosing of remdesivir is taken from the [WHO recommendations](https://www.who.int) for treatment of Ebola virus, as no specific dosing recommendations exist for COVID-19.*
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<th>Therapeutic Agents</th>
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<tr>
<td><strong>Dexamethasone</strong></td>
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<tr>
<td><strong>Adult Patients</strong></td>
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</table>
| 1. *Recommended in patients with COVID-19 who require mechanical ventilation* | Adult dosing: 6 mg PO or IV q24h | Weigh risks/benefits of use on a case-by-case basis in patients with:  
- Active bacterial or fungal infection  
- Diabetic ketoacidosis  
- Baseline immunosuppression |
| 2. *Recommend in most patients on supplemental oxygen. The benefit of dexamethasone is uncertain in patients 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.* | Pediatric dosing*: 0.15 mg/kg/dose IV q24h (max: 6 mg/dose) | 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). |
| **Pediatric Patients** |                   |          |
| *Pediatric patients were not represented in the RECOVERY RCT and the mean participant age was 66 years. 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. However, it is reasonable to consider dexamethasone for children who require mechanical ventilation, or high levels of oxygen support, particularly if they are rapidly progressing toward mechanical ventilation. Recommend consultation with Infectious Diseases.* | 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.* | Pregnancy, breastfeeding:  
- Consult OB for gestational age of viability. Alternatives may be prednisone 40 mg PO daily or hydrocortisone 80 mg IV BID. |

**Pediatric dosing**:  
0.15 mg/kg/dose IV q24h (max: 6 mg/dose)  
*Pediatric dosing is based on extrapolation from the adult dose and the RECOVERY protocol but has not been established for COVID-19*

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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| Tocilizumab | ** Dose rounding currently built into Epic order. Doses should be rounded to nearest available full vial (80 mg, 200 mg, 400 mg vials)** | Laboratory Parameters also supportive of cytokine storm:  
- Ferritin >300 ug/L (or surrogate) with doubling within 24 hours  
- Ferritin >600 ug/L at presentation and LDH >250 U/L  
- Elevated D-dimer (>1 mg/L) |
| ID APPROVAL NEEDED | Adult Dosing (≥18 years):  
8 mg/kg (max: 800 mg/dose)  
Pediatric Dosing (<18 years):  
≤30 kg:  
12 mg/kg  
>30 kg:  
8 mg/kg (max: 800 mg/dose)  
Duration: One dose | Pregnancy and Nursing Mothers:  
- Maternal-Fetal Medicine at Michigan Medicine has endorsed the use of tocilizumab in pregnancy  
- Tocilizumab may be harmful to newborns, and mothers should stop breastfeeding if receiving tocilizumab but may resume after discontinuation and discussion with provider |
| May be considered for a patient meeting all criteria (#1-#6) below, and is not a candidate for dexamethasone | Based on available data, the evidence for benefit is weak, and a risk for potential harm exists (possible risk of infection). | Serious adverse events:  
- Gastrointestinal perforation  
- Anemia  
- Hepatitis  
- Infusion reaction  
- Neutropenia  
- Infection |
| | In select patients given steroids earlier in the course of disease, who subsequently develop a CRS-like picture, consideration may be given to tocilizumab. However, given layering risks and off-label use, risks and benefits must be cautiously weighed. | | |
| | 1. COVID-19 positive  
2. All of the following respiratory findings:  
a. Abnormal chest imaging consistent with COVID-19  
b. Rapidly worsening gas exchange/respiratory status over 24-48 hours and requiring ≥4-6 L/min O₂  
3. Absence of systemic bacterial or fungal co-infection  
4. High clinical suspicion for cytokine release syndrome supported by elevated inflammatory markers (e.g., ferritin >600 ug/mL; D-dimer >1.0 mg/L) and clinical decline.  
5. Does not have a poor prognosis where they are unlikely to survive >48 hours  
6. Mechanical ventilation for ≤24 hours | Do not use (therapies without any supportive evidence and/or associated with potential harm): hydroxychloroquine, hydroxychloroquine + azithromycin, lopinavir/ritonavir, nitazoxanide, oseltamivir, baloxavir, interferon, ribavirin, IVIG |
Antibiotic Management for Pneumonia in PUI and Confirmed COVID-19 Patients

Recommendations:
1. In patients admitted with suspected COVID-19 pneumonia (testing pending), decisions whether to initiate antibiotic therapy should be based on guidance provided in the institutional pneumonia treatment and procalcitonin usage guidelines.
2. Continuation/initiation of antibiotic therapy solely due to confirmation of COVID-19 pneumonia is not indicated as described below.
3. 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. Empiric antibiotic therapy should generally be discontinued once a patient is confirmed COVID-19 positive, but may be indicated in patients with leukocytosis and/or hemodynamic instability. De-escalation/discontinuation of antibiotics should be considered based on clinical and microbiological data. Note that an extended duration of fevers is typical in COVID-19 patients.
4. In patients who test negative for COVID-19 pneumonia, antibiotic therapy should be based on guidance provided in the institutional pneumonia treatment and procalcitonin usage guidelines.

Reports thus far have not identified unusual associations between COVID-19 infection and bacterial co-infection. Additionally, no unique association with resistant pathogens, including MRSA or *Pseudomonas*, has been made.

In an observational analysis by Somers et al of 154 patients with severe COVID-19 infection requiring mechanical ventilation at Michigan Medicine:
- 40% developed a bacterial superinfection, with 32% developing bacterial pneumonia. The median time to development of infection was 8-10 days after initiation of mechanical ventilation.

In a review of studies reporting bacterial co-infections in patients with COVID-19, Lansbury et al reported that the proportion of co-infection in ICU patients was 14%, compared to a proportion of 4% in studies which grouped ICU and floor-status together. Timing of onset of infection was not reported.

In the study of adult patients by Zhou et al.:
- 15% of hospitalized COVID-19 patients developed a secondary bacterial infection (definition: clinical symptoms or signs of pneumonia or bacteremia with a positive culture).
- The median time to secondary bacterial infection was 17 days (13 to 19 days).
- Of all COVID-19 patients in their cohort, 79% had a WBC <10.
- Only 1% of survivors developed a secondary bacterial infection, yet the median duration of fever in survivors was 12 days and cough persisted for 19 days. Thus, ‘just in case’ treatment of bacterial infection can result in prolonged durations of therapy.

Data in pediatric patients are limited, but one small study (Xia et al.) suggests that procalcitonin may be higher in children with COVID-19, regardless of suspected bacterial superinfection. Decisions about antibiotic management for children should continue to be guided by clinical judgment.

Adult pneumonia treatment guidelines are summarized here, and adult and pediatric pneumonia treatment guidelines are available in their entirety at:
- Pneumonia Treatment (Adult)
- Community-Acquired Pneumonia Treatment (Pediatrics)
- Procalcitonin Use Guidelines
Procalcitonin

- Although PCT levels should not be used in isolation to decide whether to initiate antibiotics in patients with suspected bacterial pneumonia, bacterial co-infection is unlikely in a confirmed COVID-19 patient with a low procalcitonin (<0.25), and antibiotics can be safely withheld. In addition, PCT levels >0.25 are not uncommon in patients with COVID-19 pneumonia, and do not appear to be a reliable marker of bacterial superinfection. Importantly, patients with CKD and AKI have falsely elevated PCT levels, and as such PCT is not reliable in such settings. Procalcitonin should also NOT be routinely used to extend treatment duration.

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**Adult Pneumonia Treatment Summary Recommendations**

<table>
<thead>
<tr>
<th>Indication</th>
<th>1st Line Empiric Therapy (see guidelines for alternatives)</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathway A</strong> – Inpatient community-acquired with no risk factors</td>
<td>Ampicillin-sulbactam 3 g IV q6h + Azithromycin 500 mg IV/PO x1 day, then 250 mg q24h x4 days</td>
<td>Uncomplicated pneumonia: 5 days for patients who defervesce within 72 hours and have no more than 1 sign of CAP instability at the time of antibiotic discontinuation</td>
</tr>
<tr>
<td><strong>Pathway B</strong> – Inpatient pneumonia with risk factors as defined below</td>
<td>Piperacillin-tazobactam 4.5 g IV q6h (+ Tobramycin IV if admitted to ICU) + Vancomycin* IV (see Standard Dosing Guideline)</td>
<td>Uncomplicated pneumonia: 7 days</td>
</tr>
</tbody>
</table>

*Discontinue vancomycin if no evidence of MRSA colonization/infection (negative MRSA nasal swab or respiratory culture).

**PATHWAY B RISK FACTORS**

**Healthcare Exposure:**
- HAP (hospitalization ≥72h); VAP; Prior hospitalization ≥48h within previous 90 days; Current resident from LTCF, nursing home, ECF, SNF with at least partial functional dependence in ADLs (transfer, feeding, bathing, dressing, toileting, and continence)

**Disease Severity:**
- Septic shock requiring ICU admission

**Antibiotic Exposure:**
- Fluoroquinolone, linezolid or any intravenous antibiotic use within previous 90 days

**Immunosuppression:**
- AIDS, neutropenia (ANC <1000), or active malignancy undergoing intravenous chemotherapy; Kidney or liver transplant recipient within 1 year; Lung transplant recipient; Autologous stem cell transplant within 6 months; Allogeneic stem cell transplant within 1 year of transplant date or those with chronic GVHD

**Other:**
- Tube feeding; History of infection or colonization with Pseudomonas spp., MRSA, or other MDR pathogens within previous 12 months; Cystic fibrosis, chronic obstructive pulmonary disease (FEV1 <35% predicted, multiple antibiotic prescriptions in last year, multiple hospital admissions in last year), or chronic bronchiectasis

Concomitant use of NSAIDs and/or ACE-I/ARBs:
There are conflicting theories regarding the risk and benefit of non-steroidal anti-inflammatory drugs (NSAIDs) or angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACE-I/ARBs) in patients with COVID-19 infection. Currently, there are no robust data demonstrating beneficial or adverse outcomes with use of these drugs in COVID-19 infections or specifically in COVID-19 infected patients taking these medications for cardiovascular disease. The American Heart Association, American College of Cardiology, and Heart Failure Society of America do not recommend stopping ACE-I or ARBs in COVID-19 infected patients. In addition, a clinical trial (NCT04312009) is investigating whether adjunctive ARB therapy can improve outcomes in COVID-19 patients. Pending this data, we do not endorse stopping or starting such therapies solely because of COVID-19 infection.
References:


The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider’s professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

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