GUIDANCE FOR TREATMENT OF COVID-19 IN ADULTS AND CHILDREN

Patient population:
Adult and pediatric patients with COVID-19 infection, who are being admitted inpatient from the emergency department or currently admitted on an inpatient floor or to the intensive care unit. Currently, there are no recommended therapies for COVID-19 positive patients in the outpatient setting.

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:
Routine consult ID on all patients admitted with COVID-19. Urgent consult only if a specific question requires more urgent evaluation

Based on data from several randomized control trials, Remdesivir may provide a modest benefit in a subgroup of patients hospitalized with COVID-19. See further details regarding patient populations (see below) and table 2.

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>Low flow supplemental oxygen</td>
<td>• Supportive care</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone (Exception: Minimal supplemental oxygen (1-2 L) in adults with &lt;7 days of symptoms—uncertain benefit)</td>
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<tr>
<td></td>
<td>• Remdesivir</td>
</tr>
<tr>
<td>High flow supplemental oxygen or non-invasive mechanical ventilation</td>
<td>• Supportive Care</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>• Remdesivir (uncertain benefit)</td>
</tr>
<tr>
<td>Mechanical ventilation or ECMO</td>
<td>• Supportive care</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone</td>
</tr>
</tbody>
</table>

Convalescent plasma may also be added per FDA issued Emergency Use Access (See Table 2 for additional information).
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><strong>Remdesivir (ID Consult Required)</strong></td>
<td></td>
<td>Adult dosing: 200 mg IV load, then 100 mg IV q24h</td>
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<tr>
<td></td>
<td>Pediatric dosing*:</td>
<td>&lt;40 kg: 5 mg/kg IV load, then 2.5 mg/kg q24h</td>
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<tr>
<td></td>
<td></td>
<td>≥40 kg: 200 mg IV load, then 100 mg IV q24h</td>
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<tr>
<td></td>
<td>Duration:</td>
<td>5 days or until hospital discharge whichever comes first. Patients started on remdesivir and progress to requiring higher level of oxygen support (e.g., mechanical ventilation) should still complete a course of remdesivir</td>
</tr>
</tbody>
</table>

**Guidelines for Use: Patients should meet criteria a & b.**

- Laboratory confirmed SARS-CoV-2 infection by PCR from nasopharyngeal or respiratory sample and <14 days of symptoms
- Severe Covid-19 on admission or during hospitalization: SpO₂ ≤94% on room air or requires supplemental oxygen, high-flow nasal cannula*, or non-invasive mechanical ventilation*

*HFNC and NIMV are included as possible indications for remdesivir, but it is uncertain if remdesivir confers a clinical benefit among patients requiring this level of O₂ support

- Please page 30780 for approval prior to first dose of remdesivir between 7 AM and 11 PM (7 days a week).
- Routine ID consult is required, though consult service does not need to see patients in the ED prior to the first dose of Remdesivir (can page 30780 –see above).
- 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 and benefit of remdesivir likely outweighs this small risk
- The risk of hepatotoxicity with a baseline AST/ALT >5x ULN is not known due to patient exclusion from clinical trials; potential benefit versus risk should be considered

**Adverse events:**
- Increased LFTs: daily monitoring of hepatic function is recommended
<table>
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<tr>
<th>Therapeutic Agents</th>
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<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
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<tr>
<td><strong>Adult Patients</strong></td>
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</tbody>
</table>
| 1. Recommended in patients with COVID-19 who require mechanical ventilation or ECMO | 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  

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) |
| 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. | 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 |
| **Pediatric Patients** | Duration: Maximum 10 days, or until discharge |          |
| 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. | 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. |

This recommendation is based on the RECOVERY RCT, NIH and IDSA treatment guidelines for patients with COVID-19 (see references) | | |
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<tbody>
<tr>
<td><strong>COVID-19 Convalescent Plasma</strong></td>
<td>One unit of COVID-19 Convalescent Plasma of High Titer (preferred over Low Titer when available)</td>
<td>Order Set now in place—do not need to page blood blank</td>
</tr>
<tr>
<td>Insufficient data are available to provide guidance regarding efficacy or optimal target population for use. Though administration earlier in the disease course may be better. Recent RCT did not demonstrate a clinical benefit with convalescent plasma but other RCTs are ongoing. Available via FDA issued Emergency Use Authorization for hospitalized patients with COVID-19 but not considered standard of care. Decisions regarding use outside of clinical trials should be individualized.</td>
<td>Health Care Providers must review FDA Fact Sheet for Health Care Providers <a href="https://www.fda.gov/media/141478/download">https://www.fda.gov/media/141478/download</a></td>
<td>Health Care Providers must provide recipients with the Fact Sheet for Patients/Caregivers and communicate the following information to the recipients <a href="https://www.fda.gov/media/141479/download">https://www.fda.gov/media/141479/download</a></td>
</tr>
</tbody>
</table>

1. FDA has authorized emergency use of COVID-19 convalescent plasma, which is not an FDA-approved biological product

2. The patient or caregiver has the option to accept or refuse administration of COVID-19 convalescent plasma

3. The significant known and potential risks and benefits of COVID-19 convalescent plasma 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.

**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. Similarly, Vaughn et al reported that 3.5% of all patients hospitalized with COVID-19 had a community-onset bacterial co-infection and that 11% of patients admitted directly to the ICU had a community-onset bacterial co-infection.

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\textsuperscript{11}. 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.

### 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>
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<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 x 4 days</td>
<td><strong>Uncomplicated pneumonia:</strong> 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> - Community onset pneumonia with risk factors for drug resistant pathogens (see risk factors 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>
<tr>
<td><strong>Pathway C</strong> Hospital-acquired Pneumonia</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>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>*Discontinue vancomycin if no evidence of MRSA colonization/infection (negative MRSA nasal swab or respiratory culture).</td>
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</tbody>
</table>

**PATHWAY B RISK FACTORS**

- History of infection or colonization with Pseudomonas spp., MRSA, or pathogens resistant to standard CAP therapy (ampicillin-sulbactam or ceftriaxone) within previous 12 months
- Severe community-acquired pneumonia (septic shock OR requiring mechanical ventilation OR high clinical concern for needing ICU care\textsuperscript{3}), AND meeting 1 of the following criteria:
  - Hospitalization for at least 48 hours AND use of any intravenous antibiotic, fluoroquinolone, or linezolid within previous 90 days OR
  - Immunocompromised, defined as:
    - AIDS (CD4 <200)
    - Neutropenia (ANC <1000)
    - Kidney or liver or heart transplant recipient within previous 1 year
    - Solid organ transplant recipient treated for rejection within previous 6 months
    - Lung transplant recipient
    - Allogeneic stem cell transplant within previous 1 year or those with chronic GVHD
    - Autoimmune disorders on biologic agents (TNF\textalpha inhibitors, rituximab, etc.)

**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.
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.

If obtained from a source other than med.umich.edu/asp, please visit the webpage for the most up-to-date document.

References:

<table>
<thead>
<tr>
<th>Antimicrobial Subcommittee Approval:</th>
<th>N/A</th>
<th>Originated:</th>
<th>03/2020</th>
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<tr>
<td>P&amp;T Approval:</td>
<td>N/A</td>
<td>Last Revised:</td>
<td>10/2020</td>
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</tbody>
</table>

Revision History:
- 3/16: Removed testing recommendations - added link to testing document
- 3/17: Added tocilizumab, adjusted pediatric hydroxychloroquine dosing
- 3/19: Revised tocilizumab criteria, added pneumonia guidance
- 3/20: Revised tocilizumab dosing to weight based due to changes in Epic dose rounding capabilities, added limited data for corticosteroids in ARDS
- 3/24: Added guidance on azithromycin, revised tocilizumab dosing, added clinical study enrollment appendix
- 3/25: Revised criteria for HCQ use.
- 3/26: Revised tocilizumab criteria & included sarilumab study caveat
- 3/27: Removed study flow diagram
- 3/31: 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: Added suggested labs, revised remdesivir clinical trial information
- 4/3: Added hyperlink to Appendix A - review of HCQ data
- 4/6: Revised testing guidance hyperlink
- 4/7: Revised tocilizumab criteria
- 4/10: Revised tocilizumab criteria
- 4/15: Revised tocilizumab criteria
- 5/15: Revised tocilizumab criteria, revised remdesivir comments
- 6/3: Revised secondary infection information, revised remdesivir obtainment information
- 7/10: Added dexamethasone section
- 8/3: Added remdesivir criteria
- 9/15: Added convalescent plasma section
- 10/5: Removed tocilizumab, updated remdesivir comments, updated convalescent plasma comments
- 10/14: Revised remdesivir criteria
- 10/28: Revised Patient Population, revised Table 1, revised remdesivir section