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 uncomplicated upper respiratory tract viral infection to pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock (Table 1)

Diagnosis:
See link to current COVID-19 testing recommendations: Send testing for COVID-19

Treatment:
The current body of literature and local experience does not support the routine use of any specific treatment regimen, including hydroxychloroquine, for patients with confirmed COVID-19 infection.

Michigan Medicine is committed to participation in randomized controlled clinical trials to facilitate the generation of robust evidence concerning the effectiveness of products in treating COVID-19 and to appropriately delineate risk-vs-benefit assessments for various treatment strategies. Infectious Diseases will review every case for trial eligibility and continue to make treatment decisions that are most optimal for each individual patient.

Supportive care:
Appropriate treatment of concomitant pneumonia, respiratory failure, ARDS, sepsis, septic shock.

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.

Limited evidence supporting routine use of corticosteroids:
Prior studies assessing outcomes in patients receiving systemic corticosteroids for infections due to closely related viruses (SARS-CoV and MERS-CoV) found a lack of effectiveness and possible harm. However, early published and unpublished observations from China suggest that corticosteroids may reduce mortality in COVID-19 infected patients with ARDS and evidence of progression. If steroids are contemplated, it is recommended to use moderate doses of methylprednisolone (1-2 mg/kg) for 3-5 days.

Further details regarding the clinical syndrome and management of COVID-19 infections can be found in the below reference:
Table 1. Clinical syndromes associated with COVID-19 infection

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Uncomplicated illness</strong></td>
<td>Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, muscle pain or malaise. The elderly and immunosuppressed may present with atypical symptoms. These patients do not have any signs of dehydration, sepsis or shortness of breath.</td>
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<tr>
<td><strong>Mild pneumonia</strong></td>
<td>Patient with pneumonia and no signs of severe pneumonia. Child with non-severe pneumonia has cough or difficulty breathing + fast breathing: fast breathing (in breaths/min): &lt;2 months, &gt;60; 2–11 months, &gt;50; 1–5 years, &gt;40 and no signs of severe pneumonia.</td>
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<td><strong>Severe pneumonia</strong></td>
<td>Adolescent or adult: fever or suspected respiratory infection, plus one of respiratory rate &gt;30 breaths/min, severe respiratory distress, or SpO2 &lt;90% on room air (adapted from [1]). Child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO2 &lt;90%; severe respiratory distress (e.g. grunting, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): &lt;2 months, &gt;60; 2–11 months, &gt;50; 1–5 years, &gt;40. The diagnosis is clinical; chest imaging can exclude complications.</td>
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<tr>
<td><strong>Acute Respiratory Distress Syndrome</strong></td>
<td>Onset: new or worsening respiratory symptoms within one week of known clinical insult. Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. Origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of oedema if no risk factor present. Oxygenation (adults): Mild ARDS: 200 mmHg &lt; PaO2/FIO2 ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O or non-ventilated). Moderate ARDS: 100 mmHg &lt; PaO2/FIO2 ≤200 mmHg with PEEP ≥5 cmH2O, or non-ventilated. Severe ARDS: PaO2/FIO2 ≤ 100 mmHg with PEEP ≥5 cmH2O or non-ventilated. When PaO2 is not available, SpO2/FIO2 ≤315 suggests ARDS (including in non-ventilated patients). Oxygenation (children; note OI = Oxygenation Index and OSI = Oxygenation Index using SpO2): Mild ARDS (ventilated): 0 ≤ OI &lt; 8 or 5 ≤ OSI &lt; 7.5. Moderate ARDS (ventilated): 8 ≤ OI &lt; 16 or 7.5 ≤ OSI &lt; 12.3. Severe ARDS (ventilated): OI ≥ 16 or OSI ≥ 12.3.</td>
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<tr>
<td><strong>Sepsis</strong></td>
<td>Adults: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction*. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia. Children: suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count.</td>
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<tr>
<td><strong>Septic shock</strong></td>
<td>Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level &gt;2 mmol/L. Children (based on [2]): any hypotension (SBP &lt;5th centile or &gt;2 SD below normal for age) or 2 of the following: altered mental state; tachycardia or bradycardia (HR &lt;90 bpm or &gt;160 bpm in infants and HR &lt;70 bpm or &gt;150 bpm in children); prolonged capillary refill (&gt;2 sec) or warm vasoconstriction with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.</td>
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</table>

Abbreviations: ARI, acute respiratory infection; BP, blood pressure; bpm, beats/minute; CPAP, continuous positive airway pressure; FIO2, fraction of inspired oxygen; MAP, mean arterial pressure; NIV, noninvasive ventilation; OI, Oxygenation Index; OSI, Oxygenation Index using SpO2; PaO2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SpO2, oxygen saturation. *If altitude is higher than 1000m, then correction factor should be calculated as follows: PaO2/FIO2 x Barometric pressure/760. 

The SOFA score ranges from 0 to 24 and includes points related to 6 organ systems: respiratory (hypoxemia defined by low PaO2/FIO2), coagulation (low platelets), liver (high bilirubin), cardiovascular (hypotension), central nervous system (low level of consciousness defined by Glasgow Coma Scale), and renal (low urine output or high creatinine). Sepsis is defined by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score ≥2 of ≥2 points. Assume the baseline score is zero if data are not available.

Source: World Health Organization
Table 2: Agents under investigation for treatment of COVID-19
NOTE: Routine treatment with investigational therapies is not endorsed outside clinical trials. Infectious Diseases will review every case for potential benefit and screen COVID-19 infected patients for eligibility in trials (see “Treatment” on Page 1). The below provides information regarding investigational therapies that may be recommended by ID.

<table>
<thead>
<tr>
<th>Antiviral therapy</th>
<th>Dosing &amp; Duration</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Hydroxychloroquine | Per Future Research Protocol | Adverse events: Retinopathy rash, nausea, glucose fluctuations, and diarrhea. GI symptoms can be mitigated by taking hydroxychloroquine with food.  
- Use with caution in diabetic patients; hypoglycemia may occur. Insulin requirements may decrease.  
- Use with caution in patient at risk for QT prolongation.  
- Recommend obtaining G6PD test. Post-marketing studies suggest the risk of hemolysis is very low. It is reasonable to start hydroxychloroquine in most patients while awaiting G6PD testing.  
- Recommend avoid taking hydroxychloroquine with antacids. Separate administration by at least 4 hours.  
- Hydroxychloroquine can be crushed. |

**Contraindications:**  
- Porphyria  

**Pregnant and Nursing Mothers:**  
- Maternal-Fetal Medicine at Michigan Medicine has endorsed the use of hydroxychloroquine in pregnancy.  
- Hydroxychloroquine is excreted into breast milk in minute amounts. Thorough evaluation of the risk:benefit should be discussed with the patient prior to starting therapy. The American Academy of Pediatrics considers hydroxychloroquine compatible with breastfeeding.  

The current body of literature and local experience does not support the routine use of hydroxychloroquine for patients with confirmed COVID-19 infection.
<table>
<thead>
<tr>
<th>Antiviral therapy</th>
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<tbody>
<tr>
<td>Remdesivir</td>
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<tr>
<td><strong>Adult dosing:</strong></td>
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<tr>
<td>200 mg IV load, then 100 mg IV q24h</td>
<td>UM is enrolling patients in 2 clinical trials with remdesivir. These trials currently exclude children and pregnant patients.</td>
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<tr>
<td><strong>Pediatric dosing</strong>:</td>
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<tr>
<td>&lt;40 kg:</td>
<td>Remdesivir may be available for children and pregnant women with severe COVID-19 infection through Gilead with approved investigational new drug (IND) application.</td>
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<tr>
<td>5 mg/kg IV load, then 2.5 mg/kg q24h</td>
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<tr>
<td>≥40 kg:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg IV load, then 100 mg IV q24h</td>
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<tr>
<td><strong>Duration:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol</td>
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</table>

Adverse events:
- Increased liver enzymes.

*pediatric dosing of remdesivir is taken from the WHO recommendations for treatment of Ebola virus, as no specific dosing recommendations exist for COVID-19.
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</thead>
<tbody>
<tr>
<td><strong>Tocilizumab</strong></td>
<td><strong>ID APPROVAL NEEDED</strong></td>
<td>Adjunct therapy with interleukin-6 inhibitors, like tocilizumab, may improve oxygenation and time to symptom resolution in patients with cytokine storm.</td>
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<tr>
<td></td>
<td><strong>Dose rounding currently built into Epic order. Doses should be rounded to nearest available full vial (80 mg, 200 mg, 400 mg vials)</strong></td>
<td>Laboratory Parameters also supportive of cytokine storm:</td>
</tr>
<tr>
<td></td>
<td>Adult Dosing (≥18 years): 8 mg/kg (max: 800 mg/dose)</td>
<td>• Serum IL-6 ≥3x upper normal limit</td>
</tr>
<tr>
<td></td>
<td>Pediatric Dosing (&lt;18 years):</td>
<td>• Ferritin &gt;300 ug/L (or surrogate) with doubling within 24 hours</td>
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<tr>
<td></td>
<td>&lt;30 kg: 12 mg/kg</td>
<td>• Ferritin &gt;600 ug/L at presentation and LDH &gt;250 U/L</td>
</tr>
<tr>
<td></td>
<td>≥30 kg: 8 mg/kg (max: 800 mg/dose)</td>
<td>• Elevated D-dimer (&gt;1 mg/L)</td>
</tr>
<tr>
<td></td>
<td><strong>Duration:</strong> One dose</td>
<td>Pregnancy and Nursing Mothers:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maternal-Fetal Medicine at Michigan Medicine has endorsed the use of tocilizumab in pregnancy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tocilizumab may be harmful to newborns, and mothers should stop breastfeeding if receiving tocilizumab but may resume after discontinuation and discussion with provider.</td>
</tr>
</tbody>
</table>

Serious adverse events:  
- Gastrointestinal perforation  
- Anemia  
- Hepatitis  
- Infusion reaction  

**Do not use** (therapies without any supportive evidence and/or associated with potential harm): lopinavir/ritonavir, nitazoxanide, oseltamivir, baloxavir, interferon, ribavirin, IVIG

**Recommend against the use of azithromycin for COVID-19 treatment:**  
Preliminary data evaluating the combination of hydroxychloroquine and azithromycin for treatment of COVID-19 were recently published (Gautret et al.). The authors of this study conclude that combination therapy (only in 6 patients) led to greater viral load reduction compared to monotherapy with hydroxychloroquine. However, more patients receiving hydroxychloroquine monotherapy had higher baseline viral burden (estimated by cycle threshold values). When limiting the analysis to those with comparable baseline cycle threshold values, combination therapy with hydroxychloroquine and azithromycin led to a similar proportion of negative testing by day 6 compared to hydroxychloroquine monotherapy. Furthermore, the study does not report the clinical outcomes of these patients, and it is unknown if reductions in viral load correlate with improvements in clinical outcomes. A subsequent study, which has not been peer-reviewed, suffers from only including patients with very mild illness and a lack of a control group. Thus, based on this limited and weak evidence and concern for harm, we recommend against the use of azithromycin for the treatment of COVID-19 at this time. Azithromycin can still be used if patients require antibiotic therapy for legionella or as part of an empiric regimen for community acquired pneumonia.
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, secondary bacterial 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 a study of 24 critically-ill patients in Seattle-area hospitals:
- 75% required mechanical ventilation and 71% needed vasopressors. Pulmonary secretions were generally characterized as moderate or thick and purulent, and all chest radiographs showed bilateral pulmonary opacities.
- Coexisting bacterial infection was not identified in any patient (blood and sputum cultures drawn in 20 and 15 patients, respectively)

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.

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>Pathway A – 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>Pathway B – Inpatient pneumonia with risk factors as defined below</td>
<td>Piperacillin-azobactam 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
References:

9. https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm

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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