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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:

There is no current evidence from RCTs to recommend any specific anti-COVID-19 treatment for patients with suspected or confirmed COVID-19 infection.

Treatment should be considered in symptomatic patients requiring hospitalization or those with conditions associated with severe disease (**Table 2**). All agents described in **Table 3** are considered investigational/for compassionate use, and decision to use these should be made only with close attention to the patient's clinical status, comorbidities, and interacting medications.

Supportive care:

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

No evidence supporting 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, corticosteroids may still be warranted for other medical indications (i.e., COPD exacerbation).

Further details regarding the clinical syndrome and management of COVID-19 infections can be found in the below reference:

World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected. Interim guidance. Jan 28th 2020. https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf

Table 1. Clinical syndromes associated with COVID-19 infection

Uncomplicated illness	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.
Mild pneumonia	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): <2 months, ≥60; 2–11 months, ≥50; 1–5 years, ≥40 and no signs of severe pneumonia.
Severe pneumonia	Adolescent or adult: fever or suspected respiratory infection, plus one of respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 <90% on room air (adapted from [1]). Child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO_2 <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): <2 months, ≥60; 2–11 months, ≥50; 1–5 years, ≥40.[2] The diagnosis is clinical; chest imaging can exclude complications.
Acute Respiratory Distress Syndrome[7-9]	**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 < PaO_2/FiO_2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cmH_2O,[7] or non-ventilated[8]) • Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤200 mmHg with PEEP ≥5 cmH_2O,[7] or non-ventilated[8]) • Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥5 cmH_2O,[7] or non-ventilated[8]) • When PaO_2 is not available, SpO_2/FiO_2 ≤315 suggests ARDS (including in non-ventilated patients) **Oxygenation (children; note OI = Oxygenation Index and OSI = Oxygenation Index using SpO_2):** • Bilevel NIV or CPAP ≥5 cmH_2O via full face mask: PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3
Sepsis[10,11]	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.
Septic shock[10,12]	Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level >2 mmol/L. Children (based on [12]): any hypotension (SBP <5th centile or >2 SD below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR <90 bpm or >160 bpm in infants and HR <70 bpm or >150 bpm in children); prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

Abbreviations: ARI, acute respiratory infection; BP, blood pressure; bpm, beats/minute; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; NIV, noninvasive ventilation; OI, Oxygenation Index; OSI, Oxygenation Index using SpO_2; PaO_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SpO_2, oxygen saturation. *If altitude is higher than 1000m, then correction factor should be calculated as follows: PaO_2/FiO_2 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 PaO_2/FiO_2), 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[13] of ≥2 points. Assume the baseline score is zero if data are not available

Source: World Health Organization

Table 2: Factors associated with severe COVID-19

Age >65 years
Chronic cardiovascular, pulmonary, hepatic, renal, hematologic, or neurologic conditions
Immunocompromised

Table 3: Agents under investigation for treatment of COVID-19

Antiviral therapy	Dosing & Duration	Comments
Hydroxychloroquine • Empiric therapy for PUI patients should be prescribed for critically ill patients awaiting COVID-19 test results • Preferred therapy for hospitalized patients unable to obtain remdesivir. • Start hydroxychloroquine while awaiting remdesivir approval and arrival to the hospital. Will need to discontinue hydroxychloroquine when remdesivir is started (per the research protocol)	Adult dosing (≥18 years): 600 mg PO BID x2 doses (load), then 200 mg PO TID Pediatric dosing (<18 years): 10 mg/kg (max: 600 mg/dose) PO BID x2 (load), then 3 mg/kg PO TID (max: 200 mg/dose) Duration: 5 days In select patients with extended ventilation or profound immunosuppression duration may be extended	Consider adding tocilizumab (see criteria below) 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 G6DP 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 hydroxychlorquine with antacids. Separate administration by at least 4 hours. • Hydroxychloroquine can be crushed. Pregnant and Nursing Mothers: Hydroxychloroquine has been associated with fetal ocular toxicity in animal studies. Additionally, hydroxychloroquine is excreted into breast milk. Thorough evaluation of the risk:benefit should be discussed with the patient prior to starting therapy.

Antiviral therapy	Dosing & Duration	Comments
Tocilizumab Consider adding to antiviral therapy for patients meeting criteria #1 AND #2 below: 1. COVID-19 positive 2. All of the following respiratory findings: a. Rapidly worsening respiratory gas exchange b. Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), c. Clinical assessment (evidence of rales/crackles on physical examination) AND SpO_2 ≤93% on room air OR greater than 6 L/min O_2 In COVID-19 positive patients who don't meet criteria #2 above, tocilizumab may still be appropriate if (1) high risk for severe disease (Table 2) **AND** (2) high risk for developing cytokine storm. <u>Criteria for patients at high-risk for developing cytokine storm (1 or more of the following):</u> • Serum IL-6 ≥3x upper normal limit • Ferritin >300 ug/L (or surrogate) with doubling within 24 hours • Ferritin >600 ug/L at presentation and LDH >250 • Elevated D-dimer (>1 mg/L)	**Doses should be rounded to nearest full vial (80 mg, 200 mg, 400 mg vials available) ** <u>Adult Dosing (≥18 years):</u> *50-59 kg:* 400 mg IV *60-85 kg:* 600 mg IV *>85 kg*: 800 mg IV <u>Pediatric Dosing (<18 years):</u> *<6 kg:* 12 mg/kg (actual body weight) IV *6-10 kg:* 80 mg IV *10-14 kg:* 160 mg IV *15-18 kg*: 200 mg IV *19-21 kg*: 240 mg IV *22-24 kg*: 280 mg IV *25-27 kg*: 320 mg IV *28-32 kg*: 360 mg IV *33-60 kg*: 400 mg IV *>60 kg*: use adult dosing <u>Duration:</u> One dose Consider giving additional dose 8-12 hours later if continued clinical decompensation	Adjunct therapy with interleukin-6 inhibitors, like tocilizumab, may improve oxygenation and time to symptom resolution in patients at high risk of cytokine storm. <u>Contraindications:</u> • Avoid in pregnancy • Tocilizumab may be harmful to newborns, and mothers should stop breastfeeding if receiving tocilizumab <u>Serious adverse events:</u> • Gastrointestinal perforation • Anemia • Hepatitis • Infusion reaction

Antiviral therapy	Dosing & Duration	Comments
Remdesivir *Preferred therapy for patients hospitalized due to COVID-19 if criteria are met for obtaining product from manufacture (see comments)*	Adult dosing: 200 mg IV load, then 100 mg IV q24h Pediatric dosing*: *<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: Per protocol	**Drug only available through Gilead with approved investigational new drug (IND) application.** Criteria below are for compassionate use program. UM is in the process of becoming part of 2 clinical trials with remdesivir, which have different inclusion/exclusion criteria. Please contact COVID-19 ID attending for evaluation to enroll in the remdesivir clinical trial. Inclusion Criteria: • Hospitalization • SARS-CoV-2 by PCR • Mechanical ventilation Exclusion Criteria: • Multi-organ failure • Vasopressor requirement • ALT >5x ULN • CrCl <30 mL/min, dialysis, or CVVH • Concomitant use of other experimental antiviral agents (e.g., lopinavir/ritonavir) To start the request for remdesivir through Gilead's expanded access program, please send an email to the UMHS Expanded Access Group at (UM-Expanded-Access-Request@med.umich.edu). Email this group regardless of hours, but the expanded access program typically responds M-F during daytime hours. For urgent weekend and evening/over-night 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: https://rdvcu.gilead.com/ Adverse events: Increased liver enzymes. Also potential to have drug-drug interactions with medications metabolized through cytochrome system

Antiviral therapy	Dosing & Duration	Comments
Lopinavir-ritonavir (Kaletra®) *Alternative therapy if remdesivir and hydroxychloroquine are unavailable or if the patient has contraindications or adverse effects*	Adult dosing: 400 mg-100 mg PO BID Pediatric dosing: *14 days to 6 months old:* lopinavir component 16 mg/kg PO BID *6 months to 18 years:* 15-25 kg: 200 mg-50 mg PO BID 26-35 kg: 300 mg-75 mg PO BID >35 kg: 400 mg-100 mg PO BID Duration: 5 days In select patients with extended ventilation or profound immunosuppression duration may be extended	**Check HIV antigen/antibody prior to first dose** Adverse events: Hepatotoxicity, pancreatitis, diabetes, QT prolongation, lipid elevations, and fat redistribution Major substrate and inhibitor of Cytochrome P450, and can cause **severe drug-drug interactions**. Thorough evaluation of a patient's mediation profile should be reviewed before starting therapy. Pregnancy: Lopinavir-ritonavir is safe to use during pregnancy
Nitazoxanide *Alternative*	Adult dosing: 500 mg PO BID Pediatric dosing: *1-3 years:* 100 mg PO BID *4-11 years:* 200 mg PO BID *≥12 years*: 500 mg PO BID Duration: 5 days In select patients with extended ventilation or profound immunosuppression duration may be extended	Very limited vitro data evaluating activity and currently there is literature evaluating its use in patients with COVID-19. Adverse events: Headache, nausea, abdominal pain, urine discoloration Pregnant and Nursing Mothers: Use is safe in pregnancy after the first trimester. There is no data on excretion into breast milk.

*pediatric dosing of remdesivir is taken from the WHO recommendations for treatment of Ebola virus, as no specific dosing recommendations exist for COVID-19.

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

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Antibiotic Management for Pneumonia in PUI and Confirmed COVID-19 Patients

Summary of Recommendations:

1. In patients admitted to the RICU with suspected COVID-19 pneumonia (testing pending), initiation of 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, empiric antibiotic therapy may still be warranted if: elevated PCT (>0.25 for adult patients), elevated WBC, or clinically deemed necessary based on presentation or hemodynamic instability. De-escalation/discontinuation of antibiotics should be considered based on clinical and microbiological data.
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 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, 70% of patients had a procalcitonin level <0.1 on admission, and 88% had a level <0.25. 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.

<u>As such, the literature and experience to date suggests that adult patients with COVID-19 infection can be managed as per our standard institutional guidelines regarding antibiotic use in patients with suspected pneumonia.</u>

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

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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, and antibiotics can be safely withheld**. Michigan Medicine guidelines endorse the following algorithm for adult patients:

Procalcitonin Level (ng/mL)	Bacterial Etiology	Recommendation
<0.1	Very unlikely	Antibiotics strongly discouraged
0.1 – 0.25	Unlikely	Antibiotics discouraged
>0.25 – 0.5	Likely	Antibiotics encouraged
>0.5	Very likely	Antibiotics strongly encouraged

- If the PCT is low and no antibiotics are started, a repeat PCT measurement may be considered *if clinical suspicion for infection persists* 6-24 hours after the first measurement.
- Procalcitonin should NOT be routinely used to *extend* treatment duration.

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Adult Pneumonia Treatment Summary Recommendations

Indication	**1st Line Empiric Therapy (see guidelines for alternatives)**	**Duration of Therapy**
Pathway A – Inpatient community-acquired with no risk factors	**Ampicillin-sulbactam** 3 g IV q6h + Azithromycin 500 mg IV/PO x1 day, then 250 mg q24h x4 days	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
Pathway B – Inpatient pneumonia with risk factors as defined below	**Piperacillin-azobactam** 4.5 g IV q6h (+ **Tobramycin** IV if admitted to ICU) + **Vancomycin*** IV (see Standard Dosing Guideline) *Discontinue vancomycin if no evidence of MRSA colonization/infection (negative MRSA nasal swab or respiratory culture).	Uncomplicated pneumonia: 7 days

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

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