CLINICAL GUIDELINE | MEDICAL MANAGEMENT FOR PATIENTS WITH CONFIRMED COVID-19

(Age < 25 years)

Children's MINNESOTA

Aims: : To *dynamically** provide guidance on management for patients positive testing for COVID-19

Patient with confirmed COVID-19 (positive PCR)

→ Appropriate PPE, rooming, and staffing.
Educate family on positive test and isolation.
Alert ID and consulting services about positive test status if in hospital.

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Assess COVID-19 Illness Level (note 1)
Signs/symptoms, vital signs, hydration, respiratory status.
Consider also alternate etiologies for illness.

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*Note that information on COVID-19 is rapidly evolving. Please refer to www.CDC.gov, www.who.int, https://www.health.state.mn.us/ or Children's MN infection prevention team for updates Due to the dynamic nature of this guideline, it is not run through the Guideline Governance Council but is updated regularly by clinical leadership.

Asymptomatic

Tested for reasons other than symptoms (e.g. pre-op, behavioral health admission)

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No additional tests/ treatments needed

- Manage primary condition
- If re-test needed for discharge or transfer placement, send to MDH

Mild

Symptomatic but not generally requiring hospitalization for their COVID problem.[a]

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Guide tests/treatments on symptoms

- Supportive cares in clinic/ED and recs for home (note 2).
- Evaluate and treat suspected coinfections based on symptoms (note 3).
- [a]*Hospitalized patients with mild symptoms may be managed as above. Escalate testing/therapies if clinical status worsens.*

Moderate

Signs or symptoms of COVID-19 requiring med-surg care but not generally meeting criteria for critical care.

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Additional testing

- Obtain CBC+diff, CRP, CMP, IgG.
- If patient ≥ 12 yrs age OR has additional VTE risk factors (see VTE guideline) add PT/PTT/fibrinogen, d-dimer AND start VTE prophylaxis.
- CXR if respiratory symptoms.
- Supportive cares and symptoms management (note 2).
- Evaluate and treat suspected coinfections based on symptoms (note 3).
- Antibiotics per suspected sepsis orderset if sepsis is present
- See separate MIS-C guideline
- **Consider additional therapies specific to COVID-19 (see subsequent guideline pages for detail)**

Severe

Critically ill, requiring ICU level of care

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Additional testing

- Obtain CBC+diff, CRP, procalcitonin, CMP, IgG, PT/PTT/fibrinogen, d-dimer, rapid 4-plex cytokine panel, immune comprehensive panel, LDH, ferritin, TG, CPK, troponin, blood culture, CXR.
- VTE prophylaxis (see guideline)
- Evaluate and treat suspected coinfections based on symptoms (note 3).
- Antibiotics per suspected sepsis orderset if sepsis is present
- Consult immunology, pulmonology, ID and other specialists as indicated.
- See separate MIS-C guideline
- **Additional therapies specific to COVID-19 (see subsequent guideline pages for detail).**

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NOTE 1: SEVERITY OF ILLNESS CATEGORIES

- **Mild:** No respiratory distress or oxygen requirement; able to self-hydrate (may be after initial fluid support)
- **Moderate:** Requiring ongoing IVF support OR requiring respiratory support including low flow nasal cannula for hypoxia or high flow nasal cannula for increased work of breathing. If hypoxia and/or respiratory distress are not improved with trial of low or high flow nasal cannula, escalate to severe category. If suspected MIS-C but no cardiac dysfunction (e.g. abnormal echo, EKG or troponin, etc.) and patient without shock or hemodynamic stability may consider admitted to med-surg unit.
- **Severe:** Hypoxia or work of breathing requiring non-invasive or invasive ventilation or concern that patient status is worsening on high flow nasal cannula OR SIRS/Sepsis/Shock OR rapidly worsening status. If suspected MIS-C and any cardiac dysfunction (e.g. abnormal echo, EKG or troponin, etc.), and/or shock/hypotension or concern for rapid progression patient should be admitted to ICU.
- *Consider also risk factors for more severe COVID-19 in considering to step-up to next level of severity for disposition decisions (shared decision making with family and other providers) in your patient: immunocompromise, age < 12 months, complex chronic conditions, obesity. chronic kidney disease, chronic hepatitis, endocrine disorders. Consider also ability of family/guardian to provide supportive cares as well as follow-up options.*

NOTE 2

- If bronchodilator indicated, use MDI instead of nebulizer, follow treatment with inhaled corticosteroid (e.g. QVAR, up to Q4).
- Systemic corticosteroids may be used for asthma/croup indications. Discuss with multidisciplinary team in patients requiring persistent/escalating supplemental oxygen or mechanical ventilation.
- Acetaminophen preferred 1st line. Motrin/Ibuprofen ok for 2nd line analgesia/antipyretic.
- Maintain euvolemia, avoid overhydration as this may increase ARDS risk.

NOTE 3

While bacterial pneumonia is in the differential for COVID, patients with COVID are NOT more likely to have bacterial pneumonia. Only use antibiotics with strong suspicion for a pneumonic bacterial process due to both clinical exam and imaging findings.

***Treatment Recommendations for Pneumonia (CAP):**

- **Age ≤ 28 days OR preterm infant (less than 37 weeks gestation) with PMA less than 41 weeks**
  - Follow febrile infant guideline for workup, use Ampicillin plus Ceftazidime; Cefdinir for ongoing oral CAP treatment
- **> 28 days OR preterm infant (less than 37 weeks gestation) with PMA ≥ 41 weeks–4 months**
  - Ceftriaxone/Cefdinir
- **> 4 mo and fully immunized for age**
  - Ampicillin/Amoxicillin (PCN exposure or allergy *not anaphylaxis* - Cefuroxime/Cefprozil)
- **> 4 mo and has <u>not</u> received 2 Hib and Pneumococcal vaccine doses**
  - Ceftriaxone/Cefdinir
- **Consider adding Azithromycin for patients ≥ 5 yr.**
- *Oseltamavir if influenza positive.*
- *Antibiotics per suspected sepsis orderset if sepsis is present.*
- *Consult ID for empiric antibiotic recommendations if hospital-acquired infection suspected.*

Discharge criteria:

- Routine medical criteria
- Encourage virtual or in-clinic follow-up with PCP
- Speak with MDH/infection prevention on-call for guidance for home isolation.

Workgroup: Hester, Koutsari, Pomputius, COVID Clinical Core

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Supportive care is the cornerstone of clinical management of COVID-19. There is emerging evidence from randomized clinical trials supporting the use of certain pharmacologic agents for patients with COVID-19. The guidance below is based on available knowledge and multidisciplinary input. It is intended as a living document that will be updated in real time as more data emerges.

Last updated July 7, 2020

Clinical Syndrome Associated with COVID-19	Clinical Presentation[1]	Therapeutic Agent(s)	Comments	Monitoring
Mild illness	Uncomplicated URT viral infection, with non-specific symptoms: e.g. fever, fatigue, cough, anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache	**Supportive Care** **Prophylactic Convalescent Plasma IRB 2005-044 (peds)** • Can be given for high-risk patients under IRB-approved trial above (eligibility per Appendix A)		
Non-Severe Pneumonia	**Pediatric Patients** Cough or dyspnea plus tachypnea Tachypnea (breaths/min): • < 2 months: ≥ 60 • 2–11 months: ≥ 50 • 1–5 years: ≥ 40 • 6–12 years: ≥ 35 • 13–18 years: ≥ 30 • and no signs of severe pneumonia **Adult Patients** • No signs of severe pneumonia and no need for supplemental oxygen Clinical experience in adults has shown that **rapid clinical deterioration** can take place within a few hours. Physical exam and close monitoring of symptoms are essential. If unexpected or rapid clinical deterioration, **notify ID as soon as possible** to initiate process for obtaining **remdesivir** under compassionate use from Gilead (requires **eIND**) https://rdvcu.gilead.com/ or via Emergency Use Authorization (EUA).	**Supportive Care** For patients who initially present with non-severe pneumonia **but are worsening**, pharmacologic treatment can be considered. The **risk vs. benefit** of pharmacologic treatment should be made on a case-by-case basis **in discussion with ID and Immunology**. **Prophylactic Convalescent Plasma IRB 2005-044 (peds)** • Can be given for high-risk patients under IRB-approved trial above (eligibility per Appendix A) **Convalescent Plasma IRB 2005-051 (adults)** • Can be given for treatment under IRB-approved trial above (eligibility per Appendix A) Use of convalescent plasma for prophylaxis or treatment prior to or during hospitalization does not interfere with eligibility for initiation or continuation of remdesivir Treat **suspected pneumonic coinfections** per recommendations included in Note 3, page 2. **IVIG** Based on normal ranges for IgG by age, consider IVIG replacement at 400 mg/kg × 1 if initial IgG is below the following thresholds: 0 - 1 month: <400 mg/dL 1 - < 7 month: <200 mg/dL 7 month - <3 year: < 250 mg/dL 3 - < 6 year: <350 mg/dL 6 years - adults <500 mg/dL	Patient characteristics, such as age, immunosuppression, underlying pulmonary or cardiac disease, may affect the decision for pharmacologic treatment of non-severe pneumonia due to COVID-19.	**All hospitalized patients** • **On admission:** Baseline CBC+diff, CRP, CMP, IgG, serum to save (≥ 3 mL) • **During hospitalization:** - Daily: CBC+diff, CRP - **Symptoms progression (persistent high fever, worsening respiratory distress, increasing O_2 requirements, or transfer to ICU):** CBC+diff, CRP, rapid 4-plex cytokine panel, immune comprehensive panel, LDH, ferritin, fibrinogen, triglycerides, CPK, troponin, D-dimer, procalcitonin, coagulation studies, blood culture

Disclaimer: This is an interim guideline expected to change frequently as new scientific evidence becomes available on treatment of COVID-19; each clinician should use her or his own independent judgment to meet the needs of each individual patient. This guideline is not a substitute for professional medical advice, diagnosis or treatment.

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Clinical Syndrome Associated with COVID-19	Clinical Presentation[1]	Therapeutic Agent(s)	Comments	Monitoring
Severe Pneumonia	**Pediatric Patients** Cough or dyspnea, 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 **Adolescent and Adult Patients** Fever or suspected respiratory infection, plus one of the following: • Respiratory rate > 30 breaths/min • Severe respiratory distress • SpO_2 ≤ 93% on room air If **possible candidate for remdesivir** (see criteria for use), **notify ID as soon as possible** to assess and initiate process for obtaining **remdesivir** under compassionate use from Gilead (requires **eIND**) https://rdvcu.gilead.com/ or via Emergency Use Authorization (**EUA**)	**Remdesivir (if meets criteria for use via eIND or EUA) [Restricted to ID]** **3.5 kg to < 40 kg:** 5 mg/kg IV × 1, followed by: • 2.5 mg/kg q24h × 4 days (if no mechanical ventilation or ECMO). If no clinical improvement after a total of 5 days of treatment, treatment can be extended to up to a total of 10 days, OR • 2.5 mg/kg q24h × 9 days (if mechanical ventilation or ECMO) Note: For pediatric patients ≤ 7 days of age or born prematurely, dosing should be discussed with Gilead Medical Monitor (MM-COVID19@gilead.com) **≥ 40 kg:** 200 mg IV × 1, followed by: • 100 mg IV q24h × 4 days (if no mechanical ventilation or ECMO). If no clinical improvement after a total of 5 days of treatment, treatment can be extended to up to a total of 10 days, OR • 100 mg IV q24h × 9 days (if mechanical ventilation or ECMO) **Systemic Corticosteroids** • Consider dexamethasone 0.15 mg/kg (max 6 mg/dose) PO/NG/IV q24h for up to 10 days for patients requiring persistent supplemental O_2 or mechanical ventilation • Recommend against use in patients not requiring supplemental O_2 • In preterm neonates, risks vs. benefits should be considered based on gestational age, postnatal age, and illness severity **Convalescent Plasma IRB 2005-051 (adults)** • Can be given for treatment under IRB-approved trial above (eligibility per Appendix A) • Use prior to or during hospitalization does not interfere with eligibility for initiation or continuation of remdesivir **Empiric Antibiotics** If concern for pneumonic bacterial coinfection • **Coming from the community, and no concern for MDRO** refer to recommendations included in Note 3, page 2 • **Concern for health-care associated infection or MDRO** Cefepime IV plus vancomycin IV **IVIG** If low IgG for age consider replacement dose of IVIG (see thresholds and recommended dose under "Non-Severe Pneumonia") Discuss with **Immunology** if need for **biologic modulators** (e.g. tocilizumab) based on admission labs, clinical worsening, or need for mechanical ventilation. **Tocilizumab [Restricted to Immunology and Hem/Onc]** Consider if rapid clinical deterioration. 8 mg/kg/dose (max 800 mg/dose) IV × 1, if no response may repeat up to 3 doses q8–12 hours	**Remdesivir (via eIND)** **Inclusion Criteria (all must be met)** • < 18 years old • SARS-CoV-2 confirmed by PCR • SpO_2 < 94% on room air or requiring supplemental O_2 • ALT < 5 x ULN at baseline **Exclusion Criteria** • Significant vasopressor or inotropic support • CrCl < 30 mL/min, dialysis, or CVVH • VA ECMO • Any investigational agents for COVID-19 (except convalescent plasma) should be stopped prior to remdesivir initiation **Remdesivir (via EUA)** **Inclusion Criteria (see also ref. 21)** Suspected or laboratory confirmed severe COVID-19 disease defined as: • SpO_2 ≤ 94% on room air, OR • Requiring supplemental oxygen, OR • Requiring mechanical ventilation, OR • Requiring ECMO **Not recommended unless potential benefit outweighs potential risk for:** • Adult and pediatric patients (> 28 days old) with eGFR < 30 mL/min, OR • Full-term neonates (≥ 7 days to ≤ 28 days old) with SCr ≥ 1 mg/dL **Do not initiate if:** • ALT ≥ 5 × ULN at baseline **Dexamethasone** • Consider gastric ulcer prophylaxis **Systemic Corticosteroid Alternatives (If dexamethasone is unavailable)** • Prednisolone 1 mg/kg (max 40 mg/dose) PO/NG q24h for up to 10 days • Methylprednisolone 0.8 mg/kg (max 32 mg/dose) IV q24h for up to 10 days **Tocilizumab** AE: hepatotoxicity, leukopenia, neutropenia, infection reactivation, GI effects **Useful websites** • COVID-19 drug interactions http://www.covid19-druginteractions.org/	**All hospitalized patients** • **On admission:** Baseline CBC+diff, CRP, CMP, ferritin, LDH, CPK, D-dimer, IgA, IgG, IgM, comprehensive immune status panel, rapid 4-plex cytokine panel, blood culture, serum to save (≥ 3 mL) • **During hospitalization** – **Daily:** CBC+diff, CRP. – **Day 3 & 7** (unless patient is dischargeable): LDH, ferritin, D-dimer, CPK, rapid 4-plex cytokine panel, immune comprehensive panel – **Symptoms progression (persistent high fever, worsening respiratory distress, increasing O_2 requirements, or transfer to ICU):** CBC+diff, CRP, rapid 4-plex cytokine panel, immune comprehensive panel, LDH, ferritin, fibrinogen, triglycerides, CPK, troponin, D-dimer, procalcitonin, coagulation studies, blood culture **Patients on Remdesivir** • **Labs prior to initiation and daily:** BMP, CBC+diff, AST, ALT, alkaline phosphatase, T/D bilirubin • **Discontinue if:** – ALT ≥ 5 × ULN during treatment (may restart when ALT < 5 × ULN), OR – ALT elevation is accompanied by s/s of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR **Patients on Empiric Antibiotics** Need, duration, and spectrum of antibiotics should be assessed daily based on microbiology results and clinical status **Patients on Tocilizumab** • **Labs prior to initiation:** Quantiferon, CMV, EBV, HBV PCR, adenovirus PCR, HHV-6 PCR

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ARDS	**Pediatric ARDS Definition** Oxygenation index (OI) preferred over oxygen saturation index (OSI) • 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 **Berlin ARDS Definition for Adults[2]** PaO_2/FiO_2 ratio • Mild ARDS: – 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg • Moderate ARDS: – 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg • Severe ARDS: – PaO_2/FiO_2 ≤ 100 mmHg **If not already done, notify ID as soon as possible** to assess and initiate process for obtaining **remdesivir** under compassionate use from Gilead (requires **eIND**) https://rdvcu.gilead.com/ or via Emergency Use Authorization **(EUA)**	**Remdesivir (if meets criteria for use via eIND or EUA) [Restricted to ID]** **3.5 kg to < 40 kg:** 5 mg/kg IV × 1, followed by: • 2.5 mg/kg q24h × 4 days (if no mechanical ventilation or ECMO). If no clinical improvement after a total of 5 days of treatment, treatment can be extended to up to a total of 10 days, OR • 2.5 mg/kg q24h × 9 days (if mechanical ventilation or ECMO) Note: For pediatric patients ≤ 7 days of age or born prematurely, dosing should be discussed with Gilead Medical Monitor (MM-COVID19@gilead.com) **≥ 40 kg:** 200 mg IV × 1, followed by: • 100 mg IV q24h × 4 days (if no mechanical ventilation or ECMO). 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APPENDIX A | ELIGIBILITY CRITERIA FOR USE OF CONVALESCENT PLASMA FOR MANAGEMENT OF COVID-19 IN HOSPITALIZED PATIENTS

Patient Population	Pediatric Patients (Prophylactic)	Adult Patients (Therapeutic)
IRB#	**IRB 2005-044**	**IRB 2005-051 (Expanded Access Program via Mayo Clinic)**
Inclusion Criteria	**All** of the following criteria must be met: 1. Between 1 month and 18 years of age at the time of consent. 2. Determined to be at high-risk for severe SARS-CoV-2 disease based on any of the following: a. Immunocompromised: primary or acquired immunodeficiency e.g. recipient of a bone marrow or solid organ transplant in the last 12 months (or at any time if concurrent with graft-versus host disease), recipient of chemotherapy for a malignancy within the past 6 months, HIV with CD4 (< 30% for ≤ 12 months old; < 25% for 12–35 months; < 20% for 36–59 months or < 350 for all other ages), receiving immunosuppressive or immunomodulatory treatments (e.g., high-dose steroids [≥ 2 mg/kg/day of systemic prednisone or equivalent for ≥ 14 days], tacrolimus, sirolimus, cyclosporine, antithymocyte globulin - ATG, mycophenolate, methotrexate, etc.) b. Hemodynamically significant cardiac disease (e.g. congenital heart disease) c. Lung disease with chronic respiratory failure (e.g. patients with asthma, cystic fibrosis, bronchiectasis, chronic lung disease of prematurity, tracheostomy/ventilator dependency, restrictive lung disease, severe neuromuscular disease, etc.) d. Medically complex children on technological support (including tracheotomy) associated with developmental delay or genetic anomalies 3. Confirmed SARS-CoV-2 infection OR high-risk exposure as defined: a. **Confirmed infection:** Child who tested positive for COVID-19 and is no more than 168 hours (7 days) after onset of symptoms (and within 120 hours at the time of receipt of plasma). b. **High-risk exposure:** Susceptible child who was not previously infected or otherwise immune to SARS-CoV-2 and exposed within 96 hours prior to enrollment (and within 120 hours at the time of receipt of plasma). **Both** criteria below should be met: • A household member or daycare center (same room) exposure to a person with [confirmed SARS-CoV-2 OR with clinically compatible disease in regions with widespread ongoing transmission] • Negative for SARS-CoV-2 (nasopharyngeal swab) 4. Subject is judged by the investigator to have the initiative and means to be compliant with the protocol. 5. Subjects or their legal representatives must have the ability to read, understand, and provide written informed consent for the initiation of any study related procedures.	**All** of the following criteria must be met: 1. Age at least 18 years of age 2. Laboratory-confirmed OR clinically-suspected diagnosis of infection with SARS-CoV-2 3. Admitted to an acute care facility for the treatment of COVID-19 complications 4. **Severe** or **life threatening** COVID-19, or judged by the treating provider to be at **high risk of progression** to severe or life-threating disease. 5. Informed consent provided by the patient or healthcare proxy **Severe** COVID-19 is identified by ≥ 1 of the following: • Dyspnea • Respiratory frequency ≥ 30/min • SpO_2 ≤ 93% • PaO_2/FiO_2 < 300 • Lung infiltrates > 50% within 24 to 48 hours **Life threating** COVID-19 is identified by ≥ 1 of the following: • Respiratory failure • Septic shock • Multiple organ dysfunction or failure **High risk of progression** to severe COVID-19[14] • Moderate-to-severe asthma • Chronic kidney disease treated with dialysis • Chronic lung disease • Diabetes • Hemoglobin disorders (sickle cell, thalassemia) • Immunocompromised • Chronic liver disease • Living in nursing home or long-term care facility • Serious heart conditions • Obesity (BMI ≥ 40)
Exclusion Criteria	**Any** of the following: 1. History of severe reactions (e.g. anaphylaxis) to transfusion of blood products. Subjects with minor reactions such as fever, itching, chills, etc. that resolve spontaneously or respond to pre-medications, and that do not represent more significant allergic reactions will not be excluded. 2. Inability to complete therapy with the study product within the stipulated time frame outlined above 3. Female subjects in child-bearing age with a positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period. 4. Subject/caregiver deemed by the study team to be non-compliant with the study protocol	None specified

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Remdesivir *(continued)*

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Aims: : To *dynamically** provide guidance on management for patients positive testing for COVID-19

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Created: 04/08/20
Revised: 05/11/20 1) Added criteria for use and dosing of remdesivir per Emergency Use Authorization; 2) Revised criteria for use of remdesivir via compassionate use (eIND); 3) Added required laboratory monitoring prior to initiation and daily during remdesivir therapy; 4) Replaced cytokine panel with rapid 4-plex cytokine panel; 5) Included recommendation that doxycycline is preferred over azithromycin for empiric coverage of atypical bacteria if hydroxychloroquine is considered due to QTc prolongation concerns; 6) Included recommendation for hydroxychloroquine dose reduction by 50% if GFR < 10 mL/min, hemodialysis or peritoneal dialysis per hydroxychloroquine Emergency Use Authorization; 7) Added Appendix A for guidance with QTc prolonging pharmacotherapies; 8) Updated literature
Revised: 05/25/20 1) Added convalescent plasma as investigational option for prophylaxis or treatment of COVID-19; 2) Added Appendix B with eligibility criteria for use of convalescent plasma; 3) Updated literature
Revised: 05/29/20 1) Added clarification regarding remdesivir dosing in pediatric patients ≤ 7 days of age or born prematurely; 2) Updated literature
Revised: 06/17/20 1) Added restriction of remdesivir to Infectious Disease per P&T Committee approval on 6.17.20; 2) Removed hydroxychloroquine as treatment option; 3) Removed doxycycline as alternative to azithromycin if concern for community-acquired pneumonic bacterial coinfection; 4) Removed original Appendix A that provided guidance with QTc prolonging pharmacotherapies; 5) Updated literature
Revised: 07/07/20 1) Added dexamethasone as treatment consideration in patients requiring supplemental oxygen or mechanical ventilation; 2) Added methylprednisolone and prednisolone as alternative treatment considerations if dexamethasone is unavailable; 3) Updated convalescent plasma eligibility criteria for the pediatric study to a) include medically complex children on technological support associated with developmental delay or genetic anomalies, and b) extend the onset of symptoms up to 7 days; 4) Updated convalescent plasma eligibility criteria for the adult study to include patients with clinically-suspected diagnosis of SARS-Cov-2 infection; 5) Updated literature