

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Care of the Hospitalized Patient with Coronavirus Disease 2019 (COVID-19)
Evidence-Based Guideline

Definition: The novel coronavirus disease 2019 (COVID-19) is caused by a beta-coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). ⁽¹⁾ This is a RNA virus belonging to the *Coronaviridae* family. ⁽²⁾

Pathophysiology: Rapid mutation and recombination are properties of coronaviruses which contribute to the spread of the disease. ⁽²⁾ SARS-CoV-2 is most commonly spread by close human-to-human contact within six feet. Close physical contact allows for respiratory droplets of persons infected with SARS-CoV-2 to be inhaled. Exposure of mucus membranes to the virus can occur when in close contact with infected individuals. ⁽³⁾ In aerosol generating situations, airborne transmission can occur in people greater than six feet from the infected host. ⁽⁴⁾ SARS-CoV-2 attaches to the host cell by binding to the angiotensin converting enzyme 2 (ACE2) receptor and then penetrates the cells. The SARS-CoV-2 spike protein binds to ACE2 receptors present in respiratory epithelium of the upper airway and lungs, heart and blood vessels, intestinal tract, kidney and bladder, among other tissues. Viral mRNA participates in biosynthesis of new viruses that are released into the body. ⁽⁵⁾

Epidemiology: Globally more than 118 million cases were reported of COVID-19 with 2.6 million deaths as of March 2021. ⁽⁶⁾ More than 29 million of the reported cases of COVID-19 has occurred in the United States resulting in over 527,000 deaths. ⁽⁷⁾ All patient age groups are at risk for infection and have the potential to develop life threatening COVID-19 disease; however, in general, the acute severity of disease is lower in children compared to adults. ⁽⁴⁾ Data from the Centers for Disease Control and Prevention COVID Data Tracker, notes that patients less than 18 years of age represent 11.6% of the total reported cases of COVID-19 with demographic data in the United States as of March 2021 while representing only a small fraction of deaths. ⁽⁷⁾ The weekly incidence of COVID-19 for infants, children and young adults has increased progressively and is highest in the older age groups. ⁽⁸⁾ The true incidence of COVID-19 in children remains unknown due to limited testing for milder symptoms. ⁽⁹⁾

Inclusion Criteria

- Positive SARS-CoV-2 RT-PCR Test
- Age less than 21 years
- Acute care or critical care monitoring

Exclusion Criteria

- [Multi-System Inflammatory Syndrome in Children \(MIS-C\)](#)
- There is limited evidence for the management and treatment of COVID-19 positive infants with clinical bronchiolitis.

Differential Diagnosis ⁽¹⁰⁾

Multi-System Inflammatory Syndrome in Children (MIS-C)
 Community Acquired Pneumonia
 Strep Pharyngitis and Other Bacterial Respiratory Infections
 Other Viral Syndromes

Infection Control

The risk of transmission of COVID-19 can be decreased by infection control measures including maintaining a distance of at least six feet from others, frequent handwashing, covering coughs and sneezes, and wearing a properly fitted mask. ^(3,4)

In the hospital setting, use of personal protective equipment can reduce transmission. [Please review the Texas Children's guidance to personal protective equipment for additional information.](#)

Diagnostic Evaluation

The incubation period for SARS-CoV-2 is up to 14 days from the date of exposure with most people exhibiting symptoms by day 4 to 5. ⁽⁴⁾ The patient should be assessed for the signs and/or symptoms of COVID-19 as well as risk factors for progression to severe disease. Assessment will determine disease severity.

History: Assess for

- Risk factors for severe disease including underlying complex medical conditions, obesity, immunocompromised state (e.g. cancer, solid organ or bone marrow transplantation, lymphopenia, HIV and other immune deficiencies or from immunosuppressive medications), chronic heart, lung or kidney disease, diabetes, sickle cell disease, metabolic disorders, age less than one year and pregnancy.
- History of fever, cough, shortness of breath, difficulty breathing, fatigue, headache, myalgia, loss of taste or smell, sore throat, abdominal pain, nausea, diarrhea, poor appetite or feeding

Physical Examination

- Fever
- Cough
- Shortness of breath or difficulty breathing
- Presence of crackles, rales, wheezing or other auscultatory findings consistent with pneumonia
- Nasal congestion or rhinorrhea
- Respiratory rate
- Oxygen saturation
- Abdominal tenderness
- Rash

Disease Severity Categories

Clinical presentation of patients with COVID-19 can range from asymptomatic to critical illness. The clinical presentation of the patient will guide treatment modalities. Patients should be monitored closely for progression of disease severity until recovery is noted. ⁽⁴⁾

Severity	Definition
Asymptomatic	Positive SARS-CoV-2 RT-PCR with no associated symptoms
Mild	Patient with any of the signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have lower respiratory symptoms or abnormal chest imaging if obtained.
Moderate	Patients with symptoms of COVID 19 lower respiratory tract disease or abnormal chest imaging, who have saturation of oxygen (SpO ₂) ≥ 94%
Severe	Patients with saturation of oxygen (SpO ₂) <94% requiring supplemental oxygen or with an increase in respiratory support from baseline not meeting critical criteria
Critical	Respiratory or multiorgan failure requiring non-invasive positive pressure ventilation (BIPAP or CPAP) or mechanical ventilation and/or hemodynamic support

LRT symptoms: cough, tachypnea, retractions, shortness of breath, dyspnea

Laboratory Tests

Suggested laboratory tests for children with COVID-19 disease are listed below. Patients transferred from outside hospitals may need a SARS-CoV-2 RT-PCR test.

Severity	Suggested Laboratory Test
Mild	Consider CBC with differential and DIC Panel if age ≥ 12 years AND admitted for primary diagnosis of COVID 19
Moderate	Obtain CBC with differential Obtain DIC Panel if age ≥ 12 OR in the ICU Consider Chem 10, LFTs, CRP, Procalcitonin, Ferritin and COVID-19 serologic testing in patients with comorbidities or worsening clinical condition
Severe	Obtain CBC with differential, Chem 10, LFTs, CRP, Procalcitonin and Ferritin Obtain DIC Panel if age ≥ 12 OR in the ICU Consider LDH, COVID-19 serologic testing, BNP and Troponins
Critical	Obtain CBC with differential, Chem 10, LFTs, CRP, DIC Panel, Procalcitonin, Ferritin, COVID-19 serologic testing, BNP, and Troponins

Labs should be trended based upon findings and recommended monitoring related to specific therapies (e.g. remdesivir). Trend CRP in patients with critical disease.

Imaging

Depending upon severity of disease, patients with COVID-19 may exhibit radiologic findings on chest x-ray or chest computed tomography (CT). Patients with severe or critical disease should have a chest x-ray performed. Chest CT may be utilized in high risk and severe/critical patients with clinical indications for the procedure. ⁽¹⁰⁾ Electrocardiogram (ECG) should be obtained in patients that present with critical disease. ⁽¹¹⁾ Echocardiogram may be considered in critical disease due to risk of myocardial dysfunction.

Critical Points of Evidence*

TCH Evidence-Based Recommendations

Evidence Supports

Dexamethasone

- Low-dose dexamethasone should be administered to pediatric patients with positive SARS-CoV-2 RT-PCR requiring high flow nasal cannula, in hospitalized patients with progressive disease requiring increasing respiratory support, and in hospitalized patients who require positive pressure or mechanical ventilation. ⁽¹²⁻¹⁷⁾ - **Strong recommendation, low quality evidence**
Remarks: Dexamethasone should be dosed at 0.15 mg/kg/dose (MAX 6mg) once daily for 10 days (or until discharge) unless there is another indication for continuing treatment. Dexamethasone may be discontinued prior to 10 days for patients with rapid improvement and no longer requiring supplemental oxygen. Dexamethasone plus remdesivir should be considered in patients with progressive respiratory disease requiring increasing respiratory support and patients with severe disease.

Anticoagulation

- Anticoagulant prophylaxis should be administered for all hospitalized patients ≥ 18 years of age who have been diagnosed with primary COVID-19. ⁽¹⁸⁻³¹⁾ – **Strong recommendation, low quality evidence**
- Consider prophylactic anticoagulation for hospitalized patients < 18 years of age diagnosed with primary COVID-19 in the following scenarios after consultation with the Hematology team. – **Weak recommendation, low quality evidence**
 - Any patient admitted to the intensive care unit and requiring critical care monitoring
OR
 - Any patient ≥ 12 years of age **AND** with one or more risk factors for COVID-19 associated thromboembolism (active cancer, presence of central line, personal history of thrombosis, inherited thrombophilia, obesity [BMI $> 95^{\text{th}}$ percentile of age), D-Dimer ≥ 2 UG/ML, prolonged prothrombin time [PT], elevated fibrinogen, or thrombocytopenia [platelet count $> 30 \times 10^3/\text{ul}$ and $< 150 \times 10^3/\text{ul}$]*.**Remarks:** A multicenter retrospective review including patients from Texas Children's Hospital found an increased incidence of thrombosis in African Americans and patients of Hispanic ethnicity on univariate analysis.
NOTE: Hold anticoagulation for platelet count $< 30 \times 10^3/\text{ul}$.

Remdesivir

- Administer remdesivir in hospitalized pediatric patients with positive SARS-CoV-2 RT-PCR test result requiring supplemental oxygen or an increase in baseline respiratory support, and in hospitalized patients with progressive disease requiring increasing respiratory support. ⁽³²⁻⁴¹⁾ – **Weak recommendation, low quality evidence**
Remarks: Evidence suggests that treatment with remdesivir is most beneficial early in the course of illness. The benefit in critically ill patients is less clear. We recommend starting remdesivir as a 5-day course or until hospital discharge. For patients with progressive lung disease, who are critically ill, or have underlined deficiencies that increase the risk of severe disease, we recommend considering extending the course of remdesivir up to 10 days.

Evidence Inconclusive

Convalescent Plasma

- Consider the use of high titer convalescent plasma in hospitalized pediatric patients with positive SARS-CoV-2 RT-PCR test results requiring supplemental oxygen or an increase in baseline respiratory support who have impaired humoral immunity. (42-55) – **Weak recommendation, very low quality evidence**

Remarks: Evidence suggests that high titer convalescent plasma is most beneficial early in the course of the disease. Decision to treat with convalescent plasma should be based on individual patient risk / benefit assessment.

Recommendations Adapted from National Guidelines

Other Immunomodulators

- In patients requiring HFNC or noninvasive respiratory support that are recently hospitalized with a rapidly increasing need for oxygen and increased inflammatory markers, consider adding baricitinib or tocilizumab to the standard treatment of dexamethasone and remdesivir. (4) – **Weak recommendation, low quality evidence**
Remarks: Anakinra may be used in patients with a macrophage activation phenotype (e.g. elevated ferritin, liver injury, cytopenias) or when there is a concern of an immunocompromised host where a Janus kinase inhibitor may be contraindicated (risk of thrombosis, liver dysfunction, renal dysfunction, severe cytopenia). **There is currently a severe shortage of tocilizumab. Baricitinib will be substituted if tocilizumab is not available.** Local adult guidelines utilize CRP >7.5 mg/dL; May utilize lower CRP if other inflammatory markers such as ferritin, fibrinogen, LDH are also high. Decision on starting immunomodulation may require a multidisciplinary discussion between primary service and rheumatology. This recommendation was adapted from the National Institutes of Health Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.
- In patients requiring IMV and/or ECMO that are recently hospitalized with increased markers of inflammation, add tocilizumab to the standard treatment of dexamethasone. In this group of patients, baricitinib will be substituted if tocilizumab is not available. (4) – **Strong recommendation, moderate quality evidence**
Remarks: Anakinra may be used in patients with a macrophage activation phenotype (e.g. elevated ferritin, liver injury, cytopenias), when there is a concern of an immunocompromised host where a Janus kinase inhibitor may be contraindicated. **There is currently a severe shortage of tocilizumab. Baricitinib will be substituted if tocilizumab is not available.** Local adult guidelines utilize CRP >7.5 mg/dL; May utilize lower CRP if other inflammatory markers such as ferritin, fibrinogen, LDH are also high. Decision on starting immunomodulation may require a multidisciplinary discussion between primary service and rheumatology. This recommendation was adapted from the National Institutes of Health Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

Condition-Specific Elements of Clinical Management

General: Most patients with mild disease require only supportive care for non-respiratory symptoms. Patients with increased severity of disease may progress to the need for hemodynamic and respiratory support. (16) In addition to supportive care, patients with moderate, severe and critical disease may be considered for the treatments below based upon clinical presentation and risk factors for progression of disease. Along with a varying degree of respiratory disease, patients with COVID-19 may exhibit cardiac, hepatic, renal and/or central nervous system concerns.

Management of critical illness in COVID-19 should parallel that of other infectious disease processes with the addition of infection control measures to prevent the spread of disease. (4) The use of supplemental oxygen is warranted for patients exhibiting hypoxemia without respiratory distress. Advanced ventilatory support should be utilized in patients with respiratory distress including high flow nasal cannula and/or non-invasive positive pressure ventilation. (56) For patients meeting the requirement for invasive ventilatory support, early intubation by an experienced practitioner is recommended. (16)

Treatment Recommendations: Treatment for COVID-19 is based upon the patient's disease severity and presence of risk factors for progression to severe disease. (56)

Dexamethasone should be administered to pediatric patients with positive SARS-CoV-2 RT-PCR requiring high-flow nasal cannula, in hospitalized patients with progressive disease requiring increasing respiratory support, and in hospitalized patients who require positive pressure or mechanical ventilation. A low-dose regimen of dexamethasone has been shown to be effective in reducing mortality in adult patients with

severe or critical disease. The combination therapy of remdesivir and dexamethasone may be considered in patients with progressive respiratory disease requiring increasing respiratory support and patients with severe disease. (4)

Remdesivir is an antiviral approved for the treatment of COVID-19 positive individuals 28 days of age and older AND weighing at least 3 kg who are hospitalized, or not hospitalized with mild to moderate COVID-19 and are at risk for progression to severe COVID-19, including hospitalization or death. The guideline panel recommends the use of remdesivir in hospitalized pediatric patients with a positive SARS-CoV-2 RT-PCR test result requiring supplemental oxygen or an increase in baseline respiratory support, and in hospitalized patients with progressive disease requiring increasing respiratory support. Treatment with remdesivir early in the course of the disease has been found to be most beneficial. Remdesivir should be started as a 5-day course or until discharge. For patients with progressive lung disease, who are critically ill, or have underlined deficiencies that increase the risk of severe disease, the course of remdesivir may be extended up to 10 days.

Due to adverse effects and drug interactions, liver function tests (LFTs), partial thromboplastin time (PTT), renal function tests and signs or symptoms of infusion reaction should be monitored. Consider discontinuation of remdesivir with elevation of LFTs or signs/symptoms of liver inflammation. Please read the [Remdesivir Package Insert](#) and the [TCH Formulary](#) for additional information on remdesivir.

Anticoagulants are suggested for the care of hospitalized patients with COVID-19 due to the increased incidence of thrombotic complications in patients with severe and critical disease. Recent evidence in adult patients found that COVID-19 is associated with increases in coagulation laboratory measures including D-Dimer and fibrinogen. ⁽⁴⁾ The content expert team recommends that anticoagulant prophylaxis be administered for all hospitalized patients ≥18 years of age. For hospitalized patients <18 years of age diagnosed with primary COVID-19, anticoagulation may be considered if admitted to the intensive care unit and requiring critical care monitoring after consultation with the Hematology team. Research in pediatric patients have noted that certain clinical characteristics are associated with an increased incidence of thrombotic complications. As a result, anticoagulation may also be considered in hospitalized patients with age ≥12 years diagnosed with primary COVID-19 **AND** with risk factors for COVID-19 associated thromboembolism. Please review the [COVID-19 and Thromboembolism Prophylaxis: Recommendations in Children, Adolescents and Young Adults TXCH Supportive Care Practice Standard](#) for details on anticoagulation therapy in this population.

Tocilizumab is a monoclonal antibody that can be utilized to reduce inflammation by inhibiting the interleukin (IL)-6. ⁽⁵⁷⁾ **Baricitinib** is a Janus kinase inhibitor that can be utilized to reduce inflammation in patients with COVID-19. ⁽⁴⁾ Baricitinib dampens the inflammatory signal by blocking multiple immune pathways. In patients requiring HFNC or noninvasive respiratory support that are recently hospitalized with a rapidly increasing need for oxygen and increased inflammatory markers, consider adding baricitinib or tocilizumab to the standard treatment of dexamethasone and remdesivir. In patients requiring IMV and/or ECMO that are recently hospitalized with increased markers of inflammation, add tocilizumab to the standard treatment of dexamethasone. In this group of patients, baricitinib may be substituted if tocilizumab is not available. ⁽⁴⁾ Alternatively, in children with COVID pneumonia anakinra may block activation of the IL-1 pathway. It may be used in patients with a macrophage activation phenotype (e.g. elevated ferritin, liver injury, cytopenias) or when there is a concern of an immunocompromised host where a Janus kinase inhibitor may be contraindicated.

Convalescent plasma is a human blood-derived product thought to have pathogen neutralization properties. ^(1,4) An emergency use authorization (EUA) for COVID-19 convalescent plasma was issued based upon historical evidence of convalescent plasma in prior respiratory virus outbreaks and available evidence. The use of high titer convalescent plasma may be considered in hospitalized pediatric patients with positive SARS-CoV-2 RT-PCR test results requiring supplemental oxygen or an increase in baseline respiratory support who have impaired humoral immunity. Decision to treat with convalescent plasma should be based on individual patient risk / benefit assessment. Please review the [Convalescent Plasma EUA](#) and [Fact Sheet](#). The [COVID-19 Convalescent Plasma \(CCP\) Criteria for Use at Texas Children's Hospital and Pavilion for Women](#) provides details on the use and acquisition of convalescent plasma at TCH.

Other Therapy may be considered in patients with severe and critical disease with worsening clinical condition in consultation with specialty services.

Special Populations

Pregnancy

According to the National Institute of Health, vertical transmission of SARS-CoV-2 is rare. ⁽⁴⁾ When caring for pregnant women, clinicians should be aware that physiologic changes during pregnancy can alter oxygen requirement and laboratory values. The additional need for oxygen may have an impact on disease severity categories. ⁽⁴⁾ Please review the [PFW COVID-19 Resources](#) site for more information and pathways for the management of COVID-19 in pregnant women at Texas Children's Hospital.

Admission Criteria

Hospital admission should be based upon respiratory support and risk factors for progression to critical disease.

- If there is a concern for MIS-C, troponin and BNP lab should be obtained. Patient management should be based on [MIS-C Guideline](#).
- For patients with severe disease, consider initial placement in ICU if there are risk factors for progression to critical severity.

Discharge Criteria

Discharge criteria for patients with COVID-19 is consistent with that of other viral syndromes. A negative SARS-CoV-2 PCR is not necessary for discharge.

- No oxygen requirement
- Tolerating PO
- Appropriate mental status for age
- Signs of clinical improvement
- Appropriate support system (e.g., PCP, caregivers)

Consider Consults to Specialty Services

- Infectious Disease
- Hematology
- Rheumatology
- Cardiology

Measures

Process

- Length of Stay (Inpatient, ICU)

Outcome

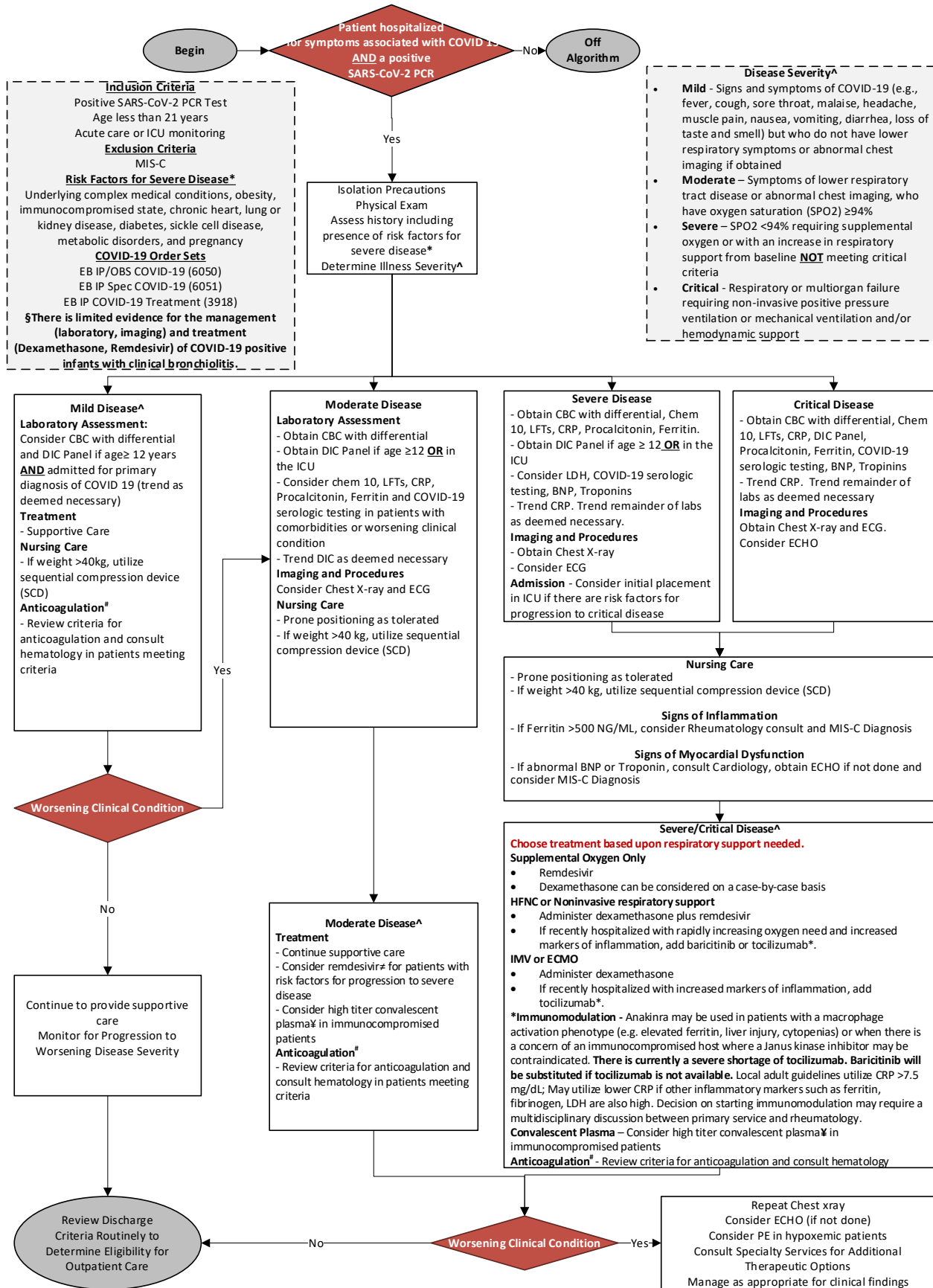
- Mortality Rate
- Ventilation Days
- Rate of Acute Respiratory Distress Syndrome
- Days on ECMO support
- Rate of Thrombotic Events
- Rate of Cardiac Complications

Dosing for Treatment and Adjunctive Therapy ^(29,58)

Medication	Dose	Additional Details
Dexamethasone	<p>Children and Adolescents <40 kg:</p> <ul style="list-style-type: none"> 0.15 mg/kg/dose (MAX 6mg) once daily for 10 days (or until discharge) <p>Children and Adolescents ≥40 kg:</p> <ul style="list-style-type: none"> 6mg once daily for 10 days (or until discharge) 	<ul style="list-style-type: none"> Equivalent steroid may be indicated for pregnant women based upon gestational age Contact pharmacy for equivalent steroid
Remdesivir	<p>Infants and Children ≥ 28 days old and <12 years:</p> <ul style="list-style-type: none"> <u>3 kg to <40 kg:</u> IV: Loading dose: 5 mg/kg/dose on day 1, followed by 2.5 mg/kg/dose once daily <u>≥40 kg:</u> IV: Loading dose: 200 mg on day 1, followed by 100 mg once daily <p>Children ≥12 years and Adolescents:</p> <ul style="list-style-type: none"> <u><40 kg:</u> IV: Loading dose: 5 mg/kg/dose on day 1, followed by 2.5 mg/kg/dose once daily <u>≥40 kg:</u> IV: Loading dose: 200 mg on day 1, followed by 100 mg once daily 	<ul style="list-style-type: none"> Monitor at baseline and trend liver function tests (LFTs), partial thromboplastin time (PTT), renal function tests and signs/symptoms of infusion reaction. Consider discontinuation with elevation of LFTs or signs/symptoms of liver inflammation. Review Remdesivir Package Insert
Tocilizumab	<p><30kg: IV: 12 mg/kg once</p> <p>≥30 kg: IV: 8 mg/kg (MAX 800mg) once</p> <p>The recommended total treatment duration of tocilizumab is one dose. If patients do not clinically improve after the first dose, one additional dose may be administered at least 8 hours later.</p>	<p>Please read the FDA Fact Sheet for Providers.</p> <ul style="list-style-type: none"> Used in patients ≥2 years in combination with corticosteroids Monitor at baseline and trend LFTs and CBC. Tocilizumab is not recommended in patients with AST or ALT >10 upper limit of normal, ANC <1000 or platelets <50. Consideration may differ for patients with underlying illness or immunocompromised state <p>Availability for use in COVID-19 patients subject to tocilizumab supply and hospital shortage restriction criteria. Baricitinib may be substituted if tocilizumab is not available.</p>
Baricitinib	<p>Age ≥9 years: 4 mg once daily* Age 2 years to <9 years: 2 mg once daily*</p> <p>*Renal adjustments are recommended, please consult FDA Fact Sheet for dosing recommendations</p> <p>The recommended total treatment duration of baricitinib is 14 days or until hospital discharge, whichever is first.</p>	<p>Please read the FDA Fact Sheet for Providers for Baricitinib.</p> <ul style="list-style-type: none"> Used in combination with corticosteroids Monitor at baseline and trend LFTs, CBC with differential, and renal function test. Consider discontinuation or dose modification for laboratory abnormalities. Contraindications per the EUA document Additional considerations for the use of other agents (e.g. anakinra) <ul style="list-style-type: none"> Ferritin >1000 with other organ dysfunction Other signs of macrophage activation syndrome Consideration may differ for patients with underlying illness or immunocompromised state <p>Tofacitinib may be used as an alternative if there is a shortage of baricitinib.</p>
Anakinra	<p><u>Starting dose:</u> 5 – 10 mg/kg/day IV or SQ in one to four divided doses, titrate to clinical response <u>Maximum dose:</u> 10 mg/kg/day OR 400 mg/day (dosed 100 mg Q6H or 200 mg Q12H) *Dose in 100 mg increments to avoid waste. **Contact Rheumatology for patient-specific guidance on initial dosing and dose escalation</p> <p>The FDA approved route of administration for anakinra is subcutaneous (SQ) injection. The off-label intravenous route may be used in patients unable to receive SQ injections or in the setting of acute illness when absorption from subcutaneous tissue is erratic.</p>	<ul style="list-style-type: none"> Use in combination with corticosteroids Monitor at baseline and trend LFTs and CBC. Consider holding in patients with AST or ALT >10 times upper limit of normal, ANC <1000, or platelets <50.
Anticoagulation	<p>Review the COVID-19 and Thromboembolism Prophylaxis: Recommendations in Children, Adolescents and Young Adults TXCH Supportive Care Practice Standard for details on dosing</p>	

**TCH Evidence-Based Outcomes Center
Care of the Hospitalized Patient with COVID-19**

Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgement in the management of any specific patient.



References

1. Bhimraj, A., Morgan, R., Shumaker, A., Lavergne, V., Baden, L., Cheng, V., Edwards, K., et al. (2021, February 22). IDSA guidelines on the treatment and management of patients with COVID-19. *Infectious Disease Society of America*. <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>
2. Zimmerman, P., & Curtis, N. (2020). Coronavirus infection in children including COVID-19: An overview of epidemiology, clinical features, diagnosis, treatment and prevention options in children. *Pediatric Infectious Disease Journal*, 39(5), 355-368. <https://doi.org/10.1097/INF.0000000000002660>
3. Centers for Disease Control and Prevention. (2020, October 28). How COVID-19 Spreads. <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html>
4. National Institutes of Health. (2021). Coronavirus disease 2019 (COVID-19) treatment guidelines. <https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf>
5. Yuki, K., Fujiogi, M., & Koutsogiannaki, S. (2020). COVID-19 pathophysiology: A review. *Clinical Immunology*, 215, 108427. <https://doi.org/10.1016/j.clim.2020.108427>
6. Johns Hopkins University. (2021, March 12). COVID-19 dashboard by the Center for Systems Science and Engineering at Johns Hopkins University. <https://coronavirus.jhu.edu/map.html>
7. Centers for Disease Control and Prevention. (2021, March 12). COVID Data Tracker. <https://covid.cdc.gov/covid-data-tracker/#datatracker-home>
8. Leidman, E., Duca, L., Omura, J., Proia, K., Stephens, J., & Schatz-Sauber, E. (2021). *Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report*, 70(3), 88-94. <https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7003e1-H.pdf>
9. Centers for Disease Control and Prevention. (2021, January 24) COVID Data Tracker. <https://covid.cdc.gov/covid-data-tracker/#demographics>
10. Centers for Disease Control and Prevention. (2020, December 30). Information for pediatric healthcare providers. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html>
11. Cardenas, M., Bustos, S., Enniga, E., Mofenson, L., & Chakraborty, R. (2021). Characterising and managing paediatric SARS-CoV-2 infection: Learning about the virus in a global classroom. *Acta Paediatr*, 110(2), 409-422.
12. Horby, P., Lim, W., Emberson, J., Mafham, M., Bell, J., Linsell, L., et al. (2020). Dexamethasone in hospitalized patients with COVID-19: Preliminary reports (Recovery Trial). *New England Journal of Medicine*, 384(8), 693-704.
13. Sterne, J., Murthy, S., Diaz, J., Slutsky, A., Villar, J., Angus, D. et al. (2020). Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID 19: A meta-analysis. *JAMA*, 324(16), 1330-1341.
14. Tomazini, B., Maia, I., Calvacanti, A., Berwanger, O., Rosa, R., Veiga, V., et al. (2020). Effect of dexamethasone on days alive and ventilator-free in patients with moderate and severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. *JAMA*, 324(13),
15. van Paasen, J., Vos, J., Hoekstra, E., Neumann, K., Boot, P., & Arbous, S. (2020). Corticosteroid use in COVID-19 patients: A systematic review and meta-analysis on clinical outcomes. *Critical Care*, 24(1), 696.
16. Waleed, A., Evans, L., Fayez, A., Moller, M., Marlies, O., Prescott, H., et al. Surviving sepsis campaign guidelines on the management of adult with coronavirus disease 2019 (COVID-19) in the ICU: First update. *Critical Care Medicine*, 49(3), e219-e234.
17. Miao, H., Li, H., Yao, Y., Wu, M., Lu, C., Wang, J., Tian, M., et al. (2020). Updated on recommendations for the diagnosis and treatment of SARS-CoV-2 infection in children. *European Journal of Clinical Microbiology & Infectious Disease*, 39(12), 2211-2223.
18. Chi, G., Lee, J., Jamil, A., Gunnam, V., Najafi, H., et al. (2020). Venous thromboembolism among hospitalized patients with COVID-19 undergoing thromboprophylaxis: A systematic review and meta-analysis. *Journal of Clinical Medicine*, 9, 2489.
19. Del Borrello, G., Giraud, I., Bondone, C., Denina, M., Garazzino, S., et al. (2021). SARS-CoV-2-associated coagulopathy and thromboembolism prophylaxis in children: A single-center observational study. *Journal of Thrombosis and Haemostasis*, 19(2), 522-530.
20. Flumigan, R., Tinoco, J., Pascoal, P., Areias, L., Cossi, M., et al. (2020). Prophylactic anticoagulants for people hospitalized with COVID 19. *Cochrane Database for Systematic Reviews*, Issue 10. Art. No.: CD013739.
21. Hasan, S., Radford, S., Kow, C., & Zaidi, S. (2020). Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic and therapeutic anticoagulation: A systematic review and meta-analysis. *Journal of Thrombosis and Thrombolysis*, 50, 814-821.
22. Kamel, A., Sobhy, M., Magdy, N., Sabry, N., & Farid, S. (2020). Anticoagulation outcomes in hospitalized COVID-19 patients: A systematic review and meta-analysis of case control and cohort studies. *Rev Med Virol*, e2180.
23. Lemos, A., do Espirito Santo, D., Salvetti, M., Gilio, R., Agra, L., et al. (2020). Therapeutic versus prophylactic anticoagulation for severe COVID 19: A randomized phase II clinical trial. *Thrombosis Research*, 196, 359-366.
24. Loomba, R., Aggarwal, G., Villarreal, E., Farias, J., Flores, S., et al. (2020). Factors associated with deep venous thrombosis in patients infected with coronavirus disease 2019: A meta-analysis. *Blood Coagulation and Fibrinolysis*, 30, 32(1), 23-28.
25. Lu, Y., Pan, L., Zhang, W., Cheng, F., Hu, S., Zhang, X., et al. (2020). A meta-analysis on the incidence of venous thromboembolic events and impact on anticoagulation on mortality in patients with COVID 19. *International Journal of Infectious Disease*, 100, 34-41.
26. McBane, R., Roldan, V., Niven, A., Pruthi, R., Franco, P., Linderbaum, J., et al. (2020). Anticoagulation in COVID 19: A systematic review, meta-analysis and rapid guidance from the Mayo Clinic. *Mayo Clinic Proc*, 95(11), 2467-2486.
27. Rentsch, C., Beckman, J., Tomlinson, L., Gellad, W., Alcorn, C., et al. (2020). Early initiation of prophylactic anticoagulation for prevention of COVID-19 mortality: a nationwide cohort study of hospitalized patients in the United States. MedRxiv, doi: 10.1101/2020.12.09.20246579.
28. Salah, H., Naser, J., Calcaterra, G., Bassareo, P., & Mehta, J. (2020). The effect of anticoagulation use on mortality in COVID-19 infection. *The American Journal of Cardiology*, 134, 155-157.
29. TCH Thromboembolism and COVID 19 Clinical Pathway
30. American Society of Hematology. (2021, February 25). COVID-19 and VTE/anticoagulation: Frequently asked questions. <https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation>
31. Thachil, J., Tang, N., Gando, S., Falanga, A., Cattaneo, M., Levi, M., Clark, C., & Iba, T. (2020). ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *Journal Thrombosis and Haemostasis*, 18(5), 1023-1026.
32. Biegel, J., Tomashek, K., Dodd, L., Mehta, A., Zingman, B. et al. (2020). Remdesivir for the treatment of COVID-19 – Final report. *The New England Journal of Medicine*, 383(19), 1813-1826. <https://doi.org/10.1056/NEJMoa2007764>
33. Elsayah, H., Elsayah, M., Abdallah, M., & Elshafie, A. (2020). Efficacy and safety of remdesivir in hospitalized COVID-19 patients: Systematic review and meta-analysis including network meta-analysis. *Reviews in Medical Virology*, e2187. <https://doi.org/10.1002/rmv.2187>
34. Goldman, J., Lye, D., Hui, D., Marks, D., Bruno, R., et al. (2020). Remdesivir for 5 or 10 days in patients with severe COVID-19. *The New England Journal of Medicine*, 383(19), 1827-1837.
35. Mendez-Echvarria, A., Perez-Martinez, A., Del Valle, L., Ara M., Melendo, S., et al. (2020) Compassionate use of remdesivir for children with COVID-19. *European Journal of Pediatrics*, 1-16.
36. Misra, S., Tech, M., Nath, M., Hadda, V., & Vibha, D. (2020). Efficacy of various treatment modalities for nCoV-2019: A systematic review and meta-analysis. *European Journal of Clinical Investigation*, 50(11), e13383.
37. Pan, H., Peto, R., Henao-Restrepo, A., Preziosi, M., Sathiyamoorthy, V. et al. (2020). Repurposed antiviral drugs for COVID-19: Interim WHO solidarity trial results. *The New England Journal of Medicine*, 384(6), 497-511.

38. Spinner, C., Gottlieb, R., Criner, G., Lopez, J., Cattelan, A., Viladomeiu, A., et al. (2020). Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: A randomized controlled trial. *Jama: The Journal of the American Medical Association*, 324(11), 1048-1057.
39. Wang, Y., Zhang, Z., Du, G., Zhao, J., Jin, Y., et al. (2020). Remdesivir in adults with severe COVID-19: A randomized, double-blind, placebo-controlled, multicenter trial. *Lancet*, 395, 1569-1578.
40. Yokoyama, Y., Briasoulis, A., Takigi, H., & Kuno, T. (2020). Effect of remdesivir on patients with COVID-19: A network meta-analysis of randomized controlled trials. *Virus Research*, 288, 198137.
41. Qaseem, A., Yost, J., Etzeandia-Ikobaltzeta, I., Abraham, G., Jokela, J., Forcica, M., et al. (2021). Should remdesivir be used for the treatment of patients with COVID-19? Rapid living practice points from the American College of Physicians (Version 1). *Annals of Internal Medicine*, 174(2), 229-236.
42. Argawal, A., Mukherjee, A., Kumar, G., Chatterjee, P., Bhatnagar, T. et al. (2020). Convalescent plasma in the management of moderate covid-19 in adults in India: Open label phase II multicentre randomised controlled trial (PLACID trial). *BMJ*, 371, m3939.
43. Avendano-Sola, C., Ramos-Martinez, A., Munez-Rubio, E., Ruiz-Antoran, B., Malo de Molina, R., et al. (2020). Convalescent plasma for COVID-19: A multicenter, randomized clinical trial. *MedRxiv*. <https://doi.org/10.1101/2020.08.26.20182444>
44. Gharbharan, A., Jordans, C., GeurtsvanKessel, C., den Hollander, J., Karim, F., et al. (2020). Convalescent plasma for COVID-19: A randomized clinical trial. *MedRxiv*. <https://doi.org/10.1101/2020.07.01.20139857>
45. Juul, S., Nielsen, E., Feinberg, J., Siddiqui, F., Jorgensen, C., Barot, K., et al. (2020). Interventions for treatment of COVID-19: A living systematic review with meta-analysis and trial sequential analysis (The living project). *PLoS Med*, 17(9), e1003293.
46. Klassen, S., Senefeld, J., Johnson, P., Carter, R., Wiggins, C., et al. (2020). Evidence favoring the efficacy of convalescent plasma for COVID 19 therapy. *MedRxiv*. doi: 10.1101/2020.07.29.20162917
47. Li, L., Zhang, W., Hu, W., Tong, X., Zheng, S., et al. (2020). Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life threatening COVID-19: A randomized controlled trial. *JAMA*, 324(5), 460-470.
48. Libster, R., Perez Marc, G., Wapner, D., Coviello, S., Bianchi, A., et al. (2021). Early high-titer plasma therapy to prevent severe covid-19 in older adults. *New England Journal of Medicine*, Advance online publication. DOI: 10.1056/NEJMoa2033700
49. Meher, B., Padhy, B., Das, S., Mohanty, R., & Agrawal, K. (2020). Effectiveness of convalescent plasma therapy in the treatment of moderate to severe COVID 19 patients: A systematic review and meta-analysis. *Journal of the Association of Physicians of India*, 68(12), 35-43.
50. Piechotta, V., Chai, K., Valk, S., Doree, C., Monsef, I., et al. (2020). Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: A living systematic review. *Cochrane Database of Systematic Reviews*, Issue 7, Art. No.: CD013600.
51. Rasheed, A., Fatak, D., Hashim, H., Maulood, M., Kabah, K., et al. (2020). The therapeutic potential of convalescent plasma therapy on treating critically- ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. *Le Infezioni in Medicina*, 3, 357-366.
52. Sakar, S., Soni, K., & Khanna, P. (2020). Convalescent plasma is a clutch at straws in COVID-19 management! A systematic review and meta-analysis. *Journal of Medical Virology*, 93(2), 1111-1118.
53. Simonovich, V., Burgos Pratz, L., Scibona, P., Beruto, M., Vallone, M. et al. (2020). A randomized trial of convalescent plasma in COVID-19 severe pneumonia. *The New England Journal of Medicine*, 384(7), 619-629.
54. Talaie, H., Hossenini, S., Nazari, M., Fakhri, Y., Mousavizadeh, A., et al. (2020). Is there any potential management against COVID-19? A systematic review and meta-analysis. *Daru Journal of Pharmaceutical Sciences*, 28, 765-777.
55. Wang, M., Wu, T., Zuo, Z., You, Y., Yang, X., et al. (2020). Evaluation of current medical approaches for COVID-19: A systematic review and meta-analysis. *BMJ Supportive and Palliative Care*, 11(1), 45-52.
56. Parisi, G. F., Indolfi, C., Decimo, F., Leonardi, S., & del Giudice, M. M. (2020). COVID-19 pneumonia in children: From etiology to management. *Frontiers in Pediatrics*, 8, 616622. <https://doi.org/10.3389/fped.2020.616622>
57. U. S. Food and Drug Administration. (2021). FDA News Release - Coronavirus (COVID-19) Update: FDA Authorizes drug for treatment of COVID-19. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19>
58. Lexicomp®. (2021). Pediatric and neonatal lexi-drugs. <http://online.lexi.com/lco/action/home>

Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
 - PICO questions established
 - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
 - American College of Physicians, Should Remdesivir Be Used for the Treatment of Patients with COVID-19, 2021; National Institutes of Health, COVID-19 Treatment Guidelines, 2021; Children's Hospital of Philadelphia, Clinical Pathway for Evaluation and Treatment of Patients with Active COVID-19 Infection, 2021; Infectious Disease Society of America, Guidelines on the Treatment and Management of Patients with COVID-19, 2021; Connecticut Children's Medical Center, Clinical Pathway: Therapies for COVID-19, 2021; Seattle Children's Hospital, Acute COVID-19 Guideline, 2021; Surviving Sepsis Campaign, Guidelines on the Management of Critically Ill Adults with Coronavirus, 2020; Boston Children's Hospital, COVID 19 Treatment: Internal Guidance, 2020; Columbia University, A Clinical Pathway for Hospitalized Pediatric Patients With Initial SARS-CoV-2 Infection, 2020; The Children's Hospital of the King's Daughter, CHKD Treatment for COVID 19 in Children, 2020; Pediatric Infectious Disease Society, Multidisciplinary Guidance Regarding the Use of Immunomodulatory Therapies for Acute Coronavirus Disease 2019 in Pediatric Patients, 2020; American Society of Hematology, COVID-19 and VTE/Anticoagulation: Frequently Asked Questions, 2020; International Society of Thrombosis and Haemostasis, ISTH Interim Guidance on Recognition and Management of Coagulopathy in COVID-19, 2020; Centers for Disease Control and Prevention, Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), 2020; Children's Hospital of Colorado, COVID-19 Anticoagulation Recommendations in Children, 2020; Canadian Pediatric Society, The Acute Management of Pediatric

Coronavirus Disease 2019 (COVID 19), 2021; Colorado Children's Hospital, Recommendations for immune modulation for critically ill patients with confirmed SARS-CoV-2 infection and cytokine storm syndrome (CSS), 2021

3. Literature Review of Relevant Evidence
 - Searched: PubMed, Cochrane
4. Critically Analyze the Evidence
 - 37 meta-analyses, 17 randomized controlled trials, and 5 nonrandomized studies, as applicable
5. Summarize the Evidence
 - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Care of the Hospitalized Patient with COVID-19 evidence-based review electronic file within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline. This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions. **"Evidence Supports"** provides evidence to support an intervention **"Evidence Against"** provides evidence against an intervention. **"Evidence Lacking/Inconclusive"** indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence*. The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of COVID-19 in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children’s Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner should use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.

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Version History

Date	Comments
May 2021	Originally Completed
Sept 2021	Revised
Nov 2021	Revised
Dec 2021	Revised – Added high titer to the algorithm wording for convalescent plasma
May 2022	Revised – Changed dosing eligibility for Remdesivir. Removed links for the Remdesivir EUA and fact sheet.
Sept 2022	Dexamethasone and Remdesivir recommendations revised; Post-Exposure Prophylaxis content removed