MCHS COVID-19 INPATIENT TREATMENT GUIDELINE: Therapeutic Options and Anticoagulation: Information as of 3-1-23

THERAPEUTIC OPTIONS:
The following are based on in-vitro or in-vivo studies suggesting potential benefit and are subject to availability.
All Severity Categories are for Patients with **CONFIRMED** SARS-CoV-2

Severity of Illness

	Non-Severe Disease: Hospitalized, NOT requiring Supplemental Oxygen	Non-Critical Disease: SpO2 ≤94% on Room Air or Requires Supplemental Oxygen	Severe Disease, Critical: Requires Invasive Mechanical Ventilation or ECMO, Septic Shock	Warnings, Restrictions, & Links
Remdesivir: 200 mg IV loading dose on day 1, followed by 100 mg IV once daily	***Consider*** for patients at high risk of disease progression, x 3 days total within 7 days of symptom onset	**Suggest Use** x 5 days total or until hospital discharge, whichever is first	**Use not shown to be beneficial in these patients; suggest against routine initiation**	**Exclusion Criteria:** 1. ALT levels > 10x ULN 2. eGFR< 30 mL/min at initiation, though this may be considered on a risk vs benefit assessment **Use not recommended > 10 days after symptom onset**
Corticosteroids, **Dexamethasone** 6 mg IV or PO daily x 10 days, higher doses permitted if indicated for other diagnoses	-	**Recommended in those requiring supplemental O2**	**Recommended**	If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used
Tocilizumab 8 mg/kg (max 800 mg) or 400 mg IV x 1 OR **Baricitinib** 4mg PO daily up to 14 days while hospitalized OR **Sarilumab** 400mg IV x 1 (use only if tocilizumab not available) • Avoid combination of **Tocilizumab** or **Sarilumab** with **Baricitinb**	-	**Abnormal chest imaging consistent with COVID-19 AND One of the following:** 1. Rapidly worsening gas exchange 2. Mechanical ventilation or shock, no more than 24 hrs after ICU admission **PLUS one of the following:** 1. CRP >7 mg/dL 2. Ferritin > 300 ng/mL with doubling within 24 hrs 3. Ferritin > 600 ng/mL at presentation		**Tocilizumab, Sarilumab, & Baricitinib[§]:** • Risk of serious infections, avoid with concurrent infection, including localized infection **Tocilizumab:** Do not initiate if ANC is <1,000/mm3, PLT <50,000/mm3, or if ALT or AST are >10 times ULN Sarilumab: Do not initiate if ANC is <2,000/mm3, PLT <150,000/mm3, or if ALT or AST are >1.5 times ULN **Baricitinib:** Dose adjust for renal impairment, ALC and ANC • Serious thrombosis has occurred, monitor closely

***Recommended* Confirmed Sars-CoV-2 Positive Hospitalized Patient Tests**

Baseline laboratory: CMP, CBC with differential, D-dimer, PT, aPTT, fibrinogen, CRP, ferritin, PCT

Daily laboratory: CMP, D-dimer, CBC with differential, CRP, ferritin
Consider repeat PCT in 48 hrs and discontinue abx as appropriate

Options for the treatment of patients hospitalized for conditions other than COVID-19 with Mild-to-Moderate COVID-19 who are high risk for progression to severe disease†, All EUA requirements must be followed[§]

Paxlovid: 300 mg nirmatrelvir with 100 mg ritonavir PO x 5 days	eGFR ≥30 to <60 mL/min: 150 mg nirmatrelvir + 100 mg ritonavir x 5 days eGFR <30 mL/min or Severe Hepatic Impairment (Child-Pugh Class C): Use not recommended	initiate therapy within 5 days of symptom onset	**Significant drug interactions exist, see EUA Checklist: PAXLOVID Screening Checklist Tool** **EUA Paxlovid:** Paxlovid HCP FS Paxlovid P/C FS (English) | Paxlovid P/C FS (Spanish)
anti-SARS-CoV-2 Monoclonal Abs	**Bebtelovimab and similar SARS-CoV-2 mAbs are no longer authorized for use for the treatment of COVID-19 because the dominant Omicron subvariants in the United States are not expected to be susceptible to these products.**		

§ See the Appendix for Restrictions and additional treatment considerations **NIH COVID-19 Treatment Guidelines:** NIH Guidance Link

†Conditions Assoc with Higher Risk for Severe COVID-19 | CDC

IDSA COVID-19 Treatment Guidelines: IDSA Guidance Link

Procalcitonin (PCT) has been shown to be associated with severity of illness in COVID-19. PCT upregulation occurs in response to inflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumor necrosis factor-α as well as bacteria.

See Trinity's COVID-19 Pharmacotherapy Treatment Guidance for anticoagulation information. The section can be quickly accessed via the table of contents page.

covid-19-treatment-guidance.pdf (trinity-health.org)

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APPENDIX A: Restrictions, Additional Treatment Considerations and Requirements

GENERAL CONSIDERATIONS:

- High risk of drug interactions exists with any of the suggested therapies for management Please see link below for table of drug interactions, especially those receiving immunosuppressive therapy http://www.covid19-druginteractions.org/

REMDESIVIR: Full Prescribing Info: Remd PI link

Laboratory: Testing prior to and during treatment: Perform eGFR, and hepatic laboratory testing prior to initiating remdesivir (VEKLURY) and during use as clinically appropriate. Evaluate for signs/symptoms of infusion reaction.

Recommended Daily Labs: CMP

Remdesivir Warnings and Adverse Effects:

- Hypersensitivity and Infusion-Related Reactions, discontinue remdesivir immediately if a severe infusion-related hypersensitivity reaction occurs.
- Hypotension / Hypertension / Tachycardia / Bradycardia
- Nausea
- Diaphoresis / Shivering / Fever
- Hypoxia / Dyspnea / Wheezing
- Angioedema / Rash
- Increased Risk of Transaminase Elevations
- **Remdesivir should be discontinued** in patients who develop:
    - ALT> 10 times the upper limit of normal during treatment with remdesivir., **OR**
    - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine

Pregnancy and lactation considerations:

- **Pregnancy:** There is limited data on the use of remdesivir during pregnancy. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.
- **Lactation:** It is not known whether remdesivir can pass into breast milk. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19

TOCILIZUMAB (ACTEMRA): Restricted

Use is restricted to the following:

- **Infectious Disease physicians**
- **Critical Care providers when the patient meets the criteria outlined in MCHS COVID-19 Inpatient Treatment Guideline**

Mechanism: humanized monoclonal antibody; interleukin 6 (IL-6) receptor antagonist; FDA approved for Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Administration: infuse over 60 min in dedicated IV line

Warnings and Adverse Effects:

- Serious and potentially fatal infections including reactivation of latent TB (if benefit outweighs risk in treatment of COVID-19, prescriber may defer TB testing). Do not administer tocilizumab to a patient with an active infection, including localiazed infections. Monitor for signs and symptoms of infection during and after treatment.
    - Infection has been reported at a higher incidence in elderly patients compared with younger adults
- Neutropenia and thrombocytopenia (platelet count < 50,000 per mm^3 and ANC <1,000 per mm^3)
- Hypersensitivity reactions including anaphylaxis
- Hepatic injury, avoid with ALT or AST >10 times the upper limit of normal, use not recommended in patients with active hepatic disease.
- Gastrointestinal perforation, use with caution in those at increased risk
- Demyelinating CNS disease: Use with caution in patients with preexisting or recent onset CNS demyelinating disorders; rare cases of CNS demyelinating disorders (multiple sclerosis and chronic inflammatory demyelinating polyneuropathy) have occurred
- Hyperlipidemia -Therapy has been associated with increases in total cholesterol, triglycerides, low-density lipoprotein, and/or high-density lipoprotein.

Pregnancy considerations: There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses in utero in the exposed fetus. Decisions about tocilizumab administration during pregnancy must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks. Pregnancy registry available, providers are encouraged to call.

SARILUMAB (KEVZARA): Restricted

Use is restricted to the following:

- **Infectious Disease physicians**
- **Critical Care providers when the patient meets the criteria outlined in MCHS COVID-19 Inpatient Treatment Guideline**
- **Use only if tocilizumab not available**

Mechanism: humanized monoclonal antibody; an interleukin 6 (IL-6) receptor antagonist; approved for treatment of rheumatoid arthritis (RA)
Administration: infuse over 60 min in dedicated IV line, with a 0.2-micron filter
Warnings and Adverse Effects:

- Serious and potentially fatal infections including reactivation of latent TB (if benefit outweighs risk in treatment of COVID-19, prescriber may defer TB testing), monitor for signs and symptoms of infection during and after treatment
    - Infection has been reported at a higher incidence in elderly patients compared with younger adults
- Avoid use of sarilumab in patients with an active infection.
- Do not initiate if ANC is <2,000/mm^3, platelets are <150,000/mm^3, or if ALT or AST are >1.5 times ULN
- Hepatic impairment: Use is not recommended in patients with active hepatic disease or hepatic impairment.
- Hypersensitivity reactions including anaphylaxis
- Gastrointestinal perforation, use with caution in those at increased risk
- Hyperlipidemia -Therapy has been associated with increases in triglycerides, LDL, and/or HDL
- The effectiveness of oral contraceptives may be decreased during therapy and for several weeks after sarilumab is discontinued.

Pregnancy considerations:
Sarilumab is a humanized monoclonal antibody (IgG1). Potential placental transfer of human IgG is dependent upon the IgG subclass and gestational age, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis. A pregnancy registry has been established to monitor outcomes of women exposed to sarilumab during pregnancy. Health care providers or pregnant patients are encouraged to register.

BARICITINIB (OLUMIANT): Restricted

- **Infectious Disease physicians**

Mechanism: inhibits Janus kinase (JAK) enzymes, resulting in a reduction of serum IgG, IgM, IgA, and C-reactive protein; approved for treatment of rheumatoid arthritis (RA)
Administration: Oral or per tube, see table for dosing, duration up to 14 days or until hospital discharge, whichever is sooner

Lab	Dosing
eGFR $\geq$ 60 mL/min/1.73 m^2	4 mg once daily
eGFR 30 - 60 mL/min/1.73 m^2	2 mg once daily
eGFR 15 - <30 mL/min/1.73 m^2	1 mg once daily
eGFR <15 mL/min/1.73 m^2	Not recommended
Absolute Lymphocyte Count (ALC)	<200 cells/µL = hold until ALC $\geq$ 200 cells/µL
Absolute Neutrophil Count (ANC)	<500 cells/µL = hold until ANC $\geq$ 500 cells/µL

- Drug Interactions: Strong OAT3 Inhibitors: reduce starting dose by one-half
- Avoid use of live vaccines with baricitinib

Warnings and Adverse Effects:

- Baricitinib is not recommended for:
  - Patients who are on dialysis, have end-stage renal disease (ESRD), EGFR <15 mL/min/1.73 m^2, or have acute kidney injury (AKI)
  - Patients with known active tuberculosis
- **Serious venous thrombosis, including pulmonary embolism and arterial thrombosis, have been observed in patients treated with baricitinib. Avoid use in patients with a history of VTE (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) within the last 12 weeks or have a history of recurrent (>1) VTE (DVT/PE).**
  - Prophylaxis for VTE is recommended unless contraindicated
- Serious and potentially fatal infections including reactivation of latent TB (if benefit outweighs risk in treatment of COVID-19, prescriber may defer TB testing), monitor for signs and symptoms of infection during and after treatment
- Discontinue baricitinib if drug-induced liver injury is suspected while on therapy
- Hypersensitivity reactions including angioedema, urticaria, and rash
- Hyperlipidemia -Dose-dependent increases in lipid parameters (eg, total, LDL, and HDL cholesterol) were observed in patients receiving baricitinib
- Gastrointestinal perforation, use with caution in those at increased risk
- Hematologic toxicity, including lymphopenia, anemia, and neutropenia, may occur and is generally reversible and managed by treatment interruption
- Increased incidence of liver enzyme elevation (≥5 × ULN for ALT and ≥10 × ULN for AST) was observed in patients taking baricitinib. Monitor LFTs as clinically indicated; interrupt therapy if LFTs are increased and drug-induced liver injury is suspected.

Pregnancy considerations:
Baricitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. Consistent with the mechanism of action, embryo-fetal toxicities including skeletal anomalies and reduced fertility have been observed in animals dosed in excess of the maximum human exposure. The limited human data on use of baricitinib in pregnant women are not sufficient to inform a drug associated risk for major birth defects or miscarriage.

CORTICOSTEROIDS:

Pregnancy considerations:

- Given the potential benefit of decreased maternal mortality, and the low risk of fetal adverse effects for this short course of therapy, the NIH Panel recommends using dexamethasone in pregnant women with COVID-19 who are mechanically ventilated **(AIII)** or who require supplemental oxygen but who are not mechanically ventilated **(BIII)**.
- Corticosteroid therapy in pregnancy is considered appropriate to control clinically active maternal illness. Fetal considerations may guide steroid choice.

Additional considerations:

- It is unknown whether other corticosteroids, such as methylprednisolone, prednisone, or hydrocortisone, have a similar benefit as dexamethasone. Dexamethasone lacks mineralocorticoid activity.
- The equivalent doses of other corticosteroids to dexamethasone 6mg are:
  - methylprednisolone 32mg which may be administered once daily or in two divided doses daily
  - prednisone 40mg once daily
  - hydrocortisone 80mg twice daily

NIRMATRELVIR + RITONAVIR (PAXLOVID):

The U.S. FDA has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

- Paxlovid is not authorized:
  - For initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19
  - For use longer than 5 consecutive days

Drug Interactions: The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions.

HYDROXYCHLOROQUINE (PLAQUENIL): The FDA has withdrawn the EUA for use in COVID-19.

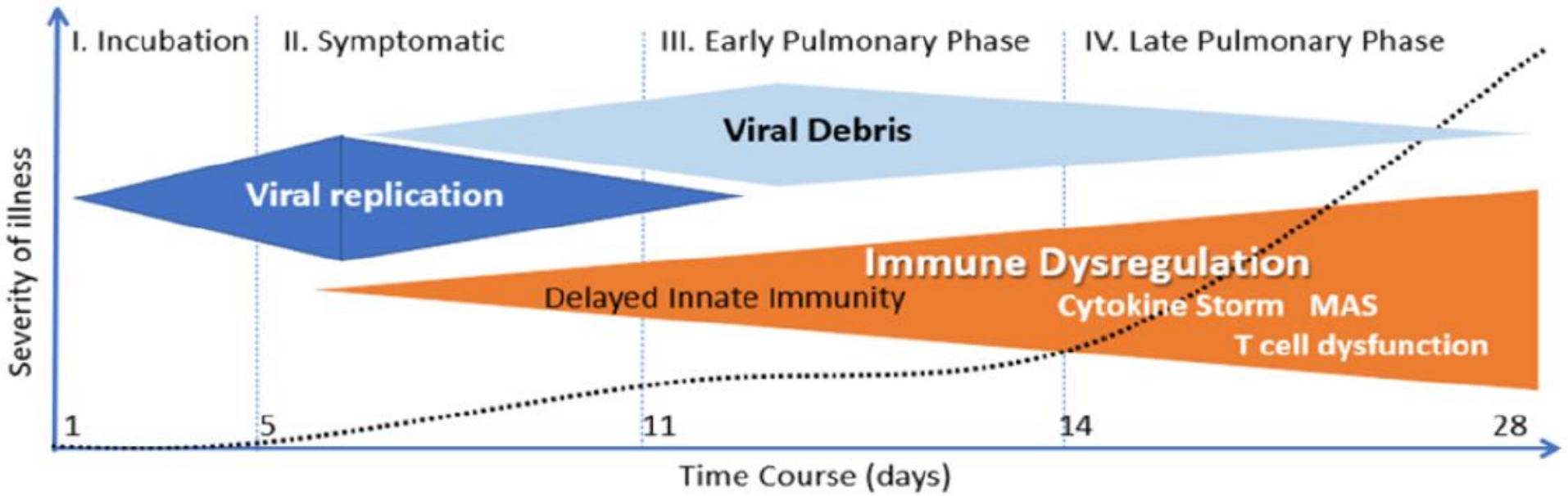
- Coadministration of remdesivir and hydroxychloroquine is not recommended based on an antagonistic effect on the antiviral activity of remdesivir.

Monoclonal antibodies and COVID-19 Vaccine: The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommends:
People who previously received antibody products (anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma) as part of COVID-19 treatment, post-exposure prophylaxis, or pre-exposure prophylaxis can be vaccinated at any time; **COVID-19 vaccination does not need to be delayed following receipt of monoclonal antibodies or convalescent plasma**. Although some reduction in vaccine-induced antibody titers was observed in people who previously received antibody products, the clinical significance of this reduction is unknown, and the balance of benefits vs. risks favors proceeding with vaccination even considering the possibility of diminished vaccine effectiveness in this situation.
Vaccines other than COVID-19 vaccines, including inactivated and live vaccines, may be administered without regard to timing of anti-SARS-CoV-2 monoclonal antibodies.

VACCINATED PEOPLE WHO SUBSEQUENTLY DEVELOP COVID-19

For vaccinated people who subsequently experience COVID-19, prior receipt of a COVID-19 vaccine should not affect treatment decisions (including use of monoclonal antibodies, convalescent plasma, antiviral treatment, or corticosteroid administration) or timing of such treatments.

COVID-19 Disease Course[8]



monoclonal antibodies, antivirals (remdesivir)

WEEK ONE (can extend through day 10):
Viral replication phase
- Incubation period (exposure to symptoms) = 2-14 days, Delta and Omicron variant symptom onset typically shorter

WARNING: steroids during this phase and prior to respiratory symptoms do not decrease mortality and may cause harm

dexamethasone, remdesivir, tocilizumab (IL-6 inhibitor), anticoagulation

WEEK TWO, 7-14 days from symptom onset: Early inflammatory phase, earlier onset in elderly and with comorbidities
- Hypoxemia, coagulation dysfunction
Virus enters lung→ pneumonia and related symptoms start to develop
- Immune system may begin to hyper-respond. WBC release chemokines to kill virus-infected cells making it difficult for gas exchange. Patients may need oxygen supplementation.
- Persistent or worsening hypoxemia despite improving CXR, consider PE

tocilizumab (IL-6 inhibitor), dexamethasone, possibly antimicrobials, anticoagulation

WEEKS THREE AND FOUR: Hyper-inflammatory phase
- Immune system hyper-responds and proinflammatory cytokines released, hypercoagulability
- Patients can develop ARDS and other organ failures
- If patient worsening, look for potential secondary bacterial/ fungal infections
- Persistent or worsening hypoxemia despite improving CXR, consider PE