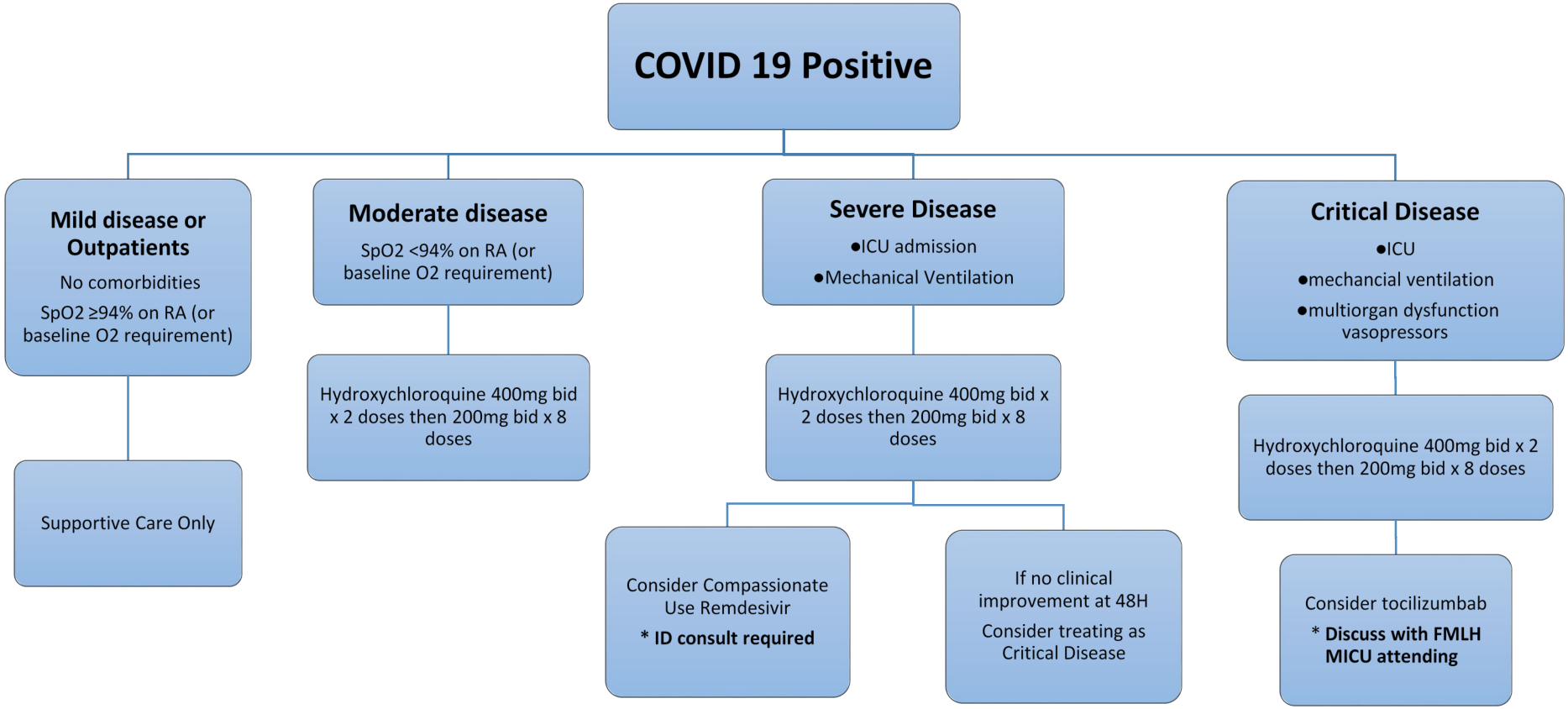
Guideline: COVID-19 Treatment



****Special Populations:**

- Pregnancy – utilize treatment algorithm above
- Immunocompromised; (HIV with CD4 <200, Prednisone or equiv ≥20mg/day for more than 4 weeks, solid organ transplant, acute leukemia, bone marrow/stem cell transplant) Consider ID consult
- Special considerations specific to transplant patients:
    - For patients with documented hypogammaglobulinemia (MM, CLL, etc): check IgG. If less than 400 and worsening of hypoxemia then consider IVIG.
    - For solid organ transplant patients with moderate to severe disease, consider holding mycophenolate mofetil or azathioprine while admitted, monitoring for rejection.
    - For solid organ or bone marrow transplant recipients and patients with acute leukemia consider adding azithromycin 500mg x1 then 250mg daily x4 days

Guideline: COVID-19 Treatment

Purpose of Guidelines: Provide a reference to guide management of patients with proven (confirmed) COVID-19 (novel coronavirus).

Background:
At the end of 2019, a new human coronavirus was found to be the causative pathogen for a group of patients with pneumonia in Wuhan, China. This virus is now called SARS-CoV-2. The clinical disease is called COVID-19 or novel coronavirus. [1,2] As of March 20, 2020, there have been over 10,000 COVID-19 cases reported in the United States. This number is expected to grow exponentially.[3,4]

There are no Food and Drug Administration (FDA)-approved antiviral therapies for treatment of COVID-19, but multiple clinical trials are in progress.[5,6] The Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) do not provide specific treatment recommendations.[3,4] There is very limited experience utilizing antiviral agents for treatment of COVID-19 and results from published literature are conflicting.[7-11]

Much of the data describing the utility of the following treatments were derived from experience with SARS-CoV and MERS-CoV, the causative viruses for 2 previous epidemics of human coronavirus.[5,6]

The recommendations below are subject to change based on emerging data or drug shortage information.

Clinical Assessment and Diagnosis:
Table 1. Treatment Recommendations Based on Severity of COVID-19 Illness[1,2,5,12-16]

Severity of Illness and Criteria	Treatment Recommendation
Mild disease OR Outpatients • SpO2 ≥ 94% on room air *(or baseline 02 requirements)*	• Supportive care only • Antiviral treatment **not** recommended
Moderate disease: • SpO2 < 94% on room air *(or baseline 02 requirements)*	‡**Hydroxychloroquine** 400 mg PO twice daily x 2 doses followed by 200 mg PO twice daily x 8 doses
Severe disease (any of the following): • Intensive Care Unit admission • Mechanical ventilation	‡**Hydroxychloroquine** 400 mg PO/NG/OG twice daily x 2 doses followed by 200 mg PO/NG/OG twice daily x 8 doses • Consider compassionate use **remdesivir** (Infectious Disease consult required) • If patient is not clinically improving after 48 hours, consider treating as critical disease (see below)
Critical disease (Meeting severe disease criteria plus any of the following): • Acute respiratory distress syndrome (ARDS) • Multi-organ dysfunction • Vasopressor requirement	‡**Hydroxychloroquine** 400 mg PO/NG/OG twice daily x 2 doses followed by 200 mg PONG/OG twice daily x 8 doses • Consider **tocilizumab** (Discuss with FMLH MICU Attending)

MEDICATIONS REQUIRING APPROVAL/CONSIDERATIONS

Remdesivir[17-19]
Consult Infectious Disease if considering compassionate use remdesivir. Remdesivir is not approved by FDA. Use may be considered under a compassionate use program. The patient must meet the following criteria to be eligible:

- Key inclusion criteria:
  - Hospitalization
  - Confirmed SARS-CoV-2 by polymerase chain reaction (PCR) assay
  - Invasive mechanical ventilation

- Key exclusion criteria:
  - Evidence of multi-organ failure
  - Vasopressor requirement to maintain blood pressure
  - ALT levels > 5x ULN
  - CrCl < 30 mL/min, dialysis, or continuous veno-venous hemofiltration (CVVH)

Tocilizumab[15,16,20]
Discuss with FMLH MICU Attending if considering tocilizumab.

Complete the following labs prior to therapy: CBC w/diff, AST/ALT, lipid panel, fibrinogen, and ferritin.

- Criteria for use (or MICU/CHD ICU Attending discretion):
  - Secondary HLH[16] (HScore > 169 – Use MD Calc)
    ---or---
  - Respiratory rate ≥ 30 breaths/min **and** SpO2 < 94% **or** PaO_2/FiO_2 < 300mmHg **or** mechanical ventilation[15]
    ---and---
  - Septic shock **or** multi-organ failure
- Dose:
  - 400 mg IV x 1 dose[15]
  - If continued clinical decompensation, consider a second dose after 8 to 12 hours to a maximum of 800 mg total dose.

TREATMENT CONSIDERATIONS FOR SPECIAL POPULATIONS

Pregnancy:

Hydroxychloroquine has been shown to cause ocular toxicities in animal reproduction studies, but this has not been replicated in available human data. Risk and benefit should be considered prior to use in pregnant patients.[21]

Tocilizumab is a monoclonal IgG antibody and has the potential to cross the placenta. Transfer is expected to increase in later stages of pregnancy (ie, third trimester). Placental transfer may affect the infant immune response. Risk and benefit should be considered prior to use in pregnant patients.[20]

Remdesivir has not been studied in pregnancy. Risk and benefit should be considered prior to use in pregnant patients.[17-19]

Immunocompromised Patients:

Consider Infectious Disease consultation for the following populations:

- Human immunodeficiency virus (HIV) with CD4 < 200
- Long-term steroids: 20 mg prednisone or equivalent for ≥ 4 weeks
- Solid organ transplant recipients*
- Acute leukemia
- Bone marrow/stem cell transplant recipients*

*Special considerations for transplant patients:

1. For patients with documented hypogammaglobulinemia (eg, secondary to multiple myeloma, chronic lymphocytic leukemia)
    - Check IgG
    - If IgG < 400 and worsening hypoxemia, consider intravenous immune globulin (IVIG).
2. For solid organ transplant patients with moderate to severe disease
    - Consider holding mycophenolate mofetil or azathioprine while admitted
    - Monitoring for rejection
3. For solid organ or bone marrow transplant recipients and patients with acute leukemia
    - Consider adding azithromycin 500 mg PO/IVPB daily x 1 dose then 250 mg PO/IVPB daily x 4 days (enteral is preferred route)

CONSIDERATIONS FOR ADJUNCTIVE THERAPIES

Corticosteroids
CDC and WHO **do not** recommended corticosteroids for treatment of COVID-19 **in the absence of other clear indications**.[3,4]

Angiotensin System Inhibitors
As of March 17, 2020, the American and European Cardiology Societies and the American Heart Association, **do not** recommend discontinuing angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) due to COVID-19. The medications **do not** put patients at increased risk for COVID-19 or increased severity of disease in COVID-19-infected patients. This does not apply to discontinuation of ACE-inhibitors or ARBs for alternative reasons (eg, other contraindications).[22]

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Appendix A. Medications for Treatment of COVID-19[17-21]

Medication ***Mechanism of Action***	**FDA-Approved Indication(s)**	**Renal Dose Adjustment**	**Administration**	**Monitoring**	**Additional Information**
Hydroxychloroquine (Plaquenil®) *Inhibits viral replication and modulates the immune system via inhibition of neutrophil and eosinophil action and impairment of complement-mediated reactions*	• Lupus erythematosus • Rheumatoid arthritis • Malaria	No adjustment (use with caution)	• Do not split or crush film-coated tablets • An oral suspension (25 mg/mL) may be compounded from tablets (30-day expiration)	• Labs at baseline and periodically: CBC, CMP • EKG Serious adverse effects: • Hypoglycemia • Cardiac arrhythmias • Cardiomyopathy • Bone marrow suppression	Temporary P&T Restriction for use in COVID-19 treatment only. *For patients on prior to admission can utilize home supply, if unavailable hold as an inpatient but will consider supplying after 7 days or with clinical need on a case-case basis.*
Tocilizumab (Actemra®) *Interleukin (IL)-6 inhibitor that inhibits actions of cytokines*	• Rheumatoid arthritis • Giant cell arteritis • Cytokine-release syndrome (CAR-T-related), severe	No adjustment (Not studied in patients with CrCL <30 mL/min)	Intravenous infusion administered over 60 minutes	• Labs at baseline and periodically: CBC w/diff, AST/ALT, lipid panel • Infusion reactions • Tuberculosis (new and reactivation) has been reported Serious adverse effects (typically associated with long-term use): hyperlipidemia, infection, demyelinating central nervous system disease	Discuss with FMLH MICU Attending
Remdesivir *Adenosine nucleotide analogue (prodrug) that inhibits viral RNA synthesis*	Only available for compassionate use treatment of COV-19	There are no dosing recommendations for patients with renal dysfunction			Infectious Disease consult required

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