- The purpose of these treatment guidelines is to offer guidance to providers when treating a patient with COVID-19 infection. Guidelines will not cover all potential clinical scenarios and clinical judgment is required for application.
- **In the current state of high prevalence Omicron BA.2, many previous therapeutic approaches are rendered ineffective. As such, this guidance has changed. It may continue to change with the evolution of the virus.**
- Remdesivir is the only agent FDA approved for treatment of COVID-19 both for mild-moderate disease for inpatients with incidental CoVID, outpatients unable to receive sotrovimab and for inpatients with moderate to severe disease.
- Outside of clinical trials, please DO NOT engage in empiric, pre-emptive, or prophylactic therapies given the limited understanding of efficacy.
- Expanded use of monoclonals is detailed in a separate mAb guideline.
- Steroids are not explicitly FDA approved for COVID-19, but benefit was demonstrated in hospitalized patients in a large randomized trial and the NIH and IDSA support use based on criteria.
- An Infectious Diseases consult is suggested for confirmed COVID-19 for high risk (defined below) or ICU level care as clinical guidance/research is rapidly evolving.
- This document does NOT cover recommendations for management of hypoxemia, fluid resuscitation, anticoagulation or the myriad complications in patients with COVID-19. See table 3 for hyperlinks.

Figure 1: Summary Flow Chart by level of care

Confirmed SARS-CoV-2 positive

Consideration of use of ALL AGENTS must be based on availability, and may require Antimicrobial Stewardship/ID or Critical Care approval.

Consider eligibility to enroll in clinical trial

Outpatient

Supportive Care & Close monitoring

Some basic information on outpatient therapies are included in this guideline. A separate BILH guideline reviews the monoclonal antibody therapies with further prioritization schema including pre-exposure prophylaxis, post exposure prophylaxis and treatment of mild to moderate disease in the face of resource allocation.

Prioritize Paxlovid, then remdesivir if feasible then Bebtelovimab.

Considerations for oral therapy with Paxlovid or molnupiravir (MOV) or are also detailed in a separate oral therapy guideline through a centralized process. Use of remdesivir in the outpatient setting for 3 days is another alternative.

Non-ICU Level of Care

Assess risk for disease complications

SpO2 ≤ 94% on room air requiring **sustained** 02 supplementation via facemask or nasal cannula **AND** Radiographic infiltrates on chest imaging

PLUS

at least 1 of the following:

1. Age > 60
2. Recent major surgery (within 2 weeks)
3. Pregnant
4. Obesity (BMI ≥ 30)
5. Active cardiac disease (HTN, CHF, CAD)
6. Pulmonary disease (COPD, CF)
7. Immunocompromise (HIV, biologics, transplant)
8. Diabetes (A1C > 7.6%)
9. Any of following: D-dimer > 1000, CPK >2x ULN, Troponin >2x ULN, Ferritin > 300, LDH > 245 U/L, Absolute lymphocytes < 800

Yes

1. Remdesivir (RDV*) recommended if requirement for 02 (not high flow oxygen or mechanically ventilated/ECMO)
2. Dexamethasone recommended if requirement for 02 supplementation or mechanical ventilation
3. See Table 4 for comments on other experimental therapeutic options (e.g., convalescent plasma, immunomodulators)

No

Supportive Care
Close monitoring
Repeat labs regularly
If admission is not for CoVID-19 and symptoms are mild-moderate, review possible use of mAb under
BILH guideline for monoclonal antibodies

ICU Level of Care

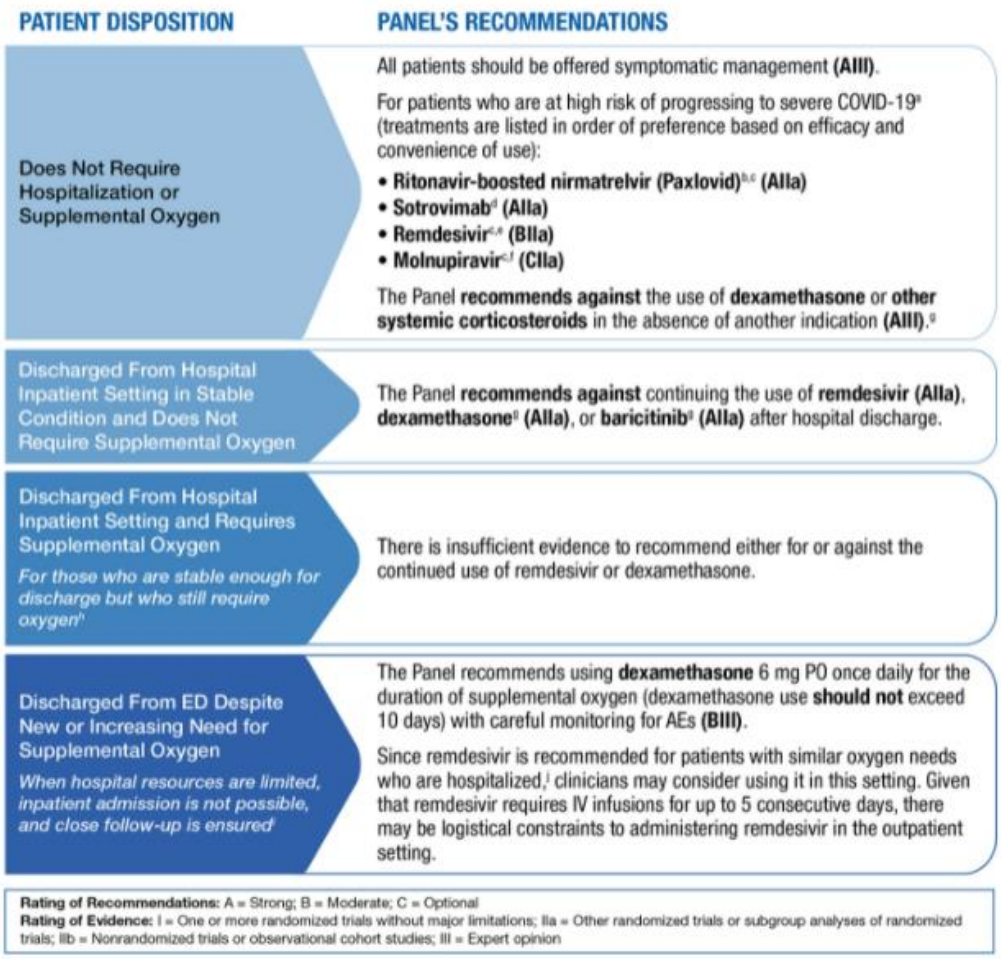
Yes

National Institutes of Health Disease Severity Panel Recommendation latest update 2/1/22

Outpatient

Multiple agents may be considered for treatment of mild-moderate disease including Sotrovimab, Remdesivir, Molnupiravir and Paxlovid, detailed later and in separate guidelines. Use of tixagevimab- cilgavimab (Evusheld), a long acting monoclonal antibody is limited to a subset of highly immunocompromised patients as a pre-exposure therapy. **The rise of Omicron BA.2 has led to a new local recommendation to prioritize Paxlovid, then Remdesivir then Bebtelovimab**. Remdesivir for outpatients for 3 days may be available as an option for some centers with infusion bed availability. This may not be possible on weekends. Oral agents are available through special order through our CoVID central ordering process via mail order/delivery.

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19



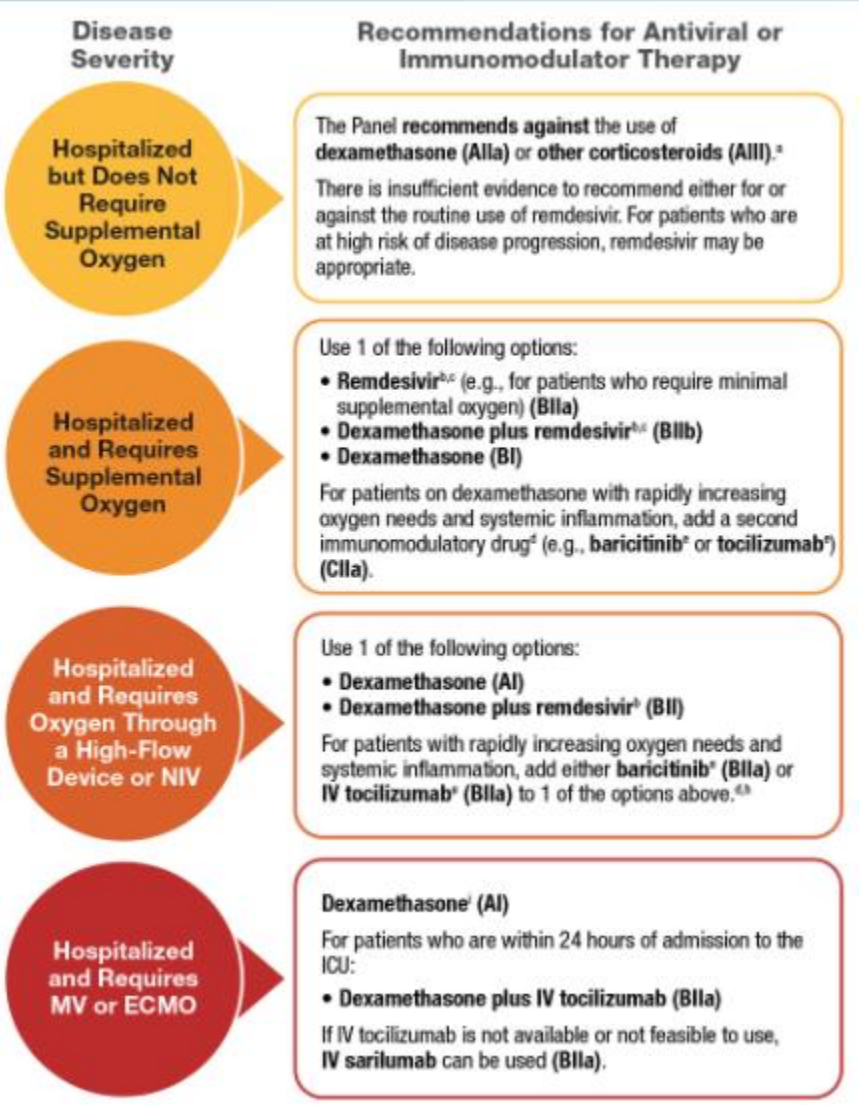
Prophylaxis

Currently, the only agent for prophylaxis that is active against the dominant variant Omicron is for pre-exposure only, tixagevimab- cilgavimab (Evusheld). This agent is only approved for patients with severe immune compromise, e.g. patients after solid organ or hematopoietic stem cell transplant. As the definitions are complex, the appropriate use of Evusheld is outlined within the BILH CoVID monoclonal antibody guidelines. **With lesser activity against BA.2 sublineage, a frank discussion with patients is important.**

Do NOT engage in unproven therapies, e.g. Ivermectin or betadine gargle, high dose vitamin supplements.

INPATIENT

National Institutes of Health Disease Severity Panel Recommendation latest 2/24/22



Laboratory Testing and Radiology

Table 1. Tests for Hospitalized Patients with Confirmed COVID-19

Daily Laboratory Testing • CBC with diff (trend total lymphocyte count) • Complete metabolic panel • Liver function tests (ALT/AST/tbili) Labs that may be used for risk stratification or trial eligibility (may be repeated if abnormal or with clinical deterioration): • CPK (creatine kinase) • Blood type and screen • D-dimer • Ferritin • LDH • CRP • Troponin[1]	Radiology: • Portable CXR at admission • CXR PA/lateral in ambulatory patients only if low suspicion for COVID-19 and result would change management or affect PUI status. If clinically indicated: • Routine blood cultures (2 sets) • For acute kidney injury (i.e., serum creatinine >0.3 above baseline), send urinalysis and spot urine protein:creatinine • Consider pregnancy test • Consider HIV 1/2 Ab/Ag

[1]Elevated troponin (> 2 times upper limit of normal) without hemodynamic compromise, can repeat troponin in 24 hours and echocardiogram not necessary. Uptrending troponin with hemodynamic compromise or other concerning cardiovascular symptoms /signs should prompt consideration of

obtaining an echocardiogram

[2]Viral serologies [HAV IgM, HBV serologies (sAb, cAb, and sAg), HCV antibody, unless positive in past] may assist in the interpretation of ALT elevations, present in ~25% of presentations.

COVID-19 Treatment

Step 1: Identify Risk Factors

Table 2. Risk Factors for Severe COVID-19 Disease

Demographic and Comorbidities	Labs
-Age > 60 -Pregnant -Obesity (BMI ≥ 30) -Pre-existing pulmonary disease -Chronic kidney disease -Diabetes with A1c > 7.6% -History of hypertension -History of cardiovascular disease -Use of biologics -History of transplant or other immunosuppression -All patients with HIV (regardless of CD4 count) -Major surgery during COVID-19 incubation period (w/in 2 weeks)	-D-dimer > 1000 ng/mL -CPK > twice upper limit of normal -CRP > 100 -LDH > 245 U/L -Troponin (>2x ULN) -Absolute lymphocyte count < 800 -Ferritin > 300 ug/L

Step 2: Treat Based on Severity

Table 3. Suggested Treatments Based on Clinical Severity

Clinical Status/ Location	Recommendation	Notes / Considerations
Outpatient pre-exposure prophylaxis in high risk patients **COVID 19 negative**	Evaluate specific risk factors that correspond to the highest potential for poor response to vaccination, e.g. severe immunocompromise due to hematologic malignancy, stem cell transplant or solid organ transplant. Submit a request for possible administration of tixagevimab-cilgavimab (Evusheld) The unpublished clinical trial PROVENT, a randomized, double-blind, placebo-controlled trial of adults > 59 years or with a prespecified chronic medical condition or at increased risk of SARS-CoV-2 infection who had not received a COVID-19 vaccine and no history of SARS-CoV-2 infection found a 77% reduced risk of COVID-19 compared to placebo.	The current drug authorization requires that individuals either have: • moderate to severely compromised immune systems due to a medical condition or due to taking immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination or; • a history of severe adverse reactions to a COVID-19 vaccine and/or component(s) of those vaccines, therefore vaccination with an available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended. More details are available in the BILH monoclonal antibody guideline **With the lesser activity against BA.2, dose increases and language for patients for more vigilance and mask wearing are encouraged.**
Mild to Moderate disease in the **outpatient setting**	Given limited data compared to other agents, antivirals are preferred, e.g. **Paxlovid or Remdesivir**. When not available a monoclonal antibody can be used. While four monoclonal antibody products are available, REGN-COV (**casirivimab and imdevimab**) **(bamlanivimab and etesevimab)** or **sotrovimab**, the predominant variant Omicron BA.2 displays significant resistance leaving **ONLY bebtelovimab active**.	Treat high-risk outpatients as defined in the EUA with **bebtelovimab under the following criteria.** Inclusion • Have one or more mild-moderate COVID-19 symptoms, with an onset no more than **7 days** prior to the date the medication is ordered. Symptoms may include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath with exertion, loss of taste/smell. • Must have a NAAT (PCR or similar) or antigen test confirming SARS-CoV-2 infection from a specimen obtained no more than **7 days** prior to the date the medication is ordered.

	COMET-ICE (NEJM 2021) study of Sotrovimab demonstrated a 79% relative risk reduction in hospitalization and all cause mortality	• Age ≥ 18 years OR age 12-17 years with weight ≥ 40 kg • The patient or legally authorized representative gives verbal consent and/or assent • Have at least one risk factor for progression to severe COVID-19 ▪ Age ≥65 years ▪ BMI 25-30 kg/m2 AND not fully vaccinated with 1-2 dose series (no vaccination or series completed less than 2 weeks prior) ▪ BMI >30 kg/m2 regardless of vaccination status ▪ If age 12-17, BMI ≥85th percentile for age/gender (CDC growth charts) ○ Pregnancy ○ Chronic kidney disease ○ Diabetes ○ Immunosuppressive disease or immunosuppressive treatment ○ Cardiovascular disease or hypertension ○ Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension) ○ Sickle cell disease ○ Neurodevelopmental disorders (for example, cerebral palsy), genetic/metabolic syndromes and severe congenital anomalies ○ Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19)) ○ Race/ethnicity that is associated with a higher risk of hospitalization or death from COVID-19, including Black or African American, Hispanic or Latinx, American Indian or Alaska Native **Exclusion Criteria** ○ Oxygen saturation (SpO2) ≤ 93% on room air due to COVID-19 in those not on chronic oxygen therapy ○ An increase in baseline oxygen flow rate due to COVID-19 in those who are on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity ○ Respiratory rate ≥ 30 per minute or Heart rate ≥ 125 per minute ○ Allergies to any of the constituent products in the antibody combination ○ Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the clinician could constitute a risk when taking a monoclonal Ab ○ Co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
Outpatients Treatment of mild-moderate disease (antivirals)	consider use of one of the following antiviral therapies in the following priority order 1. **Paxlovid unless contraindicated** 2. **Remdesivir** 3. **Molnupiravir** **Paxlovid (nirmatrelvir)** 300 mg (two 150 mg tablets) PLUS ritonavir 100 mg tablet BID x 5 days (EUA restriction)	EPIC-HR (NEJM, 2022), phase 2/3 RCT versus placebo. Demonstrated an 88.9% relative risk reduction in hospitalization or all-cause mortality at day 28. Given its mechanism and inclusion of ritonavir, Paxlovid should be used with caution in patients who are HIV 1 infected and not on active antiretroviral therapy. Not recommended in patients with estimated CrCl < 30mL/min or requiring dialysis or those with Child Pugh Class C hepatic disease. Dose reductions required in patients with CrCl ≥30 to 59 mL/min

	Significant hepatic disease, other drug inhibitors or inducers will affect this metabolism as detailed under the oral antiviral guideline. **Remdesivir** 200 mg IV once, then 100 mg IV daily x 2 days (now FDA approved)	Remdesivir: PINETREE study (NEJM 12/21). Placebo controlled RCT. Primary outcome: Reduction in hospitalization or death, was at a relative rate of 87%, corresponding with an absolute risk reduction of 4.6%. Inclusion criteria are similar to those for sotrovimab above with notable exceptions. Symptom onset no greater than **7 days** prior. Patients could not have been previously hospitalized for CoVID-19 or vaccinated. Lack of vaccine protection may explain outcome differences. **Important exclusions beyond mAbs:** • Renal dysfunction, estimated CrCl <30mL/min • Liver failure, either COVID-related or pre-existing
	Molnupiravir 800 mg po q12h x 5days (EUA restriction) Should be reserved as agent **of last resort** for outpatient treatment given teratogenic potential and mutagenicity. Avoid in pregnancy and lactation unless no other therapies available and risk outweighed by benefit. Females of childbearing potential must use reliable contraception during treatment and for four days later. Males should use reliable contraception during treatment and for 3 months thereafter.	MOVe OUT (MK-4482-002) NEJM Dec 2021, a phase 3 RCT vs placebo demonstrated a 30% relative risk reduction in hospitalization or all-cause mortality at day 29. **Exclusion Criteria for both oral antivirals:** • **Symptoms greater than 5 days prior to initiation** • Oxygen saturation (SpO2) ≤ 93% on room air due to COVID-19 in those not on chronic oxygen therapy • An increase in baseline oxygen flow rate due to COVID-19 in those who are on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity • Respiratory rate ≥ 30 per minute or Heart rate ≥ 125 per minute • Allergies to molnupiravir or Paxlovid (nirmatrelvir with ritonavir) or any excipients in the preparation • Co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days • HIV 1 infection and not on combination antiretrovirals
All hospitalized patients (regardless of severity or location)	Supportive care Evaluate eligibility for **clinical trials**	Close monitoring for progression
Patients (NON-ICU) with mild symptoms of CoVID NOT admitted for CoVID infection but at high risk for progression	Similar to above for high risk outpatients If sotrovimab is unavailable or the patient length of stay is at least 3 more days, consider use of **Remdesivir** 200 mg IV once, then 100 mg IV daily x 2 days	Symptom onset no greater than **7 days** prior. • Have one or more mild-moderate COVID-19 symptoms, with an onset no more than **7 days** prior Symptoms may include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath with exertion, loss of taste/smell. Relative exclusions • Renal failure, particularly progressive and without plan for renal replacement therapy • Liver failure, either COVID-related or pre-existing • Active liver injury ▪ ALT > 200 ▪ ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR

Patients requiring **floor-level** (NON-ICU) admission with suspected lower respiratory disease with: radiographic infiltrates by imaging **OR** evidence of rales/crackles on physical exam **OR** SpO2 ≤ 94% on room air **AND** At least one additional risk factor (see Table 2)	Evaluate remdesivir and/or steroids based on oxygenation status. **RDV Treatment guideline** Radiographic evidence of lung infection AND confirmed COVID 19 positive with a documented initial PCR+ **<7 days**, symptom onset no greater than **7 days** unless severely immunocompromised (see remdesivir guideline for definitions) AND Need for oxygen support via nasal cannula or face mask to maintain O2 saturation greater than 94% ***NOTE: Patients on high flow oxygen support do not generally benefit from remdesivir*** **RDV exclusion** • **O2 sat > 94% RA** • Non-ICU with improving clinical trajectory (e.g., decreasing oxygen requirement over time prior to RDV) • Mechanical ventilation or ECMO • Renal failure, particularly progressive and without plan for renal replacement therapy • Liver failure, either COVID-related or pre-existing • Active liver injury* ▪ ALT > 200 ▪ ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR • Comfort measures or similarly non-aggressive goals of care • Pregnancy is **NOT** an exclusion	Daily labs: Chem-7 including Scr, liver function tests (AST/ALT/bili/alk phos), and CBC. The ACTT-1 (placebo controlled RCT) and SIMPLE (open label duration comparisons) identified the greatest benefit among patients dependent upon supplemental oxygen not requiring mechanical ventilation. While overall benefit was primarily a reduction in number of hospitalization days, survival benefit was observed for this sub-group in ACTT-1 (NEJM, 10/20). The study of patients not on high flow oxygen supplementation (JAMA 8/20) demonstrated a change in the ordinal scale for improvement in the 5 day group versus placebo. There were no differences in duration of oxygen therapy, hospitalization or mortality. The SOLIDARITY trial, a large open label study, did not demonstrate an overall reduction in mortality in patients treated with remdesivir (NEJM 12/20). The DisCoVeRy trial (Lancet Inf Dis/2021) an open label adaptive randomized trial found no difference in ordinal scale improvements compared to placebo. As in previous, the benefit was reduced in patients with severe symptoms at enrollment, as well as those with symptoms exceeding 14 days with a decreased benefit in patients with symptom onset between 7 and 14 days.
	Dexamethasone (6mg IV or PO daily for 10 days) for patients **requiring oxygen supplementation** (If pregnant, see section on pregnancy) (Alternatively hydrocortisone 50 mg iv q6h for 7-10 days)	RECOVERY, CODEX and DEXA-COVID 19 demonstrate a benefit of short course dexamethasone on 28 day mortality in patients with an oxygen requirement and in those mechanically ventilated, compared with standard of care (RECOVERY)/ WHO-REACT A meta-analysis identified hydrocortisone as an alternative during dexamethasone shortage.
NON ICU	**Ongoing care: Reasonable to discontinue RDV and/or dexamethasone** if rapid improvement (e.g., <=24h) or at discharge based on trial data. **Do not** prolong admission or OPAT to continue RDV if improvement is sufficient for discharge	The published remdesivir trials all included criteria to discontinue therapy when stable enough for discharge.

NON ICU	For non-ICU patients with rapid decompensation, who require high flow oxygen or noninvasive ventilation, and have systemic inflammation, consider the use of **baricitinib**. See guideline at BILH for details.	Exclusion criteria for baricitinib: 1. Active tuberculosis or bacterial, invasive fungal, viral (not CoVID) but including hepatitis, and other opportunistic infections 2. Active thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis 3. Anemia (hemoglobin <8 g/dL), lymphopenia (ALC <500 cells/mm3) and/or neutropenia (ANC <1000 cells/mm3) 4. Severe Renal dysfunction (estimated CrCl<15mL/min)
Patients requiring **ICU-level admission**	Evaluate eligibility for **clinical trials** See above for consideration of **remdesivir.**	Process and monitoring as above. Clinical trials have not shown benefit from RDV in patients requiring mechanical ventilation or ECMO and this treatment is not recommended by NIH guidelines.
Special Considerations for the approach to: •Sedation/ Analgesia/ Paralysis •Anticoagulation	**Dexamethasone (6mg IV or PO daily for 10 days).** If pregnant, see section on pregnancy.	RECOVERY, CODEX and DEXA-COVID 19 demonstrate a benefit of short course dexamethasone on 28 day mortality in patients with an oxygen requirement and further in those mechanically ventilated, compared with standard of care (RECOVERY)/ WHO-REACT An expanded meta-analysis identified hydrocortisone as an alternative.
	For early intervention in the ICU (<24h), consider use of **baricitinib** or tocilizumab. **Tocilizumab** IV may be preferred over baricitinib in patients lacking enteral access or requiring mechanical ventilation or ECMO	**Exclusion criteria for baricitinib:** 1.Active tuberculosis or bacterial, invasive fungal, viral (not CoVID) but including hepatitis, and other opportunistic infections 2.Active thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis 3.Anemia (hemoglobin <8 g/dL), lymphopenia (ALC <500 cells/mm3) and/or neutropenia (ANC <1000 cells/mm3) 4.Severe Renal dysfunction (estimated CrCl<15mL/min) **Exclusion criteria for tocilizumab (any of these)** ▪>24 hours since ICU admission ▪Absolute neutrophil count (ANC) < 500/uL ▪ALT or AST >5 x ULN (e.g. ALT or AST > 200 IU/L) ▪Platelets < 50 K/uL ▪Known condition or active treatment with immunosuppressive agents or immunomodulators ▪Known or suspected pregnancy ▪Active/high suspicion for severe/ uncontrolled bacterial, fungal or viral infection (excluding COVID-19, including, but not limited to, active HBV, HCV, or HIV/AIDS) ▪Suspected clinical diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines ▪Concern for perforation in patients with IBD or history of diverticulitis ▪Imminent death/predicted survival < 24 - 48 hours ▪Enrolled in a clinical trial evaluating immunomodulators for proven or suspected COVID-19 infection ▪Known hypersensitivity to tocilizumab

Table 4. Considerations for Experimental COVID-19 Therapeutics
IL-6 inhibitors (based on current data can be considered under specific scenarios): o Across all randomized studies assessing mortality (with varying severity of disease), five trials concluded no benefit (Salvarini, Hermine, Stone, Rosas, Salama), two demonstrated benefit (Gordon, Horby [preprint]), and one suggested

harm (Veiga). The potential benefit is derived from open-label trials administering tocilizumab early in rapidly decompensating patients while on corticosteroids. Given the evolving data and GRADE approach via the NIH and IDSA, tocilizumab may be considered in patients meeting inclusion criteria in REMAP-CAP (ICU) RECOVERY (nonICU). Tocilizumab has been associated with neutropenia, increased secondary infections, reactivation of severe infections, hepatotoxicity, and gastric perforation. Consider risks and benefits.

Monoclonal Antibodies

- Bind the receptor-binding domain of the spike protein blocking spike protein attachment to the human ACE2 receptor, fusion, entry and replication. Binding is specific to different but overlapping epitopes in the receptor binding domain (RBD) of the S-protein. Binding is affected by mutational changes among variants to varying degrees, many of which have led to withdrawals of products with the flux of variant predominance. Our guidance documents should reflect the most recent recommendations from the FDA and CDC based on variance predominance. **Currently all products are limited to Emergency Use Approval primarily for outpatient treatment or for mild disease in hospitalized patients not admitted for CoVID 19 infection. Bamlanivimab** was the first in October 2020 but removed with variant resistance. The combination of **casirivimab and imdevimab** second in November 2020 was also removed with evolving resistance. **Bamlanivimab plus etesevimab** was approved in early February 2021 and removed. **Sotrovimab** was approved in May 2021 with the highest degree of activity against the early Omicron variant B.1.1.529 but with variable and diminished activity against BA.2 not yet to the point of reaching local predominance. **Tixagevimab/cilgavimab (Evusheld)** was approved in December 2021 for PRE-exposure prophylaxis (PREP) only given its unique long acting effect in patients with the highest degrees of immune compromise. **Bebtelovimab was approved in February 2022 and is now preferred given BA.2 activity.**

IMPORTANT NOTE: MAbs should not be used to treat inpatients with moderate to severe symptoms outside a clinical trial (one such trial was stopped by DSMB due to futility). Use for mild to moderate symptoms may be acceptable but the EUA criteria need careful review.Relative activity in vitro to Variants*

	Casirivimab & Imdevimab	**Sotrovimab**	**Tixagevimab & Cilgavimab (Evusheld)**	**Bebtelovimab**
Alpha (B.1.1.7)	Fully active	Fully active	Fully active	Fully active
Beta (B.1.351)	Fully active	Fully active	Fully active	Fully active
Gamma (P.1)	Fully active	Fully active	Fully active	Fully active
Delta (B.1.617.2)	Fully active	Fully active	Fully active	Fully active
Delta Plus (AY.1)	Visit w/RGN	Fully active	Fully active	Fully active
Epsilon (B.1.427/B.1.429)	Fully active	Fully active	Fully active	Fully active
Iota (B.1.526)	Fully active	Fully active	Fully active	Fully active
Kappa/no designation (B.1.617.1/B.1.617.3)	Fully active	Fully active	Fully active	Fully active
Lambda (C.37)	Fully active	Fully active	Fully active	Fully active
Mu (B.1.621)	Fully active	N/A	Less active	Less active
Omicron (B.1.1.529)	Inactive	Fully active	Less active	**Fully active**
Omicron (BA.1.1)	Inactive	Active	Less active	**Fully active**
Omicron (BA.2)	Inactive	Less active	Active	**Fully active**

* Not all variants harbor resistance mutations

Baricitinib

- A Janus kinase (JAK) inhibitor that modulates hematopoiesis and immune cell function, approved by the FDA for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor antagonist therapies. Granted EUA status based on a randomized,

double-blind, placebo-controlled trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID) comparing baricitinib in combination with remdesivir to remdesivir alone (ACTT-2- NEJM Dec 11 2020). Patients in the combination treatment group recovered one day faster overall. The most benefit was seen in ordinal scale improvement in the group of patients receiving high-flow oxygen or non-invasive ventilation at enrollment. The CoV-BARRIER study (Lancet, 2021) demonstrated a nonsignificant difference in clinical improvement versus standard of care but a 28-day all cause-mortality decrease: 8.1% vs 13.8% (38.2% mortality reduction) in patients requiring high flow oxygen in combination with steroids. The NIH recommends baricitinib as an alternative to tocilizumab.

Colchicine

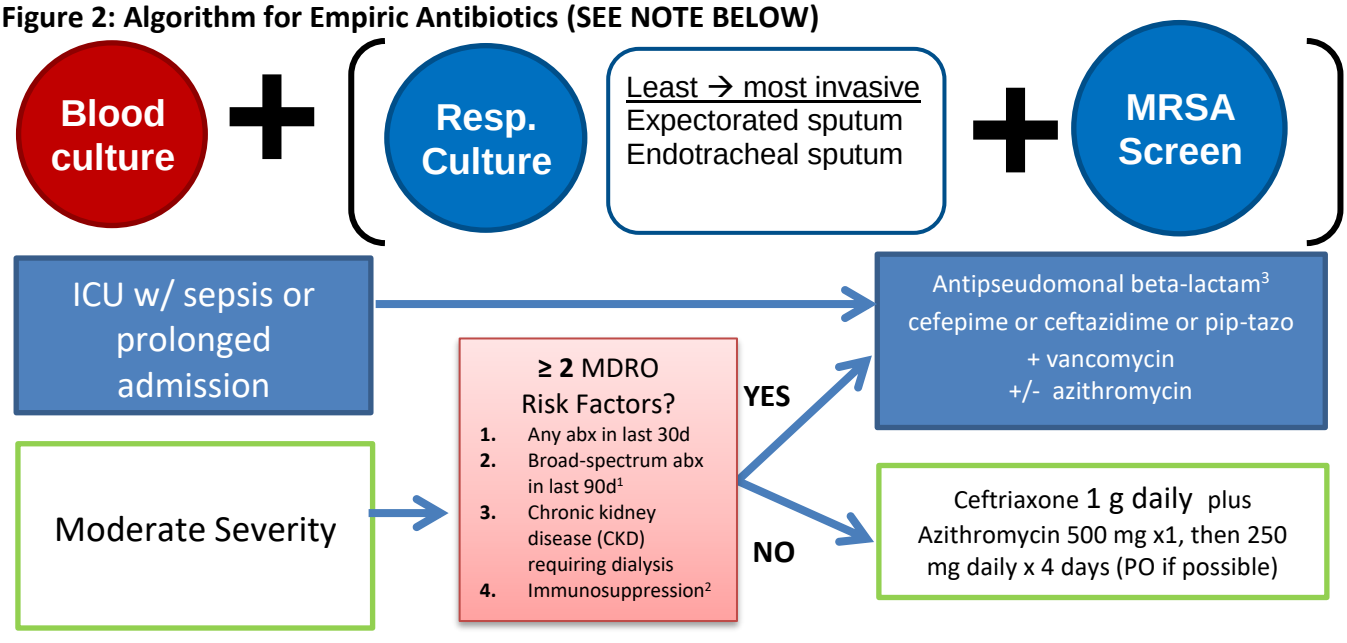
- An anti-inflammatory medication that binds to tubulin interrupting microtubule assembly thereby disrupting neutrophil activity. Inhibition or other pathways (e.g. superoxide production and NLRP3 inflammasome activation lends to a decrease in inflammatory cytokines (IL-6, TNFα) decreasing the inflammatory cascade of COVID-19 infection. Small studies in inpatients with moderate to severe disease (GRECCO-19, Lopes, et.al.) with variable dosing demonstrate a decrease in progression of disease. A preprint for outpatient prophylaxis (COLCORONA) is available but not peer reviewed. Dosing across studies was variable but included a load then maintenance. Most trial data is based on co-treatment with other agents. Drug interactions and toxicity are complex and systematic review by NIH or IDSA not yet done. **The treatment collaborative does not endorse the use but cannot conclusively deny a potential benefit. The drug was removed the RECOVERY trial given futility.**

Table 5: Patient-Specific Supportive Care and Therapeutics

- **Symptomatic care**:
  - Antitussive agents vs. expectorants
  - Acetaminophen for fever or pain control (avoid NSAIDs if possible)
- **Inhaled bronchodilators:** beta agonists/muscarinic antagonists if needed via metered dose inhaler
  - Avoid nebulization given aerosolization risk

- **Empiric treatment for bacterial pneumonia (consider possibility of co-infection with COVID-19):**
  - **Bacterial co-infection is uncommon with initial presentation of COVID-19**, but consider when concerning signs and symptoms (e.g., purulent secretions, leukocytosis) and with concern for hospital- and ventilator-associated pneumonia

Figure 2: Algorithm for Empiric Antibiotics (SEE NOTE BELOW)



****Tailor/de-escalate antibiotics using culture results and MRSA screen****

[1]*Broad spectrum: Any agent with MRSA or antipseudomonal coverage excluding fluoroquinolones*

[2]*Immunosuppression defined as: neutrophils<1.0x10^9/L, congenital immunodeficiency, splenectomy, HIV, hematologic malignancy, on immunosuppressant(s) or systemic steroid therapy (≥10 mg prednisone-equivalent per day for 2+ weeks).*

[3]*If severe (life-threatening) beta-lactam allergy and no record of subsequently tolerating other beta-lactams, options for High Risk Regimen may include aztreonam + (tobramycin or ciprofloxacin)* + vancomycin.

NOTE: In a review of the clinical experience at BIDMC, 73% of COVID + patients received empiric antibiotics with 24% with any positive culture and a higher rate of selection for resistance with antibiotic exposure.

Table 6. Agents not currently recommended

- **Convalescent Plasma (CCP):** The FDA issued an EUA August 23 2020. Multiple RCTs demonstrate little to no benefit with small study exceptions. An RCT of outpatients (NEJM, 11/21) at high risk for progression compared to placebo resulted in the same rates of disease progression. A small placebo controlled randomized trial in older outpatients (NEJM, 1/21) resulted in decreased progression, a relative risk reduction of 48%. However, with the number of agents readily available to treat mild disease in the outpatient setting without use of a blood product, WHO, IDSA and BILH do not support use for this indication. The RECOVERY trial arm examining CCP versus usual care alone in hospitalized patients with moderate to severe COVID-19 (Lancet, 5/21) found there was no improvement in survival at 28 days. Patients hospitalized with severe pneumonia randomized to placebo or CCP showed no significant difference in overall mortality or day 30 or changes in the ordinal scale (NEJM, 11/2020). WHO, IDSA and BILH do not support use for this indication. Additionally, use of convalescent plasma is not without risk, including allergic reactions, transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and risk of another infectious disease from the donor.
- **Ribavirin:** In crude and multivariable analyses, ribavirin and IFN was associated with higher 90-day mortality compared with no treatment; with no difference in these groups noted after accounting for time-varying confounders. Given this and the significant toxicities related to ribavirin (with or without IFN), we do not recommend use at this time.
- **Interferon Beta-1b**: Insufficient evidence to support the use of interferons, alone or in combination with other agents, at this time. The pathophysiology of respiratory failure caused by COVID-19 appears to involve an aberrant immune response, which may be exacerbated by interferon administration. No mortality benefit was seen in the SOLIDARITY trial (mortality was numerically worse in the interferon arm).
- **Zinc:** As of this date no study has specifically evaluated its role in COVID -19 with no recommendations in local, national or international guidelines support use of therapeutic zinc.
- **Vitamin C:** Basic science modeling and research as an immune booster, immunomodulatory agent in the sepsis cascade lends to postulation of a benefit to reduce infection-induced oxidative stress. There are ongoing randomized trials of the role of vitamin C in COVID-19. In ARDS, high dose vitamin C was associated with reduced mortality, with no benefit on surrogate markers due to survivor bias. There are no recommendations in local, national or international guidelines to use therapeutic vitamin C.
- **Vitamin D:** There are ongoing trials of vitamin D for prevention and treatment of COVID-19, and observational data suggest an association between vitamin D deficiency and mortality. However, there is no evidence that supplementation beyond correction of deficiency has an impact on disease outcome, and no recommendations in local, national or international guidelines to use therapeutic vitamin D.
- **Ivermectin:** Ivermectin may play a role in the prophylaxis of *Strongyloides* in high-risk patients birth or residence or long-term travel (>6 months) in South East Asia, Oceania, Sub-Saharan Africa, South America, and the Caribbean started on dexamethasone. Both the NIH and IDSA recommend against the use of ivermectin. In small explorations, ivermectin was shown to increase virologic clearance but with little to no benefit on symptom resolution unless relying on post hoc subgroup comparisons. Larger retrospective studies were observational with study results demonstrating an increased risk of death with Ivermectin alone compared to standard of care. Do not engage in use of ivermectin for prophylaxis or treatment of CoVID.

Table 7. Concomitant Medication Considerations

- **ACE-Inhibitors (ACEi) / Angiotensin Receptor Blockers (ARBs):**
  - SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry. It is unknown if these agents either help or worsen COVID-19 disease.
  - Currently there are no data to support either starting or stopping ACEi/ARBs on any patients with COVID-19. However, for patients receiving ACEi/ARB, if acute kidney injury, hypotension or other contraindication develops, we recommend stopping them at that time.
- **Statins:**
  - Some theoretical benefit of statins as promoters of innate antiviral immune response, as immunomodulators, and possible cardio protection. However, use must be balanced by concern regarding elevation of CPK and LFTs, which could disqualify patients from antiviral clinical trials. No mortality benefit of statins in COVID-19 infection has been demonstrated in high-quality published data. *Statins may be continued for patients already receiving these agents.*
- **Inhaled steroids:**
  - May theoretically reduce local immunity and promote viral replication, but this consideration must be balanced by potential benefits for management of reactive airways. There is no current evidence that inhaled steroids worsen the course of COVID-19
- **NSAIDs:**
  - NSAID use has been reported preceding clinical deterioration in some patients with severe COVID-19 disease, but the association is uncertain. Consider avoiding use of NSAIDs while patients are admitted if alternatives such as acetaminophen are available.

Table 8: Special Populations/Characteristics

	Recommendation	Notes
Solid organ and HSCT recipients	-Please call/consult transplant and transplant ID teams -Request bronchoscopy only if significant decompensation, versus lung biopsy (may be lower risk for aerosolization) -Reduction of immunosuppressants needs to be considered with guidance by transplant and transplant ID teams - IL-6 receptor inhibitors may cause further immunosuppression and increase risk of infection. *Consider* concomitant use of anti-bacterial agents, prophylaxis and surveillance for opportunistic infection, starting acyclovir or valacyclovir for HSV/VZV prophylaxis for 3 months following IL-6R inhibitor treatment, monitoring for CMV reactivation by blood PCR at least monthly for 3 months. -Given a potential blunting of symptoms, decisions regarding the initiation of treatment with monoclonal antibodies and duration of symptoms in the outpatient setting prior to infusion may vary from a strict 7 day maximum.	Screen for drug-drug interactions with anti-viral agents, if they are being used
If IgG <400	Consider IVIG at standard dose of 1 gm/kg daily x 2 doses	
Pregnancy	There is a small increase in risk for ICU level care, mechanical ventilation, and death in pregnant vs. non-pregnant women with COVID-19. Management guided by Maternal-Fetal Medicine / ID teams is suggested. Dexamethasone has known fetal effects. Consult Maternal-Fetal Medicine before using dexamethasone in pregnancy. Alternative regimens may include hydrocortisone, prednisone or methylprednisolone. If there is concern for risk of preterm birth, betamethasone 12 mg IM q24 hours is the preferred regimen.	Covid-19 in Pregnancy (NEJM 4/17/20) MMWR 6Nov20

	The preferred therapy for early treatment in the outpatient setting or inpatient if an undiscovered result at time of admission is sotrovimab.	
Acute Kidney Injury	Consider Nephrology consult for possible intervention	Niacinamide ASN preprint
Myocarditis/Cardiomyopathy	Consider Cardiology consult for management and possible intervention	
Multisystem inflammatory syndrome	Consult infectious diseases, consider rheumatology consult.	Current case definition <21 year of age, but may occur at ages above

Table 9: Additional Drug Information

Agent/dosing	Target / Mechanism	Dosing	Monitoring
Baricitinib	Janus kinase (JAK) inhibitor, intended to decrease a hyperimmune response, e.g. cytokine storm.	4 mg po daily x 14 days (dependent on renal function and drug interactions)	**Infections** including bacterial, fungal, viral and other opportunistic infections, risk likely increased by concomitant corticosteroids **Thrombosis** can occur during or shortly after therapy **Hematologic disorders** including anemia, lymphopenia and neutropenia **Gastrointestinal perforation** **Hypersensitivity** such as angioedema, urticaria, and rash **Liver Enzyme Elevations**
Bebtelovimab	**human IgG1κ monoclonal antibody (mAb) to the spike protein of SARS-CoV-2 and is unmodified in the Fc region.**	**175 mg once**	**Rare hypersensitivity reactions, nausea, headache, fatique.**
Colchicine	Binds to tubulin disrupting neutrophil activity and a decrease in inflammatory cytokines (IL-6, TNFα). Direct antiviral effects, disruption of viral entry and decreased replication.	1.2 mg once, then 0.6 mg po bid (dependent on renal/hepatic function and drug interactions) x 14 days	CYP3A4 and P-gp substrate; severe and fatal drug interactions have been reported with moderate or strong inhibitors Dose adjustment required in renal impairment (CrCl < 30 mL/min)/hepatic insufficiency in the setting of drug interactions. Side effects **>10% GI intolerance**: diarrhea, nausea, vomiting **Hematologic** including anemia, lymphopenia and neutropenia **Hepatotoxicity** **Peripheral neuritis** **Musculoskeletal:** myalgia, rhabdomyolysis
Dexamethasone	Multiple: binding to Mpro/3Chymotripsin Like pro (viral protease),	6 mg IV or PO once daily for 10 days	Use caution in the presence of an active co-infection, e.g. TB, fungal, HSV. Observe for potential steroid

	inhibition of neutrophil apoptosis/ demargination, promotion of anti-inflammatory genes (IL-10)		complications, e.g. hyperglycemia, delirium, GI perforation, fluid overload.
Hydrocortisone	Inhibition of neutrophil apoptosis/ demargination, promotion of anti-inflammatory genes (IL-10)	50 mg IV q6h	Use caution in the presence of an active co-infection, e.g. TB, fungal, HSV. Observe for potential steroid complications, e.g. hyperglycemia, delirium, GI perforation, fluid overload.
Molnupiravir **(see oral CoVID drug guideline)**	RNA dependent RNA polymerase inhibitor	800 mg po BID x 5 days	teratogenicity, mutagenicity, use limited to patients unable to receive other EUA or off label treatments.
Paxlovid (nirmatrelvir with ritonavir) **(see oral CoVID drug guideline)**	**Nirmatrelvir**: 3CLpro or nsp5 protease inhibitor active against SARS COV2 **Ritonavir:** HIV 1 protease inhibitor and cytochrome P450 enzyme inhibitor (booster of nirmatrelvir)	Nirmatrelvir 300 mg (**two** 150 mg tablets) PLUS ritonavir 100 mg tablet BID x 5days (requires dose adjustment for renal dysfunction)	Not recommended in patients with estimated CrCl < 30mL/min or requiring dialysis or those with Child Pugh class C hepatic dysfunction Review detailed potential drug interactions in guideline.
Remdesivir **See Remdesivir guideline**	RNA-dependent RNA polymerase inhibitor	200 mg IV x1, then 100 mg IV daily, for a total duration of 5 days Outpatient: 200 mg x 1, then 100 mg IV daily for a total duration of 3 days.	ALT elevations, hypersensitivity
Sotrovimab	Human monoclonal antibody that binds to the spike protein receptor binding domain (RBD) of SARS-CoV-2 preventing binding affinity to ACE2	500 mg IV once	Acute hypersensitivity reactions during or shortly after infusion. Observe 1h post infusion.
Tixagevimab/cilgavimab (Evusheld)	Long acting human monoclonal antibody that binds to the spike protein receptor binding domain (RBD) of SARS-CoV-2 preventing binding affinity to ACE2	300 mg total (tixagevimab 150 mg + cilgavimab 150 mg) IM once	Infection site reactions, potential bleeding/hematoma at site if thrombocytopenic or with coagulation disorder.
Tocilizumab (Actemra)	Monoclonal antibody to IL6 receptor / treats cytokine release syndrome	8mg/kg IV once, no redosing	Avoid if transaminases >5x ULN, ANC < 500, platelets < 50 AST/ALT elevations, infectious complications (TB/Hepatitis), risk for perforation in IBD, hypersensitivity

Liverpool COVID-19 Drug Interactions

Post-exposure Prophylaxis for Healthcare Workers

- Follow current Infection Control guidance around quarantine. Healthcare workers should follow instructions from Occupational Health.

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Annotated References Link