Table 1. Overview of Treatment Recommendations Based on Hospitalization and Severity of Disease

<table>
<thead>
<tr>
<th>Not Hospitalized – Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Supportive care</td>
</tr>
<tr>
<td>• Consider bamlanivimab if <strong>within 10 days of symptom onset</strong> and meet criteria (see Table 2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospitalized</th>
<th>Recommended Treatment</th>
</tr>
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</table>
| **No supplemental oxygen** (or if on chronic oxygen therapy, not requiring an increase in baseline oxygen flow rate due to COVID-19) | • Supportive care  
• Anticoagulation: refer to COVID-19 Anticoagulation and Coagulopathy Management for Adults |
| **Low-flow supplemental oxygen** (i.e., persistent SpO2 ≤ 94% on room air AND requiring supplemental oxygen) | • Remdesivir (restricted to ID physicians) for 5 days or until discharge, whichever comes first  
--PLUS--  
• Dexamethasone 6 mg IV/PO for up to 10 days or until discharge, whichever comes first  
• **Consider** convalescent plasma (restricted to ID physicians - see Table 2 for criteria for use)  
• Anticoagulation: refer to COVID-19 Anticoagulation and Coagulopathy Management for Adults |
| **Non-invasive ventilation or high-flow oxygen devices** | • Dexamethasone 6 mg IV/PO for up to 10 days or until discharge, whichever comes first (consider higher dose in select patients – refer to Table 2)  
--PLUS--  
• **Consider** remdesivir (clinical benefit uncertain - restricted to ID physicians) for 5 days or until discharge, whichever comes first  
• **Consider** convalescent plasma (restricted to ID physicians - see Table 2 for criteria for use)  
• Anticoagulation: refer to COVID-19 Anticoagulation and Coagulopathy Management for Adults |
| **Mechanical ventilation or ECMO** | • Dexamethasone 6 mg IV/PO for up to 10 days or until discharge, whichever comes first (consider higher dose in select patients – refer to Table 2)  
• Anticoagulation: refer to COVID-19 Anticoagulation and Coagulopathy Management for Adults |

**SUGGESTED LABORATORY MONITORING**  
*Obtain at baseline and with any sudden decline in oxygenation status*

• Complete blood count with diff: Leukopenia: 17-45%; Lymphopenia: 33-85%  
• Comprehensive metabolic panel: LFTs (generally elevated)  
• Lactate dehydrogenase (increased 27-75%)  
• D-dimer (generally increased)  
• Ferritin (generally increased)  
• C-reactive protein (generally increased)  
• Procalcitonin (refer to Table 3)
Table 2. Recommended Agents for Therapeutic Management of COVID-19

Bamlanivimab (Outpatient Only) - Prescriber must complete all EUA requirements

**Dosage:** 700 mg IV x 1 (infused over 60 min)

**Inclusion**
- Not hospitalized
- Positive SARS-CoV-2 test (i.e., RT-PCR or antigen, not antibody test)
- Symptom onset within the last 10 days
- High risk for progressing to severe COVID-19* (see criteria below)

**Exclusion**
- <12 yo
- <40 kg
- Requiring supplemental oxygen (or if on chronic oxygen therapy, requiring an increase in baseline oxygen flow rate due to COVID-19)

**Precautions**
- Moderate or severe hepatic impairment (Child-Pugh class B or C): risk is unknown since these patients were excluded from clinical trials. Use with caution.

**Adverse Reactions:** nausea (3%), vomiting (1%), diarrhea (1%), dizziness (3%), headache (3%), pruritus (2%), and hypersensitivity including anaphylaxis, and infusion-related reactions (2%) (e.g., fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness)

*High risk criteria for progressing to severe COVID-19 (must meet at least one of the following)*

- Body mass index (BMI) ≥35
- Chronic kidney disease (CKD)
- Diabetes
- Immunosuppressive disease
- Currently receiving immunosuppressive treatment
- 65 years of age or older
- 55 years of age AND have
  - Cardiovascular disease, OR
  - Hypertension, OR
  - Chronic obstructive pulmonary disease/other chronic respiratory disease
- 12 – 17 years of age AND have
  - BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
  - Sickle cell disease, OR
  - Congenital or acquired heart disease, OR
  - Neurodevelopmental disorders, for example, cerebral palsy, OR
  - A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  - Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control
**Remdesivir** (restricted to Infectious Disease physicians. Use will be audited by the Antimicrobial Stewardship Team)

### Inclusion
- Positive SARS-CoV-2 test (i.e., RT-PCR or antigen, not antibody test)
- Symptom onset within the last 14 days
- Persistent SpO2 ≤ 94% on room air and requiring supplemental oxygen or on non-invasive ventilation or high-flow oxygen devices

### Exclusion
- Mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
- Reinfection with COVID-19 (positive SARS-CoV-2 test within 90 days of first positive SARS-CoV-2 test)
- Weight <3.5 kg
- Patients being transferred/awaiting transfer
- Less than 6 months life expectancy as determined by the attending physician or a consulting physician (e.g., oncologist for patients with malignancy, FAST score 7C or more [or as assessed by geriatrics or palliative care] for dementia, etc)

### Precautions
- eGFR<30 ml/min: the pharmacokinetics have not been evaluated in patients with eGFR <30 ml/min. The risk of toxicity in these patients is small and benefit of remdesivir likely outweighs this risk.
- ALT > 5 x ULN at baseline: risk of hepatotoxicity in these patients is not known due to exclusion from clinical trials. Use of remdesivir should be based on potential risk versus benefit considerations.

### FDA approved for the following patients:
| Hospitalized adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization |

### EUA criteria:
| Hospitalized pediatric patients 3.5 kg to <40 kg or pediatric patients <12 yo weight at least 3.5 kg. Please see below for additional requirements for healthcare providers for use in these patients. |

### Adult Dosing:
- 200 mg IV x 1 on day 1, then 100 mg IV daily for days 2 – 5 or until hospital discharge, whichever comes first

### Pediatric Dosing*:
- < 40 kg: 5 mg/kg IV load on day 1, then 2.5 mg/kg IV q24hr for days 2-5
- ≥ 40 kg: 200 mg IV load on day 1, then 100 mg IV q24hr for days 2-5

### Laboratory Monitoring
- **Prior to initiation**: Scr/BUN, hepatic function, prothrombin time
- **During therapy**: hepatic function (every 2-3 days or daily if ALT elevated), and Scr/BUN and prothrombin time should be monitored as clinically appropriate
  - Consider discontinuing if ALT >10 x ULN
  - Discontinue if ALT elevation accompanied by signs or symptoms of liver inflammation
- Pharmacists can order necessary labs listed above for patients receiving remdesivir

### Infusion-related reactions
(e.g., hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering): Slow infusion rate, with a maximum infusion time up to 120 minutes, to potentially prevent these signs and symptoms. If clinically significant infusion-related reactions occur, immediately discontinue & initiate appropriate treatment.
Remdesivir (continued)

Pregnancy and Nursing Mothers: Insufficient data to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals.

EUA Requirements for the Health Care Provider (applicable to pediatric patients 3.5 kg to <40 kg or pediatric patients <12 yo weight at least 3.5 kg)
Must provide copy of “Fact Sheet for Patients or parent/caregivers” prior to the patient receiving remdesivir, however, “if providing this information will delay the administration of remdesivir to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after remdesivir is administered.”

1. Discuss the following information
   a. EUA does not mean FDA approved
   b. Patient or parent/caregiver can refuse
   c. Risks/benefits of remdesivir, availability of alternatives

2. Record in Epic that the patient/caregiver has been (use dotphrase .remdesivir):
   a. Given the Fact Sheet for Patients and Parents/Caregivers
   b. Informed that remdesivir is an unapproved drug that is authorized for use under EUA
   c. Informed of alternatives to receiving remdesivir

3. Required FDA Medwatch reporting
   a. Report any death or serious adverse event within 7 calendar days from the onset
   b. All medication errors
   c. FDA Medwatch: www.fda.gov/medwatch/report.htm
   d. Include “Remdesivir under EUA use” in top line of event description
      i. Serious Adverse Events are defined as: death from any cause while on therapy, life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect, medical or surgical intervention to prevent death, life-threatening event, hospitalization, disability, or congenital anomaly
      ii. Provide copy of all FDA MedWatch forms to Gilead: Safety_fc@gilead.com
Steroids

Recommended in adult patients with persistent SpO2 ≤ 94% on room air AND requiring supplemental oxygen (i.e., on low- or high-flow nasal oxygen, non-invasive or invasive mechanical ventilation, or ECMO):

- **Preferred:** Dexamethasone 6 mg IV/PO q24h *for up to 10 days (or until discharge if earlier)*:
  - Alternatives if dexamethasone is unavailable:
    - Methylprednisolone 40 mg IV q24h for up to 10 days (or until discharge if earlier)
    - Prednisone 40 mg PO q24h for up to 10 days (or until discharge if earlier)

- **For select patients on high-flow nasal oxygen, non-invasive or invasive mechanical ventilation, or ECMO (based on physician discretion):**
  - Consider high-dose steroids (maximum recommended dose dexamethasone 20mg/day or methylprednisolone 80mg/day):
    - Dexamethasone 20 mg IV/PO q24h x 5 days, then 10 mg IV/PO q24h x 5 days --OR--
    - Methylprednisolone 40 mg IV q12h x 5 days, then 40 mg IV q24h x 5 days

- **Monitor:**
  - Oxygenation status, CRP, ferritin, and LDH. If no improvement, rule out secondary bacterial infection.
  - Blood glucose in high risk individuals. Consider point-of-care blood glucose monitoring 4 times per day for 24-48 hours to monitor for steroid induced hyperglycemia, hyperglycemic crises, and new onset diabetes or for chronic diabetes management.

- For adult patients with refractory septic shock and COVID-19 the recommendation is to follow surviving sepsis guidelines with consideration for use with hydrocortisone 200 mg IV per day divided.

- **Drug-drug interactions:** The combination of dexamethasone and direct oral anticoagulants (DOACs: apixaban, rivaroxaban, dabigatran, edoxaban and betrixaban) **should be avoided.** Dexamethasone is believed to be a combined P-glycoprotein and strong CYP 3A4 inducer. When used in combination with DOACs there is a potential for reduced DOAC drug concentration and increased risk of thrombosis.

- **Stress ulcer prophylaxis:** consider in patients also on therapeutic anticoagulation, mechanical ventilation, and/or patients with coagulopathy

**Pediatric patients:** Methylprednisolone IV (at an appropriate weight-based dose) may be initiated in pediatric ICU patients by the Pediatric Intensivist on a case-by-case basis. As literature evolves, recommendations and dosing in pediatric patients will be updated.

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**Convalescent Plasma (restricted to Infectious Diseases physicians)**

**Dosage:** one unit of convalescent plasma (~200 mL) - High Titer Convalescent plasma preferred over Low Titer Convalescent plasma

- **Redosing:** additional convalescent plasma units based on prescribing physician’s medical judgment and patient’s clinical response
- **Impaired cardiac function and heart failure:** patients may require a smaller volume or more prolonged transfusion times

**Inclusion**

- Laboratory confirmation of SARS-CoV-2
- Symptom onset within the last 7 days
- **Persistent** SpO2 ≤ 94% on room air AND requiring supplemental oxygen

**Exclusion**

- Age < 18 years
- Mechanical ventilation or ECMO
- Receipt of monoclonal antibody for treatment of COVID-19
- Currently pregnant
- Contraindication to transfusion or history of prior life-threatening reactions to transfused blood products
Convalescent Plasma (continued)

- **Side Effects:** overall low rates of serious adverse events. Potential side effects are similar to other blood products (e.g., transfusion-transmitted infections [e.g. HIV, hepatitis B, hepatitis C], allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and hemolytic reactions). Theoretical risks include antibody-dependent enhancement of infection (ADE) and attenuation of immune response leading to increased susceptibility to reinfecion.

**EUA Requirements for Health Care Providers**

1. Must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion to the FDA
2. Must provide recipients with the Fact Sheet for Patients/Caregivers and must communicate the following information to the recipients*:
   - FDA has authorized emergency use of COVID-19 convalescent plasma, which is not an FDA-approved biological product
   - The patient or caregiver has the option to accept or refuse administration of COVID-19 convalescent plasma
   - The significant known and potential risks and benefits of COVID-19 convalescent plasma and the extent to which such risks and benefits are unknown
   - Information on available alternative treatments and the risks and benefits of those alternatives.

*If providing this information will delay the administration of COVID-19 convalescent plasma to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after convalescent plasma is administered.

**Table 3. Bacterial Co-infections and Other Treatment Considerations**

<table>
<thead>
<tr>
<th>Bacterial Co-Infections with COVID-19</th>
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<tbody>
<tr>
<td>Bacterial co-infections are uncommon in patients presenting with COVID-19 infection. A meta-analysis by Langford et al and Michigan cohort study (n=1705 patients) found only 3.5% of hospitalized patients had community-onset bacterial co-infection and risk was slightly higher in patients admitted directly to the ICU at 11%. Secondary bacterial infections occurred in about 14% of COVID-19 patients. A study by Zhou and colleagues found the median duration of fever to be 12 days (8-13 days) and cough persisted for 19 days in survivors.</td>
</tr>
</tbody>
</table>

**Procalcitonin:** Low procalcitonin can be used to help rule-out bacterial co-infection (PCT <0.25), but PCT >0.25 should not be used as the only reason to initiate or continue antibiotic therapy. PCT >0.25 is common in patients with COVID-19 pneumonia, especially in patients with more severe disease (possibly due to systemic inflammation); therefore, it appears to be an unreliable marker of bacterial superinfection. Also, patients with CKD and AKI have falsely elevated PCT levels, and as such PCT is not reliable in these patients.
Strongly Suspected or Confirmed MRSA pneumonia:

For patients with moderate to severe COVID-19 with suspected MRSA pneumonia:
- Anti-staphylococcal therapy is generally unnecessary, since concomitant bacterial infection appears to be uncommon
- For sites using AUC-guided dosing for vancomycin (i.e., RYO, TRY, GRP):
  - For any infection in which a vancomycin AUC goal of 400 – 600 is currently recommended switch to trough monitoring with a goal ~15 mg/L for patients with COVID-19
- If MRSA pneumonia is suspected: suggest oral linezolid instead of vancomycin to help decrease fluid volume and required blood draws
  - Check MRSA nasal swab and discontinue if negative
  - Check for drug-drug interactions prior to starting linezolid
  - Caution in patients with pre-existing myelosuppression
- For pediatric patients: linezolid is restricted to Infectious Diseases physicians
  - Infants & children < 12 years old: linezolid 10 mg/kg/dose (max: 600 mg/dose) PO every 8 hours
  - Children & adolescents ≥ 12 years: linezolid 600 mg PO every 12 hours or as recommended by Infectious Diseases

Current evidence does not support use of the agents below for treatment of hospitalized patients with COVID-19 (due to lack of efficacy and/or potential toxicity)

<table>
<thead>
<tr>
<th>Hydroxychloroquine +/- azithromycin</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir (Kaletra)</td>
<td>Immune globulin (IVIG)</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Interferon</td>
</tr>
<tr>
<td>Baloxavir</td>
<td>Ivermectin</td>
</tr>
<tr>
<td></td>
<td>Oral Vitamin C</td>
</tr>
</tbody>
</table>

Other Treatment Considerations

ACEI/ARBs therapy: Patients chronically taking ACEi/ARBS should continue therapy. It is unclear if ACEi/ARBS will worsen or improve outcomes in patients with COVID-19.

Oral Vitamin C: Oral vitamin C does not achieve high enough concentrations in the serum for any potential therapeutic benefit due to saturable absorption. Also, oral vitamin C has the potential to cause harm, specifically AKI and/or kidney stones secondary to the accumulation of oxalate. Therefore, we do not recommend the use of oral vitamin C as adjuvant therapy for the treatment of COVID-19.

Statins: Due to the lack of data, we do not recommend COVID-19 be the sole indication for statin therapy.

Stress ulcer prophylaxis: consider in patients on steroids and therapeutic anticoagulation, mechanical ventilation, and/or patients with coagulopathy
### Table 4. BH Investigational Studies

<table>
<thead>
<tr>
<th>Study Agent</th>
<th>Location</th>
<th>Study Coordinator</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone and Ketamine (SINK study)</td>
<td>RYO</td>
<td>Maureen Cooney, RN</td>
<td>1) ≤ 6L O₂ by nasal cannula randomized to low-dose naltrexone vs placebo, ketamine if O₂ requirements increase --OR-- 2) &gt; 6L O₂ by nasal cannula enrolled as open label low-dose naltrexone &amp; directly into the ketamine rescue group.</td>
</tr>
<tr>
<td>Sirukumab</td>
<td>RYO</td>
<td>Lauren Brown, RN</td>
<td>&gt; 4L oxygen with SpO₂ &lt;92% or PaO₂/FiO₂ ratio &lt;300 or on mechanical ventilation &lt; 72 hours</td>
</tr>
<tr>
<td>Convalescent Plasma (C3PO)</td>
<td>RYO</td>
<td>Blerina Pople Heather Grace</td>
<td>• One or more symptoms of COVID-19 illness and laboratory-confirmed SARS-CoV-2 infection. • Has at least one study defined risk factor for severe COVID-19 illness • Clinical team deems stable for outpatient management without supplemental oxygen • CP available at the site at the time of enrollment • Duration of symptoms ≤ 7 days at ED presentation</td>
</tr>
<tr>
<td>COVID-19 Vaccine</td>
<td>All sites</td>
<td>Maureen Cooney</td>
<td>&gt; 18 yo, in good or stable health, at increased risk of getting COVID-19, and do not have a history of confirmed diagnosis of COVID-19. For more information visit: <a href="https://www.beaumont.org/covid-trial">https://www.beaumont.org/covid-trial</a></td>
</tr>
</tbody>
</table>

### References