Christiana Care Interim Inpatient Treatment Guidelines for SARS-CoV-2 Infection (COVID-19)

Refer to the Christiana Care Infection Prevention COVID-19 Website for Additional Information

Disclaimer: There are currently NO treatment approaches approved by the FDA for the management of COVID-19. New data is being published daily in which this document could be updated frequently. The data to support current recommendations is generally based on small case reports, open-label clinical trials, or *in-vitro* data. Each case should be assessed carefully, with each treatment approach used judiciously given the potential for limited resources. Click here to jump to TREATMENT or VTE PROPHYLAXIS/TREATMENT.

I. Clinical Presentation

A. Incubation period: estimated 4 days (2 to 7 days). Data from other coronaviruses (eg: MERS-CoV, SARS-CoV) suggest the incubation period could be longer, up to 14 days.

B. Most frequently reported signs and symptoms in hospitalized patients:

Symptom	Reported incidence
Fever	83-99%
Cough	59-82%
Fatigue	44-70%
Anorexia	40-84%
Shortness of breath	31-40%
Sputum production	28-33%
Myalgias	11-35%

Other reported symptoms include: sore throat, headache, hemoptysis, diarrhea/nausea prior to fever, dysgeusia, and anosmia

C. Clinical Course:

1. Clinical presentation can vary from asymptomatic to mild infection (81%) to severe (14%) to critical (5%) or fatal illness
2. Clinical deterioration anticipated during the second week of illness. Among patients with severe illness, medium time to dyspnea ranged from 5-8 days, median time to ARDS ranged from 8-12 days, and the median time to ICU admission ranged from 10-12 days.
3. Among all hospitalized patients, a range of 26%-32% of patients were admitted to ICU. Amongst all patients, a range of 3%-17% developed ARDS.

II. Laboratory and Radiographic Findings

A. Most common laboratory abnormalities reported in hospitalized patients with pneumonia:

Symptom	Reported incidence
Lymphopenia	63%
Leukocytosis	24-30%
Leukopenia	9-25%
Elevated ALT/AST	37%
Procalcitonin	Often normal
CT chest	Bilateral involvement, with multiple areas of consolidation and ground glass opacities although 56% of patients who presented within 2 days of symptom onset had a normal CT

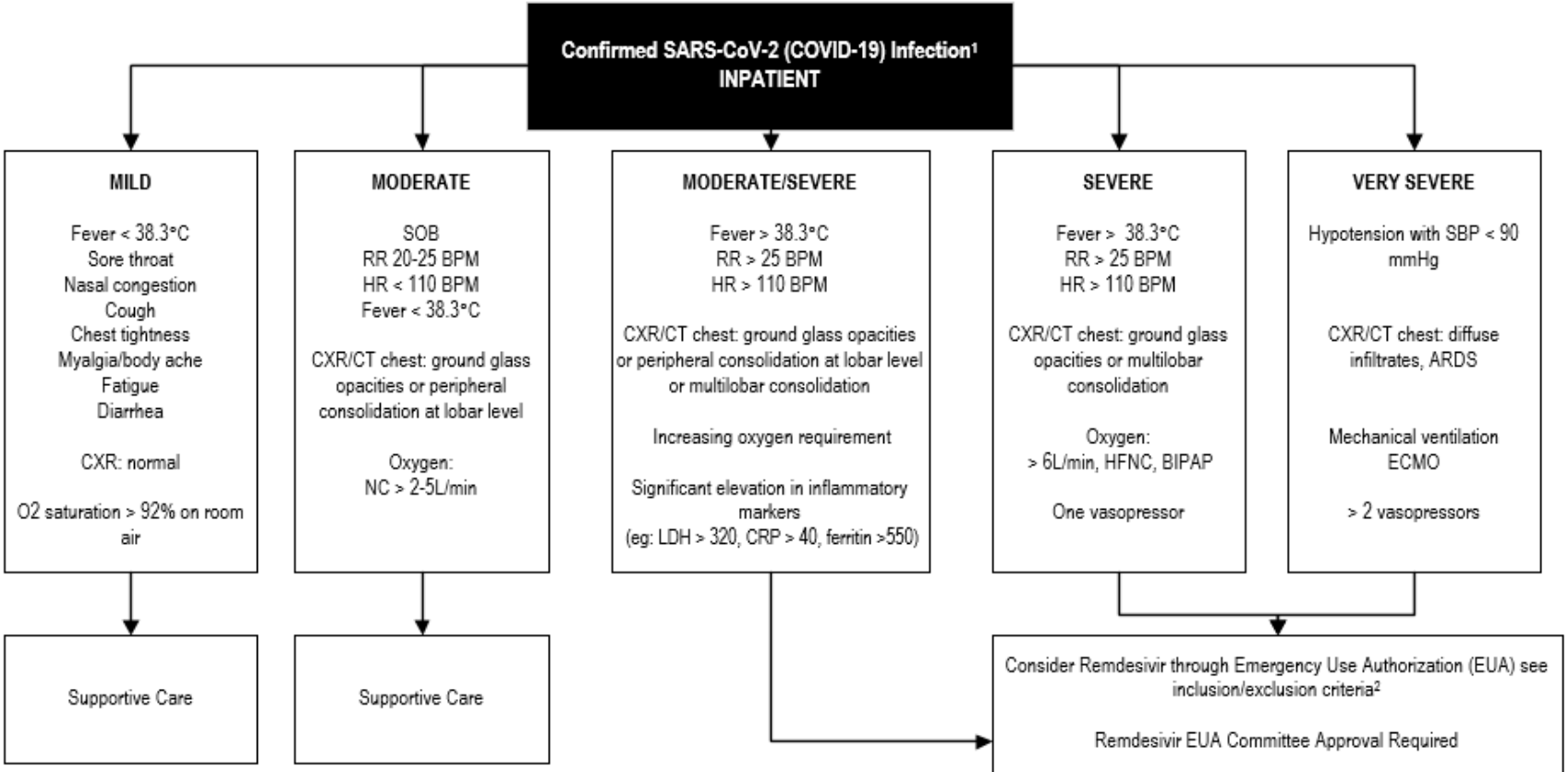
III. Diagnostic Testing

A. The COVID-19 testing platform is subject to change based on availability. For more information, refer to the Infection Prevention COVID-19 Website. For patients who have obtained a positive test result that is not retrievable in Power Chart and/or DHIN, please consider repeat testing on admission.

B. Consider the following labs. Select add-on to minimize patient exposure when possible. IL-6 is a send out test performed at Mayo 7 days a week.

Floor/Non-ICU	ICU/Critically Ill
Admission: CBC with diff, CMP, CRP, D-dimer, LDH and procalcitonin, Within 24 hours (am labs after admission): ferritin, fibrinogen, UDS, CPK (with renal failure), blood type screen (for convalescent plasma) Daily after admission: CBC with diff, CMP, CRP, LDH Periodically or if clinical deterioration: D-dimer, ferritin, fibrinogen	Admission: CBC with diff, CMP, CRP, D-dimer, ferritin, fibrinogen, LDH, UDS, CPK (with renal failure), IL-6, triglyceride (advanced disease), soluble CD25 (advanced disease), blood type screen (for convalescent plasma) Daily: CBC with diff, CMP, CRP, LDH, D-dimer Periodically or if clinical deterioration: ferritin, fibrinogen, procalcitonin, triglyceride (advanced disease), soluble CD25 (advanced disease)

IV. **Treatment**: **Tocilizumab and IVIG for COVID-19 are restricted to Infectious Diseases Providers and Pulmonary Intensivists.**



[1]In an effort to conserve supply, presumptive treatment should only be considered for inpatient use under the guidance of ID or Pulmonary Intensivists.

[2]Remdesivir EUA Inclusion criteria:

- hospitalized and laboratory confirmed COVID-19
- symptoms ≤ 10 days
- oxygen requirement: mechanical ventilation ≤ 48 hours or HFNC or NC ≥3L/min
- significant elevation in inflammatory markers
- single organ failure – respiratory/pulmonary
- no significant comorbidities (e.g. advanced cancer, cirrhosis, advanced COPD, NYHA Class IV heart failure)

Remdesivir EUA Exclusion criteria:

- CrCl < 30 ml/min
- hemodialysis and renal replacement therapy (SLED)
- ALT > 5x ULN
- life expectancy < 6 months
- pregnancy
- < 18 years of age

Remdesivir can be used with tocilizumab, methylprednisolone and convalescent plasma. Do not use with hydroxychloroquine.

[3]Tocilizumab supply limited. Consultation with ID or Pulmonary Intensivist required.

V. **VTE Prophylaxis and Treatment**:

A. Aggressive VTE prophylaxis in patients with COVID-19 is warranted due to the risk of COVID-19-associated coagulopathy (CAC) and thrombosis. Please use the guideline below to determine the preferred agent and dose for COVID-19 (SARS-CoV-2) positive patients and patients under investigation (PUI).

B. Consider holding VTE prophylaxis in patients who are actively bleeding or if platelet count is < 25/nL.

C. To minimize exposure of caregivers, it is appropriate to cluster administration and monitoring of VTE prophylaxis around other patient care activities.

D. In high risk patients at extremes of body weight or with renal dysfunction that are on enoxaparin, consider checking anti Xa level 4-6 hours after the 3rd or 4th dose (Prophylaxis goal 0.2-0.5 units/mL; Treatment goal 0.6 to 1 units/mL)

COVID-19 Inpatient VTE Prophylaxis and Treatment Guidelines			
	BMI < 40 kg/m^2	**BMI 40-50 kg/m^2**	**BMI > 50 kg/m^2**
VTE Prophylaxis	**CrCl ≥ 30 mL/min**: enoxaparin 30mg SubQ BID **CrCl < 30 mL/min**: enoxaparin 30mg SubQ daily **ESRD or acute renal failure requiring renal replacement therapy:** heparin 5000units SubQ Q8H	**CrCl ≥ 30 mL/min**: enoxaparin 40mg SubQ BID **CrCl < 30 mL/min**: heparin 7500units SubQ Q8H	**CrCl ≥ 30 mL/min**: enoxaparin 60mg SubQ BID **CrCl < 30 mL/min**: heparin 7500units SubQ Q8H
VTE Prophylaxis – PREGNANCY (< 23 weeks gestation)	**CrCl ≥ 30 mL/min**: enoxaparin 30mg SubQ BID **CrCl < 30 mL/min**: enoxaparin 30mg SubQ daily **ESRD or acute renal failure requiring renal replacement therapy:** heparin 5000units SubQ Q8H	**CrCl ≥ 30 mL/min**: enoxaparin 40mg SubQ BID **CrCl < 30 mL/min**: heparin 7500units SubQ Q8H	**CrCl ≥ 30 mL/min**: enoxaparin 60mg SubQ BID **CrCl < 30 mL/min**: heparin 7500units SubQ Q8H
VTE Prophylaxis – PREGNANCY (> 23 weeks gestation)	Heparin 10,000 units SubQ Q12H Hold heparin if concern for delivery		
VTE Treatment or Therapeutic Anticoagulation Recommended in patients with platelet count > 25/nL without active bleeding OR contraindication to anticoagulation and one of the following: • Known or suspected VTE • Atrial fibrillation • Acute MI • ECMO • C-SLED May be considered in patients with persistent elevations in inflammatory biomarkers and/or worsening oxygenation (e.g. mechanical ventilation, D-Dimer > 3000 ng/mL). The decision to anticoagulate patients in the absence of one of the risk factors above should be made based on assessment of the patient's clinical condition rather than individual laboratory values.	For admitted patients who were previously on an oral anticoagulant, discontinue the oral anticoagulant and initiate parenteral anticoagulation as outlined below. Oral anticoagulants may be resumed in patients pending discharge. **CrCl ≥ 30 mL/min**: enoxaparin 1 mg/kg SubQ BID (actual body weight) **CrCl < 30 mL/min**: enoxaparin 1 mg/kg SubQ daily (actual body weight) **ESRD or acute renal failure requiring renal replacement therapy**: heparin infusion with goal PTT 50-90 sec. If PTT is prolonged at baseline or patient is requiring > 35,000 units/hr of heparin, check anti Xa level (goal 0.3 to 0.7 units/mL). If anti Xa levels do not correlate with PTT, switch to a provider-managed protocol and monitor anti Xa levels. Anti Xa levels should be monitored Q6H until two consecutive therapeutic measurements are achieved and daily thereafter. For patients receiving empiric anticoagulation without documented or highly suspected VTE or arterial thrombus, transitioning to prophylaxis dosing as above upon clinical improvement is appropriate as determined by the care team. A surveillance ultrasound may be considered prior to discharge for patients who received therapeutic anticoagulation empirically during the course of their hospitalization (and have not already had a negative ultrasound) to determine whether they should be discharged with 3 months of full anticoagulation for provoked VTE vs. 30 days of extended VTE prophylaxis. Prescribers should weigh the risk vs. benefit of each individual case.		

E. VTE prophylaxis should be considered at DISCHARGE for patients with COVID-19 who are at high risk of VTE and with a low risk of bleeding. VTE treatment should be considered at DISCHARGE for patients that were treated inpatient for confirmed or highly suspected VTE.

COVID-19 VTE Prophylaxis and Treatment at DISCHARGE Guidelines	

VTE Prophylaxis – consider for patients with ≥ 1 high risk feature:
 	
High-risk feature:
• Prolonged ICU admission or received full dose anticoagulation while inpatient without confirmed/suspected VTE
• Reduced mobility
• Obesity (BMI ≥ 40kg/m^2)
• Age ≥ 75 years old
• Persistently elevated inflammatory biomarkers at discharge
• History of the following:
  o VTE
  o Cancer
  o Recent major surgery/trauma
  o Heart failure
	Rivaroxaban 10 mg PO daily X 30 days (0 refills) at discharge
	
	Use with caution in patients with a CrCl 15- 30 mL/min; Avoid use in patients with CrCl < 15 mL/min or ESRD
	
	The benefit of prophylaxis must be weighed against the risk of bleeding. Patients at higher risk of bleeding include patients > 85 years old, renal dysfunction (CrCl < 30 ml/min or ESRD), liver failure, bleeding within the last 3 months

VTE Prophylaxis – PREGNANCY	**1st and 2nd Trimester:** Enoxaparin 40 mg SubQ daily X 30 days (0 refills) at discharge **3rd Trimester:** Continue prophylaxis until delivery Enoxaparin 40 mg SubQ daily until 36 weeks After 36 weeks, transition patient to heparin 10000 units SubQ Q12H **Postpartum:** **Breastfeeding:** Enoxaparin 40 mg SubQ daily X 30 days (0 refills) at discharge **Not Breastfeeding:** Rivaroxaban 10 mg PO daily X 30 days (0 refills) at discharge
VTE Treatment – consider full dose therapeutic anticoagulation for confirmed or highly suspected VTE	**CrCl ≥ 30 ml/min:** Apixaban 10 mg PO BID for 7 days followed by 5 mg PO BID* x 90 days at discharge OR Rivaroxaban 15 mg PO BID with food for 21 days followed by 20 mg PO daily with food* x 90 days at discharge **CrCl < 30 ml/min or ESRD on dialysis:** Warfarin (goal INR 2-3) x 90 days at discharge OR Apixaban 10 mg PO BID for 7 days followed by 5 mg PO BID* x 90 days at discharge *A combination of parenteral and oral anticoagulation can be used to complete the initial higher dosing for apixaban (7 days) and rivaroxaban (21 days) for VTE treatment

VI. Treatment Summary Table

Drug	Data	Dose	Renal Dose Adjustment	Monitoring/Considerations
Remdesivir (Gilead investigational drug)	Inhibits SARS-CoV-2 *in-vitro*. Gilead published compassionate use experience including 53 patients (34 patients required mechanical ventilation; 19 required non-invasive oxygen prior to treatment). Median time from symptom onset to treatment was 12 days (9-15 days). 68% (36/53) had improvement in oxygen requirement; 15% (8/53) had worsening in oxygen requirement; 13% (7/53) died (6 receiving invasive ventilation, 1 NIV); 57% (17/30) were successfully extubated after mechanical ventilation; 75% (3/4) successfully stopped ECMO; 47% (25/53) were discharged (8/34 invasive ventilation vs 17/19 NIV); 60% (32/53) experienced AE (rash, 23% LFT changes, diarrhea, renal impairment, hypotension) Beigel JH, et al (NIH Study) published results indicating remdesivir shortened time to recovery in hospitalized patients with COVID-19. Among 1063 patients, the median time to recovery was 11 days for patients treated with remdesivir compared to 15 days for those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). Kaplan-Meir estimates of mortality by 14 days were numerically different but not statistically significant - 7.1% with remdesivir and 11.9% with placebo (HR for death, 0.70; 95% CI, 0.47 to 1.04). Greatest benefit was suggested in patients receiving supplemental oxygen compared to those receiving HFNC, NIV or mechanical ventilation/ECMO. Although this could be related to sample size limitations. Data collection and evaluation ongoing. Goldman JD, et al (Gilead study) reported outcomes in patients hospitalized with severe COVID-19 who received remdesivir 5d vs 10d. A total of 397 patients were included, with nearly 80% of patients requiring NIV, HFNC, or low flow supplemental oxygen in both the 5d and 10d treatment groups. Mechanically ventilated patients were excluded. Clinical improvement at day 14 on a 7 point ordinal scale (adjusting for imbalances in clinical status) was found to be similar between both groups (65% vs 54%, p = 0.14). No differences were observed with discharge (60% vs 52%) or death (8% vs 11%) at 14d suggesting 5d treatment is adequate, during a time of scarce resource. Evaluation of an additional 5600 patients including those who are mechanically ventilated is ongoing. Gilead released preliminary findings of remdesivir 5d vs 10d in patients with moderate COVID-19 disease (evidence of pneumonia without reduced oxygen levels) suggesting 5d of remdesivir had a higher rate of improvement by at least 1 point on a 7 point ordinal scale by day 11 compared to standard of care (76% vs 66% OR 1.65 95%CI 1.09-2.48, p = 0.017)). Treatment with a 10d course vs standard of care trended towards favorable outcomes but was not statistically significant (70% vs 66% OR 1.31 95%CI 0.88-1.95, p = 0.18). Wang Y, et al published results of a randomized, placebo controlled study evaluating remdesivir for the treatment of severe COVID-19 including 10 hospitals in Wuhan China. The study was prematurely halted due to lack of enrollment associated with resolution of the outbreak in China. Although not statistically significant, a numerical trend in shortened time to treatment improvement was observed (21d vs 23d HR 1.23 95% CI 0.87-1.75). Perhaps greatest benefit observed when treatment was started within 10 days of symptom onset (18d vs 23d HR 1.52 95% CI 0.95-2.43). 28d mortality and duration of mechanical ventilation was not significantly different. 66% of patients received steroids, 18% received lopinavir/ritonavir at baseline.	200 mg IV x1 on day 1, then 100 mg IV daily for 5-10 days	Not recommend in adults or pediatric patients (>28 days old) with CrCl < 30 ml/min due to accumulation of sulfobutylether-β-cyclodextrin sodium salt (SBECD), unless benefit outweighs risk.	▪ Given there are limited treatment alternatives to manage COVID-19, the FDA has made remdesivir available under Emergency Use Authorization. Remdesivir has not undergone a thorough review by the FDA as would be done for any other FDA approved medication. The FDA has turned over limited supply to individual states for distribution. The DE Department of Public Health has allocated supply to each health system based on need. Refer to ChristianaCare Remdesivir Emergency Use Authorization (EUA) – Procedure for Approval of Use and Distribution by Pharmacy. ▪ Remdesivir is still available for compassionate use for pregnancy or those < 18 years of age with severe manifestations. Contact Pulmonary Intensivist, ID Physician or ID Pharmacy Specialist for consideration. Research Nurse – Robbie Zent, Debbie Moore, or Jennifer Knox. ▪ Adverse events: infusion related reactions, hepatoxicity ▪ Drug interactions: CYP2C8, CYP2D6, and CYP3A4 substrate. OAPT and PGP substrate. CYP3A4 inhibitor. Clinical relevance has not been established. Co-administration of hydroxychloroquine and remdesivir is not recommended as *in vitro* data demonstrated an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir. Consider utilizing the University of Liverpool COVID-19 Drug Interaction Checker ▪ **Pregnancy:** There are no adequate or well controlled studies of remdesivir use in pregnancy. Use should only be considered if potential benefit outweighs risk to mom or fetus. In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effects on embryofetal development when administered to pregnant animals (rats and rabbits) at systemic at concentrations 4x the exposure in humans using the recommended human dose.

<table>
<tr><th>Drug</th><th>Data</th><th>Dose</th><th>Renal Dose Adjustment</th><th>Monitoring/Considerations</th></tr>
<tr>
<td>Methylprednisolone (Solu-medrol)</td>
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Data on the role of corticosteroids for COVID-19 is variable, without clear guidance on optimal dosing or timing of when to give.

Historical data with SARS-CoV, MERS-CoV, influenza, and RSV suggest potential concerns with corticosteroid use including delayed clearance of virus (prolonged viral shedding), psychosis, diabetes, and increased mortality.

It is well understood at this time that COVID-19 in critically ill patients, in particular those with ARDS, has been associated with an overwhelming inflammatory response and cytokine-related lung injury.

A cohort of 201 COVID-19 patients, 84 progressed to ARDS. Use of steroids was unbalanced with majority of methylprednisolone patients showing pneumonia severity index of class III and IV. No data was presented comparing patients with PSI III/IV who did and did not receive steroids. Patients who received steroids had a clinically significant reduction in the hazard of death among ARDS patients.

A review of 221 patients with COVID-19 in Wuhan, China suggested early corticosteroids use in patients with refractory fever, exacerbation of wheezing, increased interstitial exudation based on chest radiology and high levels inflammatory markers may have clinical benefit. Methylprednisolone 1-2 mg/kg/day for the shortest duration possible was recommended for severely ill patients.

The RECOVERY trial (UK adaptive trial) evaluated the role of dexamethasone for the treatment of COVID-19. Preliminary data suggested significant benefit, therefore ongoing recruitment was stopped. A total of 2104 patients were randomized to receive dexamethasone 6mg once per day (IV or PO) for 10 days and were compared with 4321 patients randomized to usual care alone. Pregnant or breastfeeding patients received prednisolone 40mg or hydrocortisone 80mg twice daily. Among the patients who received usual care alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%). Overall, dexamethasone reduced the 28-day mortality rate by 17% (0.83 [0.74 to 0.92]; p=0.0007) with a significant trend showing greatest benefit among those patients requiring mechanical ventilation. Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14). Complete publication of these results is pending. Dexamethasone was preferred perhaps due to its minimal mineralocorticoid activity and longer half-life. There currently is a national drug shortage of dexamethasone.

The COVID-19 Surviving Sepsis Guidelines recommend:

In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), routine use of corticosteroids is not recommended.
In mechanically ventilated adults with COVID-19 and respiratory failure with severe or refractory ARDS, corticosteroids may be considered

</td>
<td>1 mg/kg IV Q12H

Pulse dose: 500 mg IV daily x 3 days</td>
<td>None</td>
<td>

Given the national shortage of dexamethasone and limited conclusive data supporting dexamethasone over methylprednisolone, the COVID-19 Med Management team continues to support methylprednisolone (po prednisone).
The COVID-19 Med Management Team supports the use of tocilizumab PLUS methylprednisolone based on an internal chart review and CRS management for CAR-T cell therapy. A prolonged duration of methylprednisolone may also be advantageous, similar to the management of ARDS. Each case should be carefully evaluated on a case by case basis, weighing risk vs benefit. Tocilizumab is restricted to ID or Pulmonary Intensivist.
For critically ill patients at risk of or with ARDS consider tocilizumab PLUS methylprednisolone 1 mg/kg IV Q12H with a slow taper over 2-4 weeks with clinical improvement.
For floor patients who have persistent fever, tenuous RR/HR, significantly elevated inflammatory markers with increasing oxygen requirements (moderate/severe disease), consider tocilizumab PLUS methylprednisolone 1 mg/kg IV Q12H with a slow taper over 1-2 weeks with clinical improvement.
Oral prednisone can be used as alternative (methylprednisolone 4 mg IV = prednisone 5 mg PO)
Pulse dose steroids may be considered (500 mg IV daily x 3 days) in critically ill patients who are refractory to other immunomodulator therapy
Patients who require glucocorticoid dose equivalent to ≥20 mg of prednisone daily for greater than 4 weeks with another immunocompromising condition (eg: hematologic malignancy or additional immunosuppressive drug therapy) may be considered for PCP prophylaxis on a case by case basis. Weighing potential risk vs benefit of agents such as sulfamethoxazole/trimethoprim, atovaquone or dapsone should be considered and discussed with ID.
In general, for less severe cases of COVID-19, corticosteroids should be avoided (exception would be management of COPD). Inhaled corticosteroids should be continued for those receiving chronically (eg: COPD, asthma).
Pregnancy: pregnancy category C. Animal data and human data suggest first trimester exposure may increase risk of oral cleft palate and decreased birthweight, although information is conflicting and could be influenced by indication, dose, duration. Steroids have been used when no therapeutic alternative for rheumatic disorders, asthma, N/V in pregnancy for shortest duration possible. Risk vs benefit should be carefully considered in discussion with ID/Pulmonary Critical Care/OB and MFM.

Betamethasone for fetal lung maturation at the discretion of OB and MFM may be considered in conjunction with methylprednisolone for COVID-19 positive pregnant moms

<table>
<tr><th colspan="2">Methylprednisolone 1 mg/kg IV Q12H</th></tr>
<tr><td>Weight (kg)</td><td>Dose</td></tr>
<tr><td>40-44 kg</td><td>40 mg IV Q12H</td></tr>
<tr><td>45-54 kg</td><td>50 mg IV Q12H</td></tr>
<tr><td>55-69 kg</td><td>60 mg IV Q12H</td></tr>
<tr><td>70-89 kg</td><td>80 mg IV Q12H</td></tr>
<tr><td>90-109 kg</td><td>100 mg IV Q12H</td></tr>
<tr><td>110-120 kg</td><td>120 mg IV Q12H</td></tr>
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<tr><td>180-189 kg</td><td>180 mg IV Q12H</td></tr>
<tr><td>190-200 kg</td><td>200 mg IV Q12H</td></tr>
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Drug	Data	Dose	Renal Dose Adjustment	Monitoring/Considerations
Tocilizumab (Actemra)	COVID-19 associated with significant inflammatory response thought to be cytokine mediated including IL-6. Tocilizumab is an IL-6 receptor antagonist that may potentially combat cytokine release syndrome symptoms in severely ill patients. Preliminary data from a small sample study (N=21) found a rapid decrease in fever and reduced oxygen requirements within several days when using tocilizumab. Hazbun ME, et al reported their experience (N=21) with tocilizumab 400 mg IV plus methylprednisolone (125 mg IV q6h x 4 doses, then 60 mg IV q 12h with a slow taper over 10 days) in patients requiring mechanical ventilation. Patients also received higher intensity VTE prophylaxis or treatment and 90% of patients received either HCQ or remdesivir. The median age of patients was 56 (37-85 years), symptom onset to admission was 8 days (3-28 days). 95% (20/21) of patients were successfully extubated with 1 patient remaining a candidate for trach. 86% of patients were discharged and there were zero deaths. CRP was significantly reduced within 48 hours. All patients experienced hyperglycemia, which was managed with insulin. 2 patients developed VAP, 1 patient developed tracheobronchitis, 1 patient was readmitted with reactivation of non TB mycobacterial infection. The authors also noted 6 additional patients who received this combination avoided intubation. Kewan T, et al published a retrospective cohort study describing use of tocilizumab in patients with severe COVID-19. Patients received a single dose of tocilizumab (8 mg/kg or max dose 400 mg). N=28 received tocilizumab, N=23 control group. 94% received HCQ and azithromycin. Systemic steroids were used in both the tocilizumab and control group, although not routine for all patients with variable dosing and durations. Median time to clinical improvement in tocilizumab group was 8 days compared to 13 days in control group. Median duration of mechanical ventilation was 7 days vs 10 days. Median duration of vasopressor support was 2 days vs 5 days (statistically significant). A trend in favorable outcomes with respect to clinical improvement, shorter duration of invasive ventilation, and shorter duration of vasopressor support was observed with tocilizumab. However, the control group was not matched with respect to baseline characteristics and severity of illness. Further validation warranted.	**SUPPLY LIMITED** Initial dose of 400 mg IV X 1 infused over at least 60 minutes; if initial dose not effective, may administer a second dose of 400 mg IV x 1 at least 24 hours later; no more than 2 doses should be given	None	▪ Supply must be reserved for scheduled CAR-T cell patients. ▪ See guidance above for methylprednisolone ▪ Consultation with ID or Pulmonary intensivist required. ▪ IL-6 monitoring not available on-site at Christiana Care. Could be ordered as a send out to Mayo. Follow other surrogate inflammatory markers (eg: CRP, D-dimer, ferritin, fibrinogen, LDH) ▪ Consider monitoring of LFTs. Aminotransferase elevations occurred in 10-40% patients in RA registration trials. ALT elevations often rose 1-3 x ULN 2 weeks after each infusion but decreased to baseline within 2 to 6 weeks. 1-2% of patients experienced > 5 x ULN. ALT elevation dose related and tended to recur but not worsen with repeat dose. Often no change in serum bilirubin or alkaline phosphate levels. https://www.ncbi.nlm.nih.gov/books/NBK548243/ ▪ Serious and potentially fatal infections (including active tuberculosis, invasive fungal, bacterial, viral, protozoal, and other opportunistic infections) have been reported in patients receiving tocilizumab. Most of the serious infections have occurred in patients on concomitant immunosuppressive therapy. If serious infection occurs during treatment, withhold tocilizumab until infection is controlled. Prior to treatment initiation, carefully consider risk versus benefit in patients with chronic or recurrent infections, tuberculosis exposure, history of or current opportunistic infection, underlying conditions predisposing to infection, or patients residing in or with travel to areas of endemic tuberculosis or endemic mycosis. ▪ Possible side effects: increased risk of infection, neutropenia, thrombocytopenia, hepatoxicity, lipid abnormalities ▪ **Pregnancy:** pregnancy category C. Human registry data suggests risk after exposure to tocilizumab of spontaneous abortion (21.7%) and malformation (4.5%) is comparable to general population. Risk of preterm birth reported as 31%, higher than general population. Risk could be associated with underlying disease state and/or exposure to methotrexate. Nearly all data published is in patients exposed to tocilizumab just prior to conception or during first trimester. Experience during 2nd and 3rd trimester lacking. Risk vs benefit should be carefully considered with discussion amongst ID/Pulmonary Critical Care/OB and MFM.
Hydroxychloroquine (Plaquenil) HCQ	The RECOVERY trial (UK adaptive trial) halted enrollment for the HCQ arm given preliminary data suggesting no difference in mortality, length of stay or need for mechanical ventilation when compared to usual care. The HCQ group (N=1542) had an observed mortality rate of 25.7% compared to 23.5% (N=3132) (HR 1.11 95% CI 0.98-1.26, p = 0.10). Formal publication pending. Mehra MR, et al evaluated nearly 96,000 patients from 671 hospitals in 6 different continents through a data registry. Patients who were initiated on therapy while on mechanical ventilation (perhaps the most severely ill) or receiving remdesivir were excluded. Nearly 40% of patients received other antivirals including lopinavir/ritonavir, ribavirin, and oseltamivir. After controlling for multiple confounding factors (age, sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), when compared with mortality in the control group (9·3%), HCQ (18%; HR 1.335, 95% CI 1.223–1.457), HCQ with a macrolide (23.8%; 1·447, 1.368–1.531), chloroquine (16.4%; 1.365, 1.218–1.531), and chloroquine with a macrolide (22.2%; 1.368, 1.273–1.469) were each independently associated with an increased risk of in-hospital mortality. Compared with the control group (0.3%), HCQ (6.1%; 2.369, 1.935–2.900), HCQ with a macrolide (8.1%; 5.106, 4.106–5.983), chloroquine (4.3%; 3.561, 2.760–4.596), and chloroquine with a macrolide (6.5%; 4.011, 3.344–4.812) were independently associated with an increased risk of de-novo ventricular arrhythmia during hospitalization **This study was retracted from the Lancet**	800 mg PO x 1, then 400 mg PO daily x 4 days	None	▪ After careful consideration, the COVID-19 Med Management team NO longer supports the use of hydroxychloroquine for the treatment of COVID-19. ▪ The FDA has revoked the Emergency Use Authorization (EUA) for hydroxychloroquine given the lack of proven benefit, citing the preliminary findings from the RECOVERY trial and reported AE through the FDA Adverse Event Reporting System and Poison Control Center Data System (AAPC, NPDS). ▪ The COVID-19 Med Management Team changed the loading to dose to a single 800 mg x 1 dose to minimize timing issues/coordinate with standard admin times to limit patient entry. (https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html) ▪ Can NOT crush ▪ Extemporaneously prepared oral suspension available (25 mg/mL) ▪ Possible side effects: QTc prolongation, visual changes, neuropathy, GI upset, CNS toxicity, cytopenia, hepatotoxic toxicity (rare) ▪ Risk of hemolytic anemia in patients with G6PD deficiency is documented in hydroxychloroquine package labeling, although data to support this risk is lacking. Routine G6PD deficiency screening is not required prior to treatment in the ACR Rheumatology Guidelines. G6PD testing is a send out with a turnaround time of 2-5 days.

Drug	Data	Dose	Renal Dose Adjustment	Monitoring/Considerations
	journal given concerns about validity of the data source. Cautious interpretation is advised. *In-vitro* study found to be more potent than chloroquine in inhibiting SARS-CoV-2. 400mg PO BID x 1 day, 200 mg PO BID x 4 days recommended. Open label, non-randomized clinical trial found a significant difference in viral shedding at day 6 in patients receiving HCQ (N=20) compared to control group (N=16) (70% vs 12.5%). HCQ 200 mg daily x 10 days was administered. A randomized controlled trial (non-peer reviewed) from China evaluated HCQ PLUS standard of care (oxygen, antiviral agents – not specified, antibacterial agents – not specified, immunoglobulin with or without steroids) vs standard of care alone. Severe/critically ill patients were excluded. In the treatment group (N=31), 71% of patients had fever and cough. In the control group (N=31), 54% had fever and 48% had cough. The authors concluded HCQ was associated with pneumonia improvement on CT (80.6% vs 54.8%), shortened time to fever resolution (2.2 vs 3.2 days, p = 0.008), and shortened time to cough remission (2 vs 3.1 days, p = 0.0016) Mahevas M, et al evaluated the impact of HCQ 600 mg daily (N=84) compared to standard of care (N=89) in hospitalized patients who required oxygen. Patients who received HCQ prior to admission; concurrent tocilizumab, remdesivir, or lopinavir/ritonavir; organ failure; ARDS; ICU on admission; steroids prior to ICU admission were excluded. Median age 60 (IQR 52-68), median time between symptom onset and hospital admission was 7 days. There was no difference observed between 2 groups with respect to transfer to ICU or death at 7d (20.7% vs 21.8%; RR 0.95: 0.47-1.93); death at 7d (3.6% vs 4.8%; RR 0.56: 0.12-2.67); and ARDS at 7d (28.6% vs 23.9%; RR 1.19: 0.66-2.14). 20% of patients that received HCQ also received azithromycin. 9.5% of patients receiving HCQ experienced QTc prolongation. Magagnoli J, et al reported a national cohort study of hospitalized patients with COVID-19 utilizing the VA database in males over the age of 65. HCQ use (N=97) was associated with increased mortality when compared to control (N=158) – 27% vs 11.4% (Adj HR 2.61 (1.1-6.17) p = 0.03). HCQ with azithromycin(N=113) compared to control (N=158) had a trend of increased mortality, although not statistically significant (22.1% vs 11.4%, Adj HR 1.14 (0.56-2.32) p = 0.72). Although baseline covariates were included in the propensity score models, patients who received HCQ had more severe illness described by lower pulse Ox, higher RR, more lymphocytopenia, and higher CRP values on admission. Limitations of this study include cohort of select patient population – males/co-morbidities/older age, did not describe number of doses of HCQ/ azithromycin received, standard of care not described (role of steroids, tocilizumab, other immunomodulatory therapy, and anticoagulation). Although the authors concluded the use of HCQ with or without azithromycin did not reduce the risk of mechanical ventilation, the clinical decision of when to intubate (early vs late in disease process) could have varied at each hospital. Mercuro NJ, reported the risk of QTc prolongation with HCQ used with or without azithromycin (N=90). Those receiving concomitant azithromycin had a greater median (IQR) change in QT interval (23 [10-40]) milliseconds compared to HCQ alone 5.5 [-15.5-34.25]) milliseconds, p = 0.03). Seven (19%) of patients who received HCQ alone developed a prolonged QTc of > 500 milliseconds. Of those who received concomitant azithromycin 11 of 53 (21%) developed a QTc > 500 milliseconds. There was no control group making it difficult to understand if the risk of QTc prolongation was associated with drug therapy or COVID-19 infection alone. Each case should be considered carefully. Weighing risk vs benefit of HCQ.			▪ Risk of QTc prolongation possible. Baseline EKG (or telemetry) recommended. Risk vs benefit should be considered in patients who are at high risk for QTc prolongation. Please refer to section: Other Important Clinical Pearls. ▪ **Pregnancy: h**as been used in pregnancy for other indications – lupus, malaria

Drug	Data	Dose	Renal Dose Adjustment	Monitoring/Considerations
	Tang W, et al evaluated the benefit of HCQ in a multicenter, parallel, open-labeled randomized trial of 150 patients comparing HCQ + standard of care vs standard of care alone. Standard of care could include the use of other antiviral medications. The dose of HCQ was 1200 mg daily x 3 days, then 800 mg daily x 2-3 weeks. Mean days from disease onset to randomization was 16 days. 99% of patients had mild/moderate disease. The authors found no significant differences in negative conversion of COVID-19 PCR by day 28 (85.4% vs 81.3%), rate of symptom alleviation by day 28 (59.9% vs 66.6%), and median time to alleviation of symptoms (19d vs 21d). Improved efficacy of alleviating symptoms was more evident with HCQ when confounding effects of other antiviral agents were removed in a post hoc analysis. A significant improvement in CRP and trend of improvement in lymphocytopenia was observed with HCQ. The authors did not observe any QTc prolongation. Geleris J, et al reported single center observational experience with HCQ. HCQ (N=811) group also received steroids (27%), DOAC/warfarin (9%), tocilizumab (7%) and remdesivir (3%). The matched control group (N=274) received steroids (15%), warfarin/DOAC (9%), tocilizumab (3%) and remdesivir (2%). Utilizing propensity score analysis found no difference in risk of death or intubation (HR 1.04 95% CI 0.82-1.32) with use of HCQ. Overall the mortality rate was 17%. Overall the discharge rate was 74%. Did not include risk of harm in assessment. Authors concluded study results should not be used to rule out either benefit or harm of HCQ given the observational design. Rosenberg ES, et al reported HCQ with or without azithromycin was not associated with a lower in-hospital mortality rate amongst 1438 randomly selected patients in 25 NY hospitals during a 2 week sampling. Adjusting for sex, age, diabetes, chronic lung disease, cardiovascular disease, abnormal chest imaging, RR > 22/min, O2 sat < 90%, elevated creatinine, and AST > 40, the HR for in-hospital death was 1.35 (95% CI: 0.76-2.4) for HCQ + azithromycin vs neither drug and 1.08 (95% CI: 0.63-1.85) for HCQ vs neither drug. Patients receiving HCQ with or without azithromycin were more likely in the ICU or mechanically ventilated compared to neither drug.			
Azithromycin (Zithromax)	A single center, non-comparator, observational study of 80 patients, found rapid clearance of nasopharyngeal viral load (83% negative at day 7, 93% negative at day 8) with the combination of azithromycin and hydroxychloroquine. Although the severity of illness was rather mild in this population (only 15% had fever, 15% required oxygen), more rapid clearance of viral shedding may impact patient response and decrease spread of infection. Molina JM, et al reported on the combination of hydroxychloroquine (600 mg/day x 10 days) and azithromycin (500 mg x 1, 250 mg daily x 4 days) as part of a single center, non-comparator, evaluation of 11 COVID-19 positive patients. The median age was 58.7 (20-77) years. Ten of the 11 patients had fever and required oxygen. 80% of patients still had a COVID-19 PCR that was positive after 5-6 days of therapy. 1 patient died, 1 patient was transferred to ICU and 1 patient experienced QTc prolongation. Small sample makes the validity of this study unclear. Larger, controlled studies warranted. Chorin E, et al shared a letter the editor describing a cohort of 84 patients with COVID-19 who had received azithromycin with hydroxychloroquine. 11% of patients had a QTc interval > 500 msec. The authors observed a prolongation of the QTc from a baseline average of 435 ± 24 ms (mean ± s.d.) to a maximal average value of 463 ± 32 ms (P < 0.001 (one-sample t-test)), which occurred on day 3.6 ± 1.6 of therapy.	IV/PO: 500 mg X 1 day, 250 mg daily x 4 days	None	▪ As of April 27th, the COVID-19 Med Management has agreed the documented benefit of azithromycin does not outweigh the additive risk of QTc prolongation. Azithromycin should only be used in patients who are also being treated for bacterial pneumonia - CAP. ▪ Additive risk of QTc prolongation possible when used with hydroxychloroquine. Baseline EKG (or telemetry) recommended. Risk vs benefit should be considered in patients who are at high risk for QTc prolongation. Please refer to section: Other Important Clinical Pearls. ▪ Azithromycin oral suspension available. ▪ Has been used in pregnancy for other indications – STDs

Drug	Data	Dose	Renal Dose Adjustment	Monitoring/Considerations
Chloroquine	Inhibits SARS-CoV-2 *in-vitro* Uncontrolled study reported results on 100 patients suggesting a decrease pneumonia progression, improved lung findings, and shortening disease course. Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province recommend chloroquine for patients diagnosed as mild, moderate and severe cases of novel coronavirus pneumonia	1000 mg PO x 1, 500 mg PO daily x 4 days	CrCl < 10 ml/min or hemodialysis or peritoneal dialysis: 250 mg PO BID SLED: no data	▪ Can crush ▪ Possible side effects: QTc prolongation, visual changes, neuromuscular toxicity, CNS toxicity (agitation, confusion, extrapyramidal reaction), GI upset, hypoglycemia, cytopenia, increase in LFTs ▪ Has been used in pregnancy for other indications – malaria
Intravenous Immunoglobulin (IVIG)	Limited data exists for the role of IVIG in the management of COVID-19. It is unlikely at this time IVIG would contain COVID-19 antibodies. IVIG may have anti-inflammatory or immunomodulatory effects. A case series of 3 patients from China suggested the use of IVIG given at a dose of roughly 400 mg/kg x 5 days improved clinical symptoms. IVIG has been in short supply. Routine use of IVIG is not encouraged but may be considered on a case by case scenario, perhaps in those patients that are significantly immunocompromised.	**SUPPLY LIMITED** Flebogamma 10% to be used for COVID-19 due to product availability. 500 mg/kg IV daily x 4 days	None	▪ Use ideal body weight (IBW). If actual body weight (ABW) is > 1.2 X IBW, use adjusted body weight. If ABW < IBW, use ABW. Round to nearest 5G. ▪ Privigen (usually preferred formulary product) contains ≤ 25 mcg/mL of IgA. Baseline IgA level is not warranted. Pharmacy subject to change product. ▪ Flebogamma 10% may be used as an alternative and contains ≤ 100 mcg/mL of IgA. Baseline IgA levels may be considered. Processed onsite through the Christiana Care special chemistry lab. Hours are M-F 8-1600 with a turnaround time of about 1 hour. Turnaround time anticipated to longer on weekends and evenings, results may not be back in time for initiation of therapy. ▪ To minimize need to enter patient room, can limit infusion rate titration per protocol to once or twice rather than maximum tolerated rate. ▪ IVIG for the treatment of COVID-19 is restricted to ID or Pulmonary Intensivists
LOPinavir/ RITonavir (Kaletra)	Data to support efficacy for SARS-CoV-1 led to inclusion of lopinavir/ritonavir in Chinese guidelines for SARS-CoV-2 although there is no *in-vitro* data to support lopinavir/ritonavir is active against SARS-CoV-2. . Case reports of decrease oxygen requirements, decrease viral shedding, and clinical improvement with lopinavir/ritonavir have been published. Significant patient variability and multiple confounders (eg: other treatment modalities) makes these findings difficult to interpret. Open trial evaluating hospitalized patients with confirmed SARS-CoV-2 infection found lopinavir/ritonavir to be no different than standard of care with respect to time to clinical improvement (hazard ratio, 1.24; 95% CI, 0.90 to 1.72) and 28 day mortality (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). Increase in GI side effects were more common with lopinavir/ritonavir. Perhaps earlier initiation of therapy could impact efficacy.	400 mg/100 mg PO BID x 10 – 14 days	None	▪ Given concerns with efficacy, need to rule out HIV, and multiple drug interactions, lopinavir/ritonavir is no longer preferred in the management of SARS-CoV-2 infection ▪ If considering for use, need to rule out HIV first ▪ Can NOT crush, solution in short supply. If using oral solution via enteral tube feeds, avoid small bore/dobhoff tubes as they are polyurethane-based, and drug may be incompatible. Larger bore clear OG/NG tubes polyvinyl based and compatible. Gastric administration preferred as decreased absorption possible when delivered to small bowel. ▪ Significant drug interactions (Use University of Liverpool HIV Drug Interactions website) ▪ Caution advised in patients with severe liver impairment ▪ Possible side effects: N/V, diarrhea, LFT abnormalities, hyperglycemia, QTc prolongation, pancreatitis ▪ Has been used in pregnancy for other indications - HIV

VII. Other Important Clinical Pearls

A. Medication administration and discharge planning

1. To minimize healthcare worker exposure, please attempt to use daily dosing or standard administration times for any medication if possible. Examples:
   - CAP: ceftriaxone IV and azithromycin IV/PO once daily
   - Stress ulcer prophylaxis: pantoprazole IV once daily
   - Glucose control: consider subcutaneous insulin every 6 hours over insulin infusion given need for multiple fingerstick when possible
   - Bowel regimen: consider daily dosing when appropriate
2. To minimize exposure, the Christiana Care Outpatient Pharmacy will help facilitate discharge medications for COVID-19 positive patients by delivering via tube station.
   - Provider enters medications for discharge into PowerChart
   - Provider (or nursing or case management) sends Vocera message to “Med-To-Beds Pharmacy Retail” with message “COVID-19 D/C meds [Pt name] and [MRN]

- Pharmacy will supply medication via tube station. Turnaround time approximately 1-2 hours. If required sooner enter "STAT" in the above message.

B. Convalescent plasma
   1. Christiana Care is currently enrolled in the Expanded Access to Convalescent Plasma for the Treatment of COVID-19 through the Mayo Clinic (https://www.uscovidplasma.org/)
   2. Donated plasma will be provided by Blood Bank of Delmarva
   3. Select ID and Pulmonary Critical Care providers are registered to order convalescent plasma. Consult with ID or Pulmonary Critical Care.
   4. As of April 27th, The COVID-19 Med Management team agrees the greatest benefit of convalescent plasma perhaps is when given early, in patients having an increase in oxygen requirements with a significant elevation in inflammatory markers (moderate/severe – very severe infection). There is insufficient data at this time to suggest convalescent plasma should be used exclusively or with tocilizumab, steroids, antiviral medications, hydroxychloroquine, etc. The COVID-19 Med Management team supports use of convalescent plasma with steroids, tocilizumab, and remdesivir. Perhaps convalescent plasma could be used as a steroid sparing treatment approach for those not able to tolerate steroids.
   5. Fully recovered COVID-19 positive patients who have been symptom free for 14 days could be eligible for donating. Those who want to learn more and/or be considered for convalescent plasma donation should contact covidplasma@bbd.org or call 302-737-8405 ext128

C. QTc Prolongation: please note hydroxychloroquine with or without azithromycin is NO longer recommended.
   1. Hydroxychloroquine with or without azithromycin can increase risk of QTc prolongation and should be considered cautiously in high risk patients (eg: concurrent use of other medications that may cause QTc prolongation, electrolyte abnormalities, older age, female gender, LV dysfunction, etc.).
      - Make sure all medications are adjusted for renal impairment
      - Ensure potassium is ≥ 4 mmol/L; magnesium > ≥ 2 mg/dL
      - Consider discontinuation and avoiding all other non-critical QT prolonging medications. Link to QTc prolonging med list: https://www.crediblemeds.org/healthcare-providers/
   2. Relative contraindications for hydroxychloroquine with or without azithromycin
      - History of long QT syndrome
      - Baseline QTc > 500 msec (or > 530-550 msec in patients with QRS > 120 msec)
   3. Obtain baseline EKG. Consider repeating an EKG on day 2 or 3 of therapy or continuous telemetry monitoring for high risk patients (eg: concurrent use of other medications that may cause QTc prolongation, electrolyte abnormalities, older age, female gender, LV dysfunction, etc).
      - Obtain a repeat EKG for patients with bradycardia and increasing PVCs on telemetry
      - If QTc increases by > 60 msec or absolute QTc 500 msec (or > 530-550 msec if QRS > 120 msec), consider discontinuation of azithromycin and/or reduce dose of hydroxychloroquine (eg: 200 mg po daily) and repeat EKG daily. Weigh risk vs benefit.
      - If QTc remains increased > 60 msec and/or absolute QTc > 500 msec (or > 530-550 if QRS > 120 msec), re-evaluate risk vs benefit of continuing therapy and consider consultation with electrophysiologist

D. Bacterial and Fungal Co-Infection
   1. Rawson T, et al analyzed the published literature to assess risk of bacterial or fungal co-infection in patients with coronaviruses. Among a total of 9 studies specific for COVID-19, the incidence of bacterial or fungal co-infection was 8% (62/806). Most studies did not differentiate between ICU or non-ICU patients without a predominate organism identified. Currently, it does not appear that there are specific pathogens to be of increased concern for in COVID-19 positive patients. Given the potential for prolonged hospital exposure, nosocomial infections could be concerning including CLABSI and VAP.
   2. In mechanically ventilated patients with COVID-19 or non-mechanically ventilated patients with concern for super imposed bacterial pneumonia, empiric antibiotic therapy following the Christiana Care Community Acquired Pneumonia and Hospital Acquired Pneumonia Guidelines may be considered. Use of azithromycin over doxycycline for atypical coverage preferred given the potential for anti-inflammatory properties. De-escalation of therapy daily with the shortest duration possible is recommended to minimize risk of adverse drug reactions, *Clostridium difficile* infection, and the development of bacterial resistance.
   3. For non COVID-19 patients with bacterial pneumonia, please use doxycycline as the preferred agent with ceftriaxone in non-critically ill patients to preserve azithromycin supply.

E. MDI and nebulizer treatment
   1. The hospital supply of MDIs is limited (albuterol especially)-alternatives are being explored daily; ideal patients for MDI use include COVID-19 positive or suspected patients NOT on mechanical or non-invasive ventilation; if these patients are on nebulized medications-they are considered airborne, but if they are on inhalers, they are considered droplet precautions. This could save us PPE.
   2. As of March 30, 2020, P&T has approved the following restrictions/recommendations:
      - Restrict use of albuterol inhalers for COVID-19 positive or PUI who are NOT mechanically ventilated (invasive or non-invasive)
      - Mechanically ventilated patients that are COVID-19 positive or PUI continue to use nebulizer therapy.
      - All other patients not meeting one of the above restrictions will get nebulizer therapy only. Pharmacists can auto-convert MDI orders to nebs in these patients.

F. ACE inhibitors/ARBs
    1. Hypothetical harm: COVID-19 binds to target cells through angiotensin – converting enzyme 2 (ACE2) which is expressed in the epithelial cells of lung, intestine, kidney and blood vessels. An increase in expression or upregulation of ACE2 would be anticipated in patients being treated with an ACEi or ARB for the management of diabetes or hypertension. It has been hypothesized that patients with diabetes or hypertension being treated with an ACEi or ARB could be at increased risk of developing a more severe or fatal COVID-19 infection.
    2. Hypothetical benefit: ACEi/ARB may have protective effect against lung damage or paradoxical effect on virus binding.
    3. Li J, et al published a retrospective, single center case series of 1178 patients in Wuhan China. Of the 1178 patients, the overall in-hospital mortality was 11%. 362 had hypertension in which 115 (31.8%) were taking ACEi/ARB. The in-hospital mortality in patients with hypertension was 21.3%. The percentage of patients with hypertension taking ACEi/ARB did not differ between those with severe vs non-severe infections (32.9% vs 30.7%, p = 0.645)) or survivors vs non-survivors (27.3% vs 33%, p = 0.34).
    4. Zhang P, et al published a retrospective, multi-center study evaluating 1128 adult patients with hypertension and COVID-19, of which 188 patients were taking an ACEi/ARB. In a propensity score-matched analysis followed by adjusting imbalanced variables in mixed-effect Cox model, a lower mortality risk was observed in those who received ACEi/ARB vs those who did not (adj HR 0.37; 95% CI, 0.15-0.89, p = 0.03). Further subgroup propensity score matched analysis found, compared to use of other antihypertensive drugs, ACEi/ARB use was also associated with decreased mortality (Adj HR 0.3; 95% CI, 0.12-0.70; p = 0.01). The authors concluded the study interpretation needs be carefully considered with potential for residual confounders, but it is unlikely that in-hospital use of ACEi/ARB is associated with increased mortality risk.
    5. American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), European Society of Cardiology (ESC) recommend against stopping ACEi/ARB therapy in those who are currently prescribed for other indications and/or mortality benefit.

G. NSAIDs vs acetaminophen
    1. Hypothetical link between NSAID use and aggravation of COVID-19 symptoms related to increase expression of ACE2.
    2. As of March 19th, 2020, the FDA stated there is no scientific data to support the hypothesis that use of NSAIDs could worsen COVID-19 symptoms. In general, the preferred anti-pyretic would be acetaminophen. COVID-19 is not currently a contraindication to NSAID use.

H. Statins
    1. Limited evidence supports for or against statin use in patients with viral pneumonia. There are no large-scale observational or randomized studies specific to COVID-19 evaluating the role of statin therapy. It is important to note there is no harm in continuing a statin, unless the patient is experiencing rhabdomyolysis.
    2. The American College of Cardiology encourages the continuation of a statin if patient is currently receiving for clinical atherosclerotic cardiovascular disease, diabetes or those at high risk for ASCVD.

I. Drug Shortages: the list of medications on critical shortage is being evaluated daily. Portal announcements and communication with key stakeholders is ongoing to identify alternatives. Refer to Formulary – CCHS Links – COVID Medication Stock for more information.

J. **Post-exposure prophylaxis is currently NOT recommended**. Boulware DR, et al enrolled 821 asymptomatic participants exposed to COVID-19 to randomly receive hydroxychloroquine or placebo. Within 4 days of a high or moderate risk exposure, the use of hydroxychloroquine as prophylaxis did not reduced the incidence of new COVID-19 infection (11.8% with hydroxychloroquine vs 14.3% with placebo 95% CI -7.0 to 2.2, p = 0.35).

K. Other treatment approaches
    1. Oseltamivir, baloxavir, other protease inhibitors, ascorbic acid, and nitazoxanide have been considered for the treatment of COVID-19. As of April 7, 2020, there is insufficient data to support benefit with these treatment approaches. The Christiana Care COVID-19 Medication Management Team will evaluate newly published data weekly and adjust recommendations accordingly.
    2. Some over the counter and alternative medications have been hypothesized to be beneficial in the management of COVID-19. Please click here for more information. In the absence of demonstrated benefit, the COVID-19 Med Management team does NOT recommend routine use of these alternative treatment approaches.
    3. Ivermectin: an international, multicenter, observational, propensity score matched case-controlled study using registry data evaluated the role of ivermectin 150 mcg/kg x 1 dose at the discretion of the provider and observed a decrease in mortality. A total of 704 patients in each treatment arm (ivermectin vs control) were included. Please note this article has not been peer reviewed or formally published. Although a trend towards mortality benefit of ivermectin could be considered, the COVID-19 Med Management team does not currently recommend routine use of ivermectin. Ivermectin is currently non-formulary and requires discussion with ID provider.

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