Positive COVID-19 (SARS-Coronavirus-2)

Mild/Uncomplicated Disease
- URTI
- LRTI
- No oxygen requirement

If risk factors: CV disease, HTN, age >55-60, underlying lung disease, smoker, chronic liver disease, DM, CKD, cancer, HIV, transplant, on steroids or immunosuppression, chemotherapy, SNF/LTAC residents, obesity, pregnancy:
  - Observe
  - Low threshold to start therapy

Considered for first line:
Hydroxychloroquine (HCQ) 400 mg po BID day 1, then 200 mg po BID days 2-5

Considered for second line:
HCQ + azithromycin, only if low cardiac risk and QTc < 450. See table below for details.
OR Kaletra 400/100 mg po bid for 5-10 days

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Considered for cytokine release syndrome:
Tocilizumab via ID approval (see criteria and discussion in table below)

There is no current evidence from RCTs to recommend any treatment for patients with suspected or confirmed COVID-19. All agents described are considered investigational or for compassionate use, and decision to use these should be made only with close attention to the patient’s clinical status, comorbidities, and interacting medications. Use of any of these agents for COVID-19 requires ID approval (call 252-814-4296).

Moderate Disease
- LRTI: Cough, SOB, hypoxia, radiographic changes
- Oxygen requirement (O2 sat <93% on room air)

Severe Disease
- LRTI
- Mechanical ventilation
- Cytokine Release Syndrome
  - ARDS
  - Septic Shock
  - Capillary leak
  - Arrhythmias
  - Renal failure
  - Transaminitis
  - Coagulopathy
  - HLH

No risk factors:
Supportive care

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Vidant Health COVID-19 Treatment

General COVID-19 Information:

1. Incubation period ~5 days (ranges from 2-14 days).
2. Frequently signs and symptoms at illness onset include fever (83-98%), dry cough (76-82%), and myalgia/fatigue (11-44%). GI symptoms have also become a common occurrence (anorexia, diarrhea, vomiting, abdominal pain, anosmia, dysgeusia). In one report, 10% (n=20) presented without digestive or respiratory symptoms, 3% (n=7) with digestive symptoms but without respiratory symptoms (all except 1 did have fever), 42% (n=85) with respiratory symptoms but without digestive symptoms, and 45% (n=92) with both respiratory and digestive symptoms.
3. CXR have shown bilateral involvement in most patients. CT patterns have revealed patchy infiltrate, bilateral disease, and have been consistent with viral infection.
4. Potential for clinical deterioration during second week of illness.
5. Co-infection of COVID-19 with other viruses and bacteria is possible.
6. False negative COVID-19 results are possible. Poor quality of specimen can be a reason for false negative.
7. COVID-19 is also referred to as SARS-Coronavirus-2 or SARS-CoV-2.

Recommended Labs and Monitoring:

1. Daily: CBC with differential (follow lymphopenia) and complete metabolic panel (includes LFTs)
2. To help rule out bacterial co-infection: Procalcitonin
3. For risk stratification and worry of cytokine release syndrome: LDH, troponin, CPK, D-dimer, CRP, ESR, triglycerides, ferritin, and fibrinogen. May consider trending these as appropriate.
   a. Ideally would obtain IL-6 levels but this lab is a send out from Vidant that will take 4-7 days to result so we are not currently recommending it.
5. HIV test
6. Pregnancy test
7. Baseline and daily EKG (cardiology recommends daily EKG whether on hydroxychloroquine monotherapy or combination therapy with azithromycin)
   • If QTc > 500 may need to avoid QT prolonging drugs (hydroxychloroquine, azithromycin, and/or Kaletra)
   • If QTc 450-500, consider hydroxychloroquine monotherapy and discontinue other QT prolonging drugs. Follow up EKG after hydroxychloroquine loading dose.
   • If QTc increases by >25% on therapy, may need to consider stopping therapy
   • If high risk for QT prolongation consider telemetry monitoring to avoid frequent EKG technician exposure
   • Consider cardiology input if high risk for QT prolongation
   • Recommend controlling all factors to mitigate risk of QTc increase, such as electrolytes (keep K > 4 and Mg > 2), bradycardia, concomitant meds that could be held for a few days, etc

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## Drug Information:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Information</th>
</tr>
</thead>
</table>
| **Hydroxychloroquine (HCQ)** |  - IDSA guideline recommendation: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine in the context of a clinical trial. (Knowledge gap). See guideline for data summary.  
  - Increases endosomal pH required for virus/cell fusion and interferes with the glycosylation of cellular receptors of COVID-19. Immunomodulating activity as well (including reduction of cytokines such as IL-6).  
  - Analog of chloroquine but better tolerated, less drug-drug interactions, and more potent  
  - Pediatric dosing: 6.5 mg/kg/dose (max 400 mg) q12h x 2 doses then 3.25 mg/kg/dose (max 200 mg) q12h x 8 doses (5 days total duration)  
  - Duration can be extended from 5 days for severe cases, but should be no longer than 10 days total.  
  - Mainly hepatically metabolized, long half-life (40 days), low urinary excretion (10-25%). Unlikely to be dialyzed, minimal data. Unlikely to be removed by CRRT (large Vd and primarily non-renal elimination). No dosing adjustments for renal/hepatic impairment or obesity are suggested at this time.  
  - Pharmacy has a compounded suspension if not able to take tablets  
  - Potential for hemolytic anemia which may be severe in ethnic groups at higher risk for G6PD deficiency (Asian or Mediterranean descent, maybe African descent). G6PD testing needed but should not delay starting therapy.  
  - Adverse effects can include: dizziness, headache, nausea, vomiting, LFT abnormalities, QTc prolongation, cytopenias, retinopathy, etc. Risk of QTc prolongation increased with concomitant azithromycin. |
| **+/− Azithromycin to HCQ** |  - IDSA guideline recommendation: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin “only” in the context of a clinical trial. (Knowledge gap). The guideline panel used the word “only” in recommendations about therapeutic agents with higher uncertainty and/or more potential for harm. These recommendations acknowledge the current “knowledge gap” and aim at avoiding premature favorable recommendations for potentially ineffective or harmful interventions. See guideline for data summary.  
  - One theory is it is possible that azithromycin is playing some role in mRNA translation of the virus (post-insertion replication step for this ssRNA virus).  
  - If used, preference is to use Zpak dosing (500 mg day 1 then 250 mg days 2-5) and oral formulation of azithromycin. Can crush tablets as needed. If absolutely need, IV can be used at 500 mg, because prepared as 500 mg mini bag plus.  
  - Concern for additive QTc prolongation when added to HCQ. Recommend daily EKG and discontinuing azithromycin if QTc > 450 (see more details in monitoring section above). |
| **Tocilizumab** |  - IDSA guideline recommendation: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap). The guideline panel used the word “only” in recommendations about therapeutic agents with higher uncertainty and/or more potential for harm. These recommendations acknowledge the current “knowledge gap” and aim at avoiding premature favorable recommendations for potentially ineffective or harmful interventions. See guideline for data summary. |
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- Monoclonal antibody that binds to IL-6 receptor and inhibits IL-6 mediated cytokine storm. At Vidant, IL-6 is a send out lab to LabCorp and would take 4-7 days to get the result so not recommending this at this time.
- After review of existing COVID-19 and non-COVID-19 data (please see separate tocilizumab COVID document), current Vidant proposed dosing is as follows (requires ID approval):
  - Dose: 4 mg/kg based on actual body weight (max dose 800 mg). Round dose to nearest vial size (either 80 mg or 200 mg vials depending on availability – will have to check with pharmacy at time of order). After patient receives tocilizumab repeat inflammatory markers at 12 and 24 hours. Consider repeat dosing in 24 hours if CRP at 24 hours does not drop 50% or greater than baseline pre-dosing CRP level AND patient has persistent respiratory failure with no improvement in the clinical parameters for which the initial dose was given (clinical parameters include P/F ratio, hemodynamics, or persistent fever).
  - Criteria for use can be found in the separate tocilizumab COVID document
- Risk of latent TB reactivation, so suggest Quantiferon-TB Gold Plus (but would not wait on result as it might take 3-4 days to return)
- Unlikely to removed by HD/CRRT. Long half-life and larger Vd. No recommended renal adjustments, eliminated through linear/non-linear pathways.
- Initiation in patients with an absolute neutrophil count below 2000/mm(3), platelet count below 100,000/mm(3), or ALT or AST above 1.5 times ULN is not recommended, but consider risk versus benefit in those with severe or life-threatening cytokine release syndrome and cytopenias or in the presence of elevated liver enzymes.
- Check for drug-drug interactions
- Adverse effects can include cytopenias, GI perforation, hepatitis, infusion reaction, bacterial infection
- VMC GPO inpatient cost of 200 mg vial is $1081.65. Supplies are limited.

### Lopinavir/ritonavir (Kaletra)
- IDSA guideline recommendation: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir “only” in the context of a clinical trial. (Knowledge gap). The guideline panel used the word “only” in recommendations about therapeutic agents with higher uncertainty and/or more potential for harm. These recommendations acknowledge the current “knowledge gap” and aim at avoiding premature favorable recommendations for potentially ineffective or harmful interventions. See guideline for data summary.
- HIV protease inhibitor that inhibits viral replication that was noted to have some in vitro activity against SARS-CoV-1
- No dosing adjustments for renal or hepatic dysfunction
- Safe in pregnancy
- Liquid formation exists (crushing tablets is not ideal because can have significantly lower drug exposure)
- Check for drug-drug interactions (strong CYP3A4 inhibitor)
- HIV testing needed
- Adverse effects can include GI upset including n/v, transaminitis, metabolic changes, QTc prolongation, severe cutaneous drug eruptions

### Remdesivir (GS5734)
- Broad-spectrum antiviral nucleotide prodrug with potent in vitro activity against a range of RNA viruses including Ebola virus, Marburg, MERS-CoV, SARS-CoV, respiratory syncytial virus,
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<table>
<thead>
<tr>
<th>Drug Considerations</th>
<th>Nipah virus, and Hendra virus. The mechanism of action of remdesivir is premature termination of viral RNA transcription.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• Gilead cannot keep up with demand and has shut down emergency/compassionate use programs</td>
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<td>o Exception: Emergency use is still available for patients who are pregnant or &lt;18 years old with confirmed cases and severe disease. Though this is emergency use it may still take 24-48 hours to receive.</td>
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<td>• Other Gilead options for obtaining drug</td>
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<td>o Expanded Access Program: Company still has to approve drug use. Will require paperwork and has to go through IRB. Will likely not receive drug quickly. Information on how to enroll still TBD.</td>
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<tr>
<td></td>
<td>o Clinical trial enrollment: Vidant has not been selected as a clinical trial site as of now.</td>
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<td></td>
<td>o Either option means submitting patient data for research purposes.</td>
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<tr>
<td>Convalescent plasma</td>
<td>• IDSA guideline recommendation: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. (Knowledge gap). See guideline for data summary.</td>
</tr>
</tbody>
</table>

**General Drug Considerations:**

1. If no contraindications, continue **statins** or consider starting in those with a guideline indication for one.
2. Do not need to stop home **ACEI/ARB** therapy, unless there is another compelling reason.
3. **Steroids** are generally not recommended, unless there is another compelling indication. Compelling indications for use of steroids may include COPD, shock, ARDS, hyperinflammation, etc. The IDSA guideline recommends: Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence). Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap). See guideline for data summary.
4. Avoid starting new prescriptions for **NSAIDs**. Can see IDSA guideline for some discussion of NSAIDs.
5. Use **inhalers** over nebulizers.
6. Many institutions are noting that patients with COVID-19 tend to have higher than normal baseline triglyceride levels secondary to an HLH-type syndrome and many institutions are avoiding discontinuation of their **propofol** infusions in these patients until TG levels are closer to 750/1000 mg/dL. This would avoid having to change to an alternative/less desired sedative agent in these patients (ie: benzodiazepines which are less than ideal due to the longer elimination time and association with longer intubation times). It is recommended to continue to monitor these patients closely for any signs and symptoms of PRIS while on propofol therapy.
7. Due to the frequency of every one hour blood glucose checks for patients who are receiving intravenous **insulin** with Endotool, it would be preferred to manage these patients with basal/bolus regimen of insulin if possible or tolerate a blood glucose that is slightly above our goal. This will aide in decreasing the number of times the nurse has to enter the room to obtain a finger stick for insulin drip titrations.
8. In patients who are intubated **scheduled eye care** is administered in the form of Clear Eyes solution and petrolatum ointment both given every 4 hours alternating which results in an eye drop being administered every 2 hours to aide in lubrication secondary to dryness that results from the ventilator. In an effort to reduce nursing exposure and since most patients should be maintained at a light level of sedation, it is recommended to omit the petrolatum ointment and use only the Clear Eyes solution in these patients with a frequency of ‘four times day’ or ‘three times a day’ with the specific times correlating with other medication administration times.

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9. In an effort to minimize aerosolization during extubation consider strategies of prevention of post extubation coughing and gagging. IV lidocaine 1 mg/kg (max 100 mg) can be given 3-5 minutes prior to extubation or 1 mg/kg of 2% lidocaine solution can be instilled intratracheally into the outer aperture of the ETT 5 minutes prior to extubation to blunt the post extubation cough response. In patients with heart block/bradycardia without a pacemaker AVOID IV lidocaine administration and can consider utilization of 0.5 mg/kg of 2% lidocaine solution via the ETT in these patients.

10. Due to increased risks for coagulopathy in COVID-19 patients, chemical prophylaxis should be utilized in these patients. If a patient has elevations in their D-dimer, this should prompt the provider to evaluate for presence of a clot via ultrasound of the extremities and start therapeutic anticoagulation if a clot is found. If the patient has no contraindications to use, the recommendation would be to treat with enoxaparin 1mg/kg Q12hr over heparin continuous infusion due to the ease of dose (twice a day) and reduced monitoring associated with use. If patient’s renal function precludes the use of enoxaparin consider utilization of a concentrated heparin drip for management. Reports from NYC Health + Hospitals Bellevue indicate higher number of DVTs in patients with elevated D-dimers, which has led to more routine lower extremity ultrasounds to evaluate for clots.

References:

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