Vidant Health COVID-19 Treatment

Positive COVID-19 (SARS-Coronavirus-2)

Mild/Uncomplicated Disease

- URTI
- LRTI
- No oxygen requirement

Supportive care

If risk factors for severe disease, low threshold to start therapy

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:

Consider (see drug info table below for help deciding):

- Convalescent plasma
- Remdesivir
- Baricitinib clinical trial (not yet open for enrollment but very soon)
- MK-4482 clinical trial (not yet open for enrollment)

If outpatient:

- BLAZE-1 outpatient clinical trial
- Bamlanivimab via EUA (not yet available for use but very soon)
- Remdesivir outpatient clinical trial (coming soon)

Requiring O2

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

Consider (see drug info table below for help deciding):

- Dexamethasone
- Remdesivir
- Convalescent plasma
- Sirukumab clinical trial
- Baricitinib clinical trial (not yet open for enrollment but very soon)
- MK-4482 clinical trial (not yet open for enrollment)

Mechanically Ventilated

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

Consider (see drug info table below for help deciding):

- Dexamethasone
- Sirukumab clinical trial
- Ruxolitinib clinical trial
- Remdesivir (but less likely to have an impact at this stage of disease)

Decision to use these agents should be made only with close attention to the patient's clinical status, comorbidities, interacting medications, and with the understanding that there are limited/controversial data available to support use. Use of any of these agents for COVID-19 (besides dexamethasone) requires ID or investigator approval (details below).

Last updated November 11, 2020 – this document is subject to frequent revisions
Updates since the October 29, 2020 version are noted by the red font color

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Drug Information:

Remdesivir (GS5734)	• IDSA guideline recommendation: Among hospitalized patients with severe COVID-19, the IDSA panel suggests remdesivir over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence). Severe illness is defined as patients with SpO_2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO. For consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply), remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or extracorporeal mechanical oxygenation (ECMO). Among patients with severe COVID-19 on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, low certainty of evidence). In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days. In patients with COVID-19 admitted to the hospital without the need for supplemental oxygen and oxygen saturation >94% on room air, IDSA suggests against the routine use of remdesivir. (Conditional recommendation, Very low certainty of evidence). See guideline for data summary.
	• NIH recommends prioritizing use for patients who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO.
	• Mechanism: 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, Nipah virus, and Hendra virus. The mechanism of action of remdesivir is premature termination of viral RNA transcription.
	• Options for obtaining remdesivir:
	  ○ FDA approved on October 22, 2020 and available via wholesaler
	  ○ Emergency Use Authorization (EUA) still required for hospitalized children weighing 3.5 kg-40 kg or hospitalized children less than 12 years of age
	• **ID approval by any ID attending is required. Call 252-814-4296 between the hours of 0800 – 1700 seven days a week. Cortext or page (252-329-6610) Dr. Paul Cook between the hours of 1700 - 2100 seven days a week. Any request for remdesivir after 2100 will need to be approved and started the following morning. For pediatric patients please contact Dr. William Alex Dalzell, Dr. Salma Syed, or Dr. Yamini Mandelia.**
	• **Greatest benefit may be in patients early in the course of disease (<7 days of symptoms).**
	• Adult dosing: Suggested dose is a single loading dose of remdesivir 200 mg IV on Day 1, followed by once-daily maintenance doses of remdesivir 100 mg IV for 4 days. Remdesivir is to be administered via IV infusion in a total volume of up to 250 mL 0.9% saline. Doses of 200 mg will be infused over 2 hours and doses of 100 mg will be infused over 1 hour.
	• Monitoring: Suggest daily renal and hepatic function monitoring
	• On June 15, 2020: The FDA's Intergovernmental Affairs (IGA) team would like to bring your attention [fda.gov] to a newly discovered potential drug interaction related to the investigational antiviral drug remdesivir. Based on a recently completed non-clinical

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	laboratory study, the FDA is revising the fact sheet for health care providers that accompanies the drug to state that co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended as it may result in reduced antiviral activity of remdesivir. The agency is not aware of instances of this reduced activity occurring in the clinical setting but is continuing to evaluate all data related to remdesivir. • Coming soon: Outpatient clinical trial with 3 days IV remdesivir.
Convalescent plasma	• IDSA guideline recommendation: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma 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. • Please go to the Greenville blood connection website for a link for patients who want to be assessed as a donor. Donors are needed. • Beginning 8/28/20 at 11:59PM convalescent plasma can be given by anyone without consent for participating in a research protocol (access changed from expanded access program to EUA). It will require ID approval and distribution of an FDA fact sheet. **Call ID at 252-814-4296 between the hours of 0800 – 1700 seven days a week. Cortext or page (252-329-6610) Dr. Paul Cook between the hours of 1700 - 2100 seven days a week. Any request after 2100 will need to be approved and started the following morning. ID approval can be given by any ID attending.** • Greatest benefit may be in patients early in disease (~4 days from diagnosis or ~7 days of symptoms.
Sirukumab Clinical Trial CNTO136COV2001	• Taking place at VMC only • The purpose of the study is to evaluate the clinical response of sirukumab in addition to standard of care treatment compared to placebo plus standard of care treatment in person with COVID-19. • PI: Dr. Paul Cook • Primary Objective: To evaluate the clinical response of sirukumab (administered as a single IV dose) + standard of care compared to placebo + standard of care in confirmed severe or critical COVID-19 disease • Inclusion Criteria: 1. Male or female ≥18 and <85 years of age. 2. Hospitalized. 3. Has laboratory-confirmed SARS-CoV-2 infection as determined by real time-PCR or any other commercial or public health assay, at any time before randomization. 4. Evidence of infiltrates by chest X-ray, chest CT or chest auscultation (rales, crackles). 5. Severe or critical COVID-19 disease, defined as: • Not receiving supplemental oxygen and having blood oxygen saturation ≤ 93% sustained for 5 minutes • Severe disease: Requires supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device (ie, above pre-COVID baseline oxygen requirement, if any, by the participant).

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- Critical disease: Requires supplemental oxygen delivered by nonrebreather mask or high-flow nasal cannula OR use of non-invasive or invasive ventilation OR requiring treatment in an ICU:
  *PaO2/FiO2 ratio <300 mmHg while on invasive mechanical ventilation (with invasive mechanical ventilation for less than 24 hours prior to screening) (corresponds to category 5 on the 6-point ordinal scale).
  *On ECMO for <48 hours at time of screening

6. Informed consent must be obtained from the participant (or their legally acceptable representative must sign based on local regulations) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

- <u>Exclusion Criteria</u>

1. On invasive mechanical ventilation for >48 hours at time of screening.
2. Meets local or global criteria to not receive mechanical ventilation or has designated themselves as DNR per a living will.
3. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned dose of study intervention.
4. Current confirmed or high suspicion for pulmonary embolus, hemodynamic significant pericardial effusion, myocarditis, or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification AND/OR current evidence of active cardiac ischemia.
5. Currently active clinically significant and uncontrolled arrhythmia.
6. Liver function impairment defined as Child Pugh Class B/C based on medical history.
7. Has congenital bleeding diathesis based on medical history.
8. Has a history of chronic respiratory condition (ie, asthma, COPD, cystic fibrosis, fibrotic lung disease) that requires home oxygen supplementation, supportive non-invasive ventilation, or is status/post lung volume reduction surgery (LVRS).
9. On renal replacement therapy (defined as peritoneal dialysis or hemodialysis).
10. Screening laboratory test result as follows:
- Absolute neutrophil count (ANC) <1.0 × 103 cells/µL (SI: <1.0 × 109 cells/L)
- Platelet count <50 × 103 cells/µL (SI: <50 × 109 cells/L)
- Estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m2
- Bilirubin >2xULN unless bilirubin rise is due to Gilbert's syndrome or of nonhepatic origin
- ALT >5xULN
- Prothrombin time (PT)/international normalized ratio (INR) >1.5xULN or activated partial thromboplastin time (aPTT) >1.5xULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder).
11. Pregnant or breastfeeding, unless in the opinion of the investigator, the benefit outweighs the risks.
12. Has active hepatitis B or C infection or HIV/AIDS based on medical history and/or concomitant medication.
13. Known active TB, history of incompletely treated TB, suspected or known extrapulmonary TB based on medical history and/or concomitant medication.
14. Evidence of active bacterial (including but not limited to bacterial pneumonia), fungal, viral or opportunistic infection (other than SARS-CoV-2).

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	15. Known allergies, hypersensitivity, or intolerance to sirukumab or its excipients or to other monoclonal antibodies (refer to the IB). 16. Unlikely to be able to complete the study (including but not limited to: likely to be transferred to another hospital, surgery is anticipated to be necessary, in the opinion of the investigator unlikely to survive for >48 hours from screening). 17. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. 18. Participants on chronic (for >3 months in duration) prednisone in a dose higher than 10 mg/day or other oral corticosteroids at an equivalent dose for any condition or taking any disallowed therapies as noted in Section 6.8, Concomitant Therapy before the planned dose of study intervention. 19. History of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence). 20. Organ transplant recipient on immunosuppressant therapy.
Ruxolitinib Clinical Trial INCB 18424-369 (RUXCOVID-DEVENT)	• Taking place at <u>VMC only</u> • The <u>purpose</u> of this study is to evaluate the efficacy and safety of ruxolitinib in the treatment of participants with COVID-19–associated ARDS who require mechanical ventilation. • <u>PI: Dr. Darla Liles</u> • <u>Sub-Investigators:</u> Dr. Paul Bolin, Dr. Mark Bowling, Dr. Badih Kabchi, Dr. Charles Knupp, Dr. Matthew Ledous, and Dr. Judith Ugale-Wilson • <u>Primary Objective:</u> To evaluate the 28-day mortality rate of ruxolitinib 5 mg BID + standard of care therapy and ruxolitinib 15 mg BID + standard of care therapy compared with placebo + standard of care therapy, in participants with COVID-19–associated ARDS who require mechanical ventilation. • <u>Inclusion Criteria:</u> 1. Participant must provide informed consent before any study specific assessment is performed; informed consent may be obtained from a health care proxy where appropriate and/or institutionally approved method of consenting when applicable (verbal consent) as defined in their local consent form. 2. Male or female participants aged ≥ 12 years. 3. Participants with coronavirus (SARS-CoV-2) infection confirmed ≤ 2 weeks prior to randomization by any test with local regulatory approval. 4. Participants who are currently hospitalized, intubated and receiving invasive mechanical ventilation due to COVID-19–associated ARDS. Participants must have confirmed PaO2/FiO2 of ≤ 300 mmHg within 6 hours of randomization. 5. Participants with lung imaging showing bilateral or diffuse pulmonary infiltrates on chest x-ray or CT scan. • <u>Exclusion Criteria:</u> 1. Known history of hypersensitivity to any drugs or metabolites of similar chemical classes as ruxolitinib. 2. Presence of severely impaired renal function defined by estimated creatinine clearance < 15 mL/min measured or calculated by Cockroft-Gault equation or calculated by the updated bedside Schwartz equation. Participants must not be receiving CRRT or intermittent hemodialysis at screening.

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	3. Suspected active uncontrolled bacterial, fungal, viral, or other infection (besides COVID-19). 4. Known active TB infection. 5. In the opinion of the investigator, unlikely to survive for > 24 hours from randomization. 6. Currently receiving ECMO, nitric oxide therapy, or high-frequency oscillatory ventilation. 7. Participant may not be sharing a ventilator, or coventilating, with any other patient. 8. Participants who are on long-term use of antirejection or immunomodulatory drugs (eg, JAK inhibitors, IL-6/IL-6R/IL-1RA or IL-1β inhibitors). Note: Participants who are taking tacrolimus, cyclosporine, and mycophenolate mofetil are eligible for study. 9. Treatment with anti–IL-6, IL-6R, IL-1RA, IL-1β, or GM-CSF antagonists, or a BTK inhibitor, within 7 days of randomization. 10. Treatment with a JAK inhibitor within 30 days of randomization. 11. Concurrent participation in any other interventional clinical study or experimental treatment for COVID-19 or ARDS. 12. ALT or AST > 5 × ULN detected within 24 hours at screening (according to local laboratory reference ranges). 13. Participants who have known evidence of liver cirrhosis (Child-Pugh A to C). 14. Active metastatic malignancy within 1 year of screening, unless with medical monitor approval. 15. ANC < 1.0 × 109/L at screening (according to local laboratory). 16. Platelet count < 50 × 109/L at screening (according to local laboratory). 17. Pregnant or nursing (lactating) women. 18. Females of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception as defined below, throughout the study and for up to 30 days after stopping treatment.
Baricitinib Clinical Trial I4V-MC-KHAA (COV-Barrier)	• **NOT YET OPEN FOR ENROLLMENT. Likely to open in next week or so.** • Study: I4V-MC-KHAA (COV-Barrier); A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Study of Baricitinib in Patients with COVID-19 Infection • PI: Dr. Paul Cook • Mechanism: Inhibitor of JAK1 and JAK2. Baricitinib is proposed to reduce an inflammatory response and have potential antiviral activity against COVID-19. This study will determine if baricitinib given orally once a day for up to 14 days will have a positive impact on disease progression in persons with COVID-19 infection. Data to determine efficacy will include the proportion of patients who die or require additional supportive measures for breathing/oxygenation. • Inclusion Criteria: 1. Are male or female patients from 18 years of age (inclusive), at the time of enrollment 2. Hospitalized with coronavirus (SARS-CoV-2) infection, confirmed by polymerase chain reaction (PCR) test or other commercial or public health assay in any specimen 3. Have evidence of pneumonia (SpO2 <94 or PaO2/FiO2 [or SpO2/FiO2] ratio <300 mmHg or chest imaging findings consistent with pneumonia), OR have evidence of active COVID infection (with clinical symptoms including any of the following: fever,

	vomiting, diarrhea, dry cough, tachypnea defined as respiratory rate >24 breaths/min) 4. Have indicators of risk of progression: at least 1 inflammatory markers >ULN (CRP, D-dimer, LDH, ferritin) with at least 1 instance of elevation >ULN within 2 days before study entry • Exclusion Criteria: 1. Are receiving cytotoxic or biologic treatments (such as TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], T-cell or B-cell targeted therapies (rituximab), interferon, or Janus kinase (JAK) inhibitors for any indication at study entry 2. Have ever received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19 3. Have received high dose corticosteroids at doses >20 mg per day (or prednisone equivalent) administered for >14 consecutive days in the month prior to study entry. a. Note: Use of dexamethasone and/or other systemic corticosteroids that do not exceed the above specified dose and duration in the month prior to study entry is acceptable. 4. Strong inhibitors of OAT3 (such as probenecid) that cannot be discontinued at study entry. 5. Have diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening tests required) 6. Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product 7. Have received any live vaccine within 4 weeks before screening, or intend to receive a live vaccine during the study 8. Require invasive mechanical ventilation, including ECMO at study entry 9. Current diagnosis of active malignancy that, in the opinion of the investigator, could constitute a risk when taking investigational product 10. Have a history of VTE (DVT and/or PE) within 12 weeks prior to randomization or have a history of recurrent (>1) VTE (DVT/PE) 11. Anticipated discharge from the hospital, or transfer to another hospital (or another unit), which is not a study site within 72 hours after study entry 12. Have neutropenia (absolute neutrophil count <1000) 13. Have lymphopenia (absolute lymphocyte count <200) 14. Have ALT or AST >5 times ULN 15. eGFR (Modification of Diet in Renal Disease [MDRD]) <30 mL/min/1.73 m2. 16. Have a known hypersensitivity to baricitinib or any of its excipients. 17. Are currently enrolled in any other clinical study involving an investigation product or any other type of medical research judged not to be scientifically or medically compatible with this study 18. Are pregnant, or intend to become pregnant or breastfeed during the study 19. Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

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	20. Are using or will use extracorporeal blood purification (EBP) device to remove proinflammatory cytokines from the blood such as a cytokine absorption or filtering device, for example, CytoSorb®. 21. Are, in the opinion of the investigator, unlikely to survive for at least 48 hours after screening
MK-4482 (molnupiravir) Clinical Trial	• **NOT YET OPEN FOR ENROLLMENT** • Study: MK-4482; A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19 • PI: Dr. Paul Cook • Mechanism: MK-4482 is an oral ribonucleoside analog prodrug with broad spectrum antiviral activity against a range of RNA viruses. This study aims to evaluate the safety, tolerability and efficacy of molnupiravir (MK-4482) compared to placebo. The primary hypothesis is that molnupiravir is superior to placebo as assessed by the rate of sustained recovery through Day 29 in hospitalized patients with COVID-19. • Inclusion: 1. Male/Female at least 18 years of age 2. Has documentation of PCR-confirmed SARS-CoV-2 infection with sample collection </= 10 days prior to randomization 3. Had initial onset of signs/symptoms attributable to COVID-19 for </= 10 days prior to randomization and >/= 1 sign/symptom attributable to COVID-19 present at randomization 4. Requires medical care in hospital for ongoing clinical manifestations of COVID-19 5. Is willing and able to take oral medication • Exclusion: 1. Has critical COVID-19 with any of the following: a. Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula, noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure b. Shock (defined by SBP <90 mmHg, or DBP < 60 mmHg or requiring vasopressors) c. Multi-organ dysfunction, failure 2. Is on dialysis or GFR < 30 ml/min 3. Has any of the following conditions a. HIV with a recent viral load >50 copies/ml or CD4 <200 cell/mm3 b. Chemotherapy required within 6 weeks before randomization c. A neutrophilic granulocyte absolute count <500/mm3 d. Autologous or allogenic hematopoietic stem cell transplant recipient 4. Active diagnosis of hepatitis due to any cause 5. Has a platelet count < 100,000/µL or received a platelet transfusion in the 5 days prior to randomization 6. History of acute pancreatitis within 3 months prior to randomization or a history of chronic pancreatitis 7. Has a baseline heart rate <50 beats per min at rest 8. Has hypersensitivity or other contraindication to any of the components of the study interventions as determined by the investigator

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	9. Has any condition for which in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments included but not limited to: a. Participants who are not expected to survive longer than 48 hours after randomization b. Participants who are expected to require mechanical ventilation within 48 hours after randomization c. Participants with recent history of mechanical ventilation not associated with COVID-19 d. Participants with conditions that could limit gastrointestinal absorption of capsule contents
Tocilizumab	• Tocilizumab was officially removed from Vidant algorithm in the September 18, 2020 update. • IDSA guideline recommendation: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel suggests against the routine use of tocilizumab (Conditional recommendation, low certainty of evidence). See guideline for data summary. • Consider use of sirukumab via clinical trial and study protocol above for patients with concern for cytokine release syndrome.
LY3127804 Clinical Trial	• HALTED patient recruitment as of August 15, 2020. The trial proceeded to an ad hoc futility analysis with the 95 randomized patients at the recommendation from the data monitoring committee. This was not driven by safety concerns. *As of September 25, 2020 the study has been discontinued due to futility.* • Protocol I7W-MC-UDAA: A Randomized, Double-blind, Placebo-controlled, Clinical Trial of LY3127804 in Patients who are Hospitalized with Pneumonia and Presumed or Confirmed COVID-19 • Background: Angiopoietin 2 (Ang2) levels in plasma are strongly correlated with increased ARDS risk in several human studies. LY3127804 is an anti-Ang2 monoclonal antibody. The intent of this study is to test whether LY3127804 can reduce the high proportion of patients who progress with pulmonary insufficiency, as assessed by ventilator free days, after being admitted to the hospital with a pneumonia and presumed or confirmed COVID-19.
Hydroxychloroquine (HCQ)	• HCQ was officially removed from Vidant algorithm in the June 16, 2020 update. On June 15, 2020, based on FDA's continued review of the scientific evidence available for HCQ and chloroquine (CQ) to treat COVID-19, FDA has determined that the statutory criteria for EUA as outlined in Section 564(c)(2) of the Food, Drug, and Cosmetic Act are no longer met. Specifically, FDA has determined that CQ and HCQ are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other serious side effects, the known and potential benefits of CQ and HCQ no longer outweigh the known and potential risks for the authorized use. This warrants revocation of the EUA for HCQ and CQ for the treatment of COVID-19. • IDSA guideline recommendation: Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine. See guideline for data summary.

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HCQ + Azithromycin	• HCQ + azithromycin combination was officially removed from Vidant algorithm in the April 30, 2020 update. • IDSA guideline recommendation: Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine plus azithromycin. See guideline for data summary.
Lopinavir/ritonavir (Kaletra)	• Kaletra was officially removed from Vidant algorithm in the May 8, 2020 update. • 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.
Interferon Beta-1a	• Mechanism: Subcutaneous interferon beta-1a is approved in the U.S. and more than 90 other countries for the treatment of multiple sclerosis. Interferon beta-1a has the same amino acid sequence as a naturally occurring protein called interferon beta, which is part of a class of proteins called type 1 interferons. Infected cells normally produce type 1 interferons to help the immune system fight pathogens, especially viruses. Interferon beta has both antiviral and anti-inflammatory properties. • A randomized, controlled clinical trial evaluating the safety and efficacy of a treatment regimen consisting of the antiviral remdesivir plus the immunomodulator interferon beta-1a in patients with coronavirus disease 2019 (COVID-19) has begun. The study, called the Adaptive COVID-19 Treatment Trial 3 (ACTT 3), is anticipated to enroll more than 1,000 hospitalized adults with COVID-19 at as many as 100 sites in the United States and abroad. • Clinical trial is the only way to obtain drug and Vidant is not part of this clinical trial. The closest site in NC is Duke. • More data can be found here: https://clinicaltrials.gov/ct2/show/NCT04492475
NCT04427501 Outpatient Clinical Trial (BLAZE-1)	• For outpatients only. Patients can travel from anywhere to Greenville and only have to be seen in Greenville once. Please call to make sure the patient is eligible before they travel to Greenville. • Mechanism: LY-CoV555 is a potent, neutralizing IgG1 monoclonal antibody directed against the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus, potentially preventing and treating COVID-19. LY-COV555 has unique binding properties utilizing a validated monotherapy antiviral antibody approach. As with Ebola and RSV, the only two historically successful therapies in this class, the hope is that individual potent neutralizing antibodies are an effective way to treat viral pathogens. • Contact Dr. Paul Cook (PI), Dr. Paul Bolin (co-investigator), or Jamie Wigent (study coordinator at 252-744-1913). • Summary: The purpose of this study is to measure how well LY3819253 and LY3832479 work against the virus that causes COVID-19. LY3819253 and LY3832479 will be given to participants with early symptoms of COVID-19, via an injection into a vein. Samples will be taken from the back of the nose to determine how much virus is in the body at various times during the study. Participation could last about 12 weeks and includes one

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required visit to the study site, with the remainder of assessments performed in the home or by phone.

- Inclusion Criteria:
  1. Are currently not hospitalized
  2. Have one or more mild or moderate COVID-19 symptoms: Fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath with exertion
  3. Must have sample taken for test confirming viral infection no more than 3 days prior to starting the drug infusion
  4. Are men or non-pregnant women who agree to contraceptive requirements
  5. Understand and agree to comply with planned study procedures
  6. Agree to the collection of nasopharyngeal swabs and venous blood
  7. The participant or legally authorized representative give signed informed consent
  8. Treatment arms 7 and 8 only (the only ones still enrolling): Participants are ≥ 65 years of age at the time of randomization OR have a BMI ≥ 35 OR are ≥ 55 years of age and have a BMI ≥ 30 and have a history of myocardial infarction or stroke
- Exclusion Criteria:
  1. Have oxygen saturation (SpO2) less than or equal to (≤)93 percent (%) on room air at sea level or ratio of arterial oxygen partial pressure (PaO2 in millimeters of mercury) to fractional inspired oxygen (FiO2) less than (<)300, respiratory rate greater than or equal to (≥)30 per minute, heart rate ≥125 per minute
  2. Require mechanical ventilation or anticipated impending need for mechanical ventilation
  3. Have known allergies to any of the components used in the formulation of the interventions
  4. Have hemodynamic instability requiring use of pressors within 24 hours of randomization
  5. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention
  6. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
  7. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study
  8. Have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study
  9. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
  10. Have received treatment with a SARS-CoV-2 specific monoclonal antibody
  11. Have a history of convalescent COVID-19 plasma treatment
  12. Have participated in a previous SARS-CoV-2 vaccine study
  13. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed
  14. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
  15. Are pregnant or breast feeding

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Bamlanivimab (Outpatient only)	• **NOT YET AVAILABLE FOR USE. Likely available within the next week.**
	• Mechanism: Bamlanivimab is a recombinant neutralizing human IgG1 monoclonal antibody directed against the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus.
	• The Secretary of the Department of Health and Human Services has declared a public health emergency that justifies the emergency use of bamlanivimab to treat COVID-19 caused by SARS-CoV-2 infection. In response, the US FDA has issued an Emergency Use Authorization (EUA) for the unapproved product, bamlanivimab, for the treatment of COVID-19.
	• On 11/10/20 NC received a first state allocation of bamlanivimab from ASPR/HHS. They are making local allocation decisions. HHS/ASPR is referring to this as Phase 1 of this bamlanivimab process. During Phase 1 states have been directed to allocate bamlanivimab to hospitals and hospital affiliated locations only. During Phase 2 of this process states will then be able to allocate to additional outpatient facilities. HHS/ASPR has not set a timeline for phase 1 or phase 2. They are taking a wait and see approach to see how these first few weeks of phase 1 go before making any decisions about phase 2. At this time HHS/ASPR has indicated that they do not intend to provide prioritization guidance related to use of bamlanivimab and referred to the "high-risk" criteria spelled out in the EUA when determining who should receive this product.
	• The EUA allows bamlanivimab to be used to treat mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. It is NOT authorized for use in those who are hospitalized due to COVID-19, or who require oxygen therapy due to COVID-19, or who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
	• High risk is defined as patients who meet at least one of the following criteria:
	  ○ Have a body mass index (BMI) ≥35
	  ○ Have chronic kidney disease
	  ○ Have diabetes
	  ○ Have immunosuppressive disease
	  ○ Are currently receiving immunosuppressive treatment
	  ○ Are ≥65 years of age
	  ○ Are ≥55 years of age AND have cardiovascular disease, OR hypertension, OR chronic obstructive pulmonary disease/other chronic respiratory disease
	  ○ Are 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 such as tracheostomy, gastrostomy, positive pressure ventilation (not related to COVID-19), OR
	  ▪ asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.
	• **ID approval will be required (252-814-4296). Details TBD.**

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	• Administration:
	  ○ Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS potentially related to bamlanivimab. See Sections 8 and 9 of the Fact Sheet for Healthcare Providers for reporting instructions below.
	  ○ The authorized dosage for bamlanivimab is a single intravenous (IV) infusion of 700 mg administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.
	  ○ Bamlanivimab is available as concentrated solution and must be diluted prior to administration.
	  ○ Administer bamlanivimab 700 mg via IV infusion over at least 60 minutes via pump or gravity.
	  ○ Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.
	  ○ Patients treated with bamlanivimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.
	• Documentation: Healthcare providers must communicate to patients or parents/caregivers, as age appropriate, information consistent with the Fact Sheet for Patients, Parents and Caregivers prior to the patient receiving bamlanivimab. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been: Given the Fact Sheet for Patients, Parents and Caregivers, informed of alternatives to receiving authorized bamlanivimab, and informed that bamlanivimab is an unapproved drug that is authorized for use under this Emergency Use Authorization. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and serious adverse events occurring within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Bamlanivimab treatment under Emergency Use Authorization (EUA)" in the description section of the report. The must be submitted to FDA MedWatch and to Eli Lilly.

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General COVID-19 Information:

1. COVID-19 is also referred to as SARS-Coronavirus-2 or SARS-CoV-2.
2. Incubation period ~5 days (ranges from 2-14 days).
3. 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.
4. CXR have shown bilateral involvement in most patients. CT patterns have revealed patchy infiltrate, bilateral disease, and have been consistent with viral infection.
5. Potential for clinical deterioration during second week of illness.
6. Co-infection of COVID-19 with other viruses and bacteria is possible.
7. False negative COVID-19 results are possible. Poor quality of specimen can be a reason for false negative.

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.
4. Pregnancy test
5. Vitamin D, total (VITDT)

General Drug Considerations:

1. There are clinical trials of HCQ that include supplemental zinc, vitamin C, and vitamin D. For all COVID-19 positive patients suggest 14 days of the following **nutritional supplements**:
    a. **Multivitamin with minerals** (Theragran-M tablet) twice daily. The preference is to use the Theragran-M tablet product, even if need to crush finely and administer per tube, due to the copper concentration in this vitamin (2 mg/tab) vs Centrum liquid (0 mg). If absolutely needed, can use the Centrum liquid multivitamin with iron-minerals. But, the copper supplementation may be important due to Zinc binding copper absorption.
    b. **Zinc sulfate** 220 mg capsule daily (50 mg elemental zinc) or oral suspension if need liquid (220 mg/5mL). Zinc has anti-viral activity, including inhibition of viral RNA dependent RNA polymerase (like remdesivir). Zinc deficiency is common in elderly people and is associated with anosmia (an early sign of COVID-19 disease).
    c. **Ergocalciferol** 50,000 IU twice weekly or ergocalciferol drops if liquid needed (50,000 IU/6.25 mL). Need for further supplementation should be based on vitamin D level results. Vitamin D is a known immunomodulator and deficiency is more common in African Americans, who are at higher risk for severe disease. Vitamin D inhibits proinflammatory cytokines, including IL-6. We are giving ergocalciferol over cholecalciferol based on the high dose and available supplies. The shorter half-life of the ergocalciferol also will help to see effects earlier and reach steady state more quickly.

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2. The Vidant Health **anticoagulation** subcommittee has developed a guideline for inpatient prophylaxis, discharge prophylaxis, and treatment of VTE in COVID-19 patients. Please see their separate document.
3. **Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier)**. An equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg. IDSA guideline recommendations are as follows: Among hospitalized critically ill patients with COVID-19, the IDSA guideline panel recommends dexamethasone rather than no dexamethasone (Strong recommendation, moderate certainty of evidence). Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS. Among hospitalized patients with severe, but non-critical COVID-19 the IDSA guideline panel suggests dexamethasone rather than no dexamethasone (Conditional recommendation, moderate certainty of evidence). Severe illness is defined as patients with SpO2 ≤ 94% on room air, including patients on supplemental oxygen. Among hospitalized patients with non-severe COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. Non-severe illness is defined as patients with a SpO2 >94% not requiring supplemental oxygen. See guideline for data summary.
4. If no contraindications, continue **statins** or consider starting in those with a guideline indication for one.
5. Do not need to stop home **ACEI/ARB** therapy, unless there is another compelling reason.
6. Avoid starting new prescriptions for **NSAIDs.** Can see IDSA guideline for some discussion of NSAIDs.
7. Use **inhalers** over nebulizers.
8. 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.
9. 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. See separate document for subcutaneous insulin management of mild/moderate DKA in the COVID-19 patient.
10. 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.
11. 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.
12. Anecdotal reports from China suggest that patients infected with coronavirus who were receiving **famotidine**, a H2 receptor antagonist to treat conditions such as acid reflux and peptic ulcer disease, had improved survival vs those receiving proton pump inhibitors. This post hoc finding has led to interest in the drug, though no predominant theory describing a mechanism for its efficacy yet exists. One theory is that famotidine, like many other compounds,

binds and therefore inhibits the coronavirus main protease, 3C-like main protease (3Clpro). Among hospitalized patients with severe COVID-19, the IDSA panel suggests against famotidine use for the sole purpose of treating COVID-19 outside of the context of a clinical trial (conditional recommendation, very low certainty of evidence). See guideline for data summary. If stress ulcer prophylaxis is indicated, consider choosing famotidine over PPIs. This is already in agreement with current MICU practices for critically ill intubated patients.

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