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
- MK-4482 clinical trial (on hold)

If outpatient:

- BLAZE-1 outpatient clinical trial
- Bamlanivimab/etesevimab (Hotline 252-847-6500, M-F, 0800-1700)

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
- MK-4482 clinical trial (on hold)
- Baricitinib
- Tocilizumab

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
- Remdesivir (but less likely to have an impact at this stage of disease)
- Baricitinib
- Tocilizumab

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 April 9, 2021 – this document is subject to frequent revisions
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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 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. Duration can be shortened if otherwise ready for discharge.
	• Monitoring: Suggest daily renal and hepatic function monitoring
	• Renal dysfunction: There are now several case reports describing use of remdesivir in patients with AKI or ESRD. These patients can be considered on a case by case basis. Dose and duration should be the same. When given on HD days make sure dose is after HD (as drug is cleared by HD).

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	• 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 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. • Outpatient clinical trial with remdesivir was closed as of April 2021
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	• Study has reached enrollment goal and is now closed. • 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 • Mechanism: Sirukumab is a human anti-IL-6 IgG1κ mAb that binds to human IL-6 with high affinity and specificity. As such, treatment could reduce pulmonary and systemic levels of IL-6 resulting in a clinically meaningful benefit.
Ruxolitinib Clinical Trial INCB 18424-369 (RUXCOVID-DEVENT)	• As of December 14, 2020 further enrollment has been suspended pending the outcome of a planned interim analysis. Recent results from a Phase 3 trial with this drug for hospitalized non-intubated patients showed the primary endpoint was not met and there was no clinically relevant benefit observed among secondary and exploratory endpoints. No significant safety concerns were identified. • Primary Objective: 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.

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Baricitinib	• IDSA guideline recommendation: Among hospitalized patients with severe COVID-19 who cannot receive corticosteroids because of a contraindication, the IDSA guideline panel suggests use of baricitinib (4 mg daily dose for 14 days or until hospital discharge) with remdesivir rather than remdesivir alone (conditional recommendation, low certainty of evidence). Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen, oxygen through a high-flow device, or non-invasive ventilation. The benefits of baricitinib plus remdesivir for persons on mechanical ventilation are uncertain. Among hospitalized patients with COVID-19, the IDSA guideline panel recommends treatment with baricitinib plus remdesivir plus corticosteroids only in the context of a clinical trial (knowledge gap). See guideline for data summary. • VMC 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. Study has reached enrollment goal and is now closed. • Mechanism: Inhibitor of JAK1 and JAK2. Baricitinib is proposed to reduce an inflammatory response and have potential antiviral activity against COVID-19. • **Data currently being evaluated. Criteria for use being worked on. Has been added to Vidant Health formulary. Until order is live in EHR, call pharmacy to have them enter order as a non-formulary order.** • **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 after 2100 will need to be approved and started the following morning.**
MK-4482 (molnupiravir) Clinical Trial	• Taking place at VMC only. Temporarily closed for a planned interim analysis. • 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

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	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 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
Inhaled Sargramostim (PTX-001-002)	• Study has reached enrollment goal and is now closed. • Study: A Phase 2 trial evaluating sargramostim in patients with COVID-19 associated acute hypoxemia (PTX-001-002) • Mechanism: Sargramostim is a recombinant human granulocyte-macrophage colony stimulating factor (rhu-GM-CSF), and has been approved since 1991. GM-CSF, a pleiotropic cytokine, is an important leukocyte growth factor known to play a key role in hematopoiesis, effecting the growth and maturation of multiple cell lineages as well as the functional activities of these cells in antigen presentation and cell mediated immunity. The preliminary results in patients with COVID-19 in a Belgium study indicate that cytokine storm is not occurring with the use of sargramostim in the studied patient population.
Tocilizumab	• Tocilizumab was officially removed from Vidant algorithm in the September 18, 2020 update. **It is being reconsidered as of the Mar 5, 2021 update and can be considered on a case by case basis as criteria for use are being worked on. 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 after 2100 will need to be approved and started the following morning. EHR order may say "for outpatient use only except for**

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	heme/onc and transplant patients", however, this can be bypassed if you have ID approval for COVID-19. • IDSA guideline recommendation: Among hospitalized adults with progressive severe (SpO_2 ≤94% on RA) or critical (on mechanical ventilation or ECMO including ARDS) COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e. steroids) rather than standard of care alone (conditional recommendation, low certainty of evidence). Patients, particularly those who respond to steroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab. In the largest trial on the treatment of tocilizumab, criterion for systemic inflammation was defined as CRP ≥ 75 mg/L. See guideline for data summary. • Mechanism: monoclonal anti-IL-6 receptor blocking antibody proposed as a therapeutic agent to mitigate hyperinflammation associated with COVID-19. FDA approved for various rheumatologic conditions as well as cytokine release syndrome associated with CAR-T cell therapy.
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.
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

	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/ etesevimab (Outpatient only – can be given inpatient if admission is for a non-COVID reason and would otherwise qualify for outpatient infusion)	• Available for VMC and VH community hospitals. For self or patient referrals contact the hotline at 252-847-6500 Monday through Friday from 0800-1700. • Inpatient approval per Dr. Darla Liles, Dr. James Manning, or Dr. Ryan Gallaher. • VDUP ED pilot allows approval by: Jacklyn Araica, PA; Nathaniel Barrett, PA-C; Satti Bilal, MD; Jonathan Campbell, PC-C; Michael Cullura, MD; Yousef Naji, MD; Robert Oldt, MD; Vijay Randive, MD; Eduardo San Miguel, MD; Brooks Schomp, PA-C; Jessica Gray Taylor, PA. • As of the end of Feb 2021, the FDA has released 3 EUA's for neutralizing monoclonal antibodies: bamlanivimab (Nov 9, 2020), casirivimab/imdevimab (Nov 21, 2020), and bamlanivimab/etesevimab (Feb 9, 2021). • NC DHHS will no longer ship single agent bamlanivimab due to increasing SARS-CoV-2 variants. As of ~April 13, 2021, we will be switching from bamlanivimab monotherapy to bamlanivimab/etesevimab combination therapy. • IDSA guideline recommendation: Among hospitalized patients with severe COVID-19, the IDSA guideline panel recommends against bamlanivimab monotherapy (strong recommendation, moderate certainty of evidence). Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests bamlanivimab/etesevimab rather than no bamlanivimab/etesevimab (conditional recommendation, low certainty of evidence). Ambulatory patients or patients with mild-moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive bamlanivimab/etesevimab. For patients at high risk for progression to severe disease, the data are strongest for bamlanivimab/etesevimab. Bamlanivimab monotherapy or casirivimab/imdevimab may have similar clinical benefit, but data are more limited. There are limited data on efficacy of bamlanivimab/etesevimab in high risk patients between 12 and 18 years of age. See guideline for data summary. • Mechanism of neutralizing antibodies: Neutralizing antibodies directed at the receptor-binding domain of SARS-CoV-2 spike protein have been evaluated as prophylactic and therapeutic agents for COVID-19. In animal models there is evidence that antibody therapy may more rapidly reduce viral load in the upper and lower airways of infected animals resulting in reduced viral-induced pathology. Potential advantages of neutralizing antibodies include the ability to standardize the amount of neutralizing activity and the possibility of conferring protection more rapidly than with vaccine-induced immune responses (which generally take several weeks). • The EUA allows them 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

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	○ 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. • Administration: ○ Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS. ○ The authorized dosage for bamlanivimab is a single IV infusion of 700 mg and etesevimab 1400 mg administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. ○ Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete. ○ Patients treated 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 drug. 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, and informed that these are unapproved drugs that are 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. Must be submitted to FDA MedWatch and to Eli Lilly.
Ivermectin	• IDSA guideline recommendation: In hospitalized patients with severe COVID-19, the IDSA panel suggests against ivermectin use outside of the context of a clinical trial (conditional recommendation, very low certainty of evidence). In outpatients with COVID-19, the IDSA panel suggests against ivermectin use outside of the context of a clinical trial (conditional recommendation, very low certainty of evidence). See guideline for data summary. • Mechanism: Anti-parasitic agent FDA approved for some indications. Has in-vitro activity against some viruses, including SARS-CoV-2 but no proven therapeutic utility. Concentrations needed to obtain the in-vitro IC50 for SARS-CoV-2 are considerably higher than those achieved in human plasma and lung tissue.

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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.
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 hospitalized patients with COVID-19, the IDSA guideline panel recommends against the use of the combination lopinavir/ritonavir. 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

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.
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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References:

1. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID19: results of an open-label non randomized clinical trial. International Journal of Antimicrobial Agents. In Press 17 March 2020. DOI: 10.1016/j.ijantimicag.2020.105949
2. Michigan Medicine: University of Michigan. Inpatient guidance for diagnosis and treatment of covid-19 in adults and children. March 2020 but updated regularly.
3. UW Medicine Interim Treatment Guidelines for SARS-CoV-2 Infection/COVID-19. UW Medicine 3/17/2020, V 1.3.
4. Interim clinical guidance for patients suspected of/confirmed with COVID-19 in Belgium - 16 Mar 2020; Version 3.
5. Yao X, Ye F, Zhang, M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), *Clinical Infectious Diseases*, , ciaa237, https://doi.org/10.1093/cid/ciaa237
6. Live CME Webcast March 25, 2020 by Contagion Infectious Diseases Today.
7. McCreary EK and Pogue JM. COVID-19: Treatment: A Review of Early and Emerging Options. Accepted manuscript Open Forum Infectious Diseases, https://doi.org/10.1093/ofid/ofaa105
8. McCreary EK and Pogue JM. Updates March 19-24, 2020.
9. Xu X et al. Effective treatment of severe COVID-19 patients with tocilizumab. Pre Print.
10. Cao B, Wang Y, Wen W, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. NEJM 2020. DOI: 10.1056/NEJMoa2001282
11. Mehta P, McAuley DF, Brown M, et al. Correspondence: COVID-19: Consider cytokine storm syndromes and immunosuppression. Published online March 13, 2020. https://doi.org/10.1016/S0140-6736(20)30628-0
12. Nicastri E, Petrosillo N, Bartoli TA, et al. National Institute for the ID "L. Spallanzani", IRCCS. Recommendations for COVID-19 clinical management. Infectious Diseases Reports 2020; volume 12:8543.
13. Chen Z, Hu J, Zhang, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Preprint. https://doi.org/10.1101/2020.03.22.20040758
14. Bhimraj A, Morgan RL, Shumaker AH, et al. IDSA Guidelines on the Treatment and Management of Patients with COVID-19 Infection. Published April 11 2020 but last updated Mar 18, 2021. www.idsociety.org/COVID19guidelines
15. Sanders JM, Monogue ML, Jodlowski TZ, et al. Pharmacologic treatments for Coronavirus disease 2019 (COVID-19) a review. JAMA. Published online April 13, 2020. doi:10.1001/jama.2020.6019
16. Muscogiuri G, Barrea L, Savastano S, et al. Nutritional recommendations for COVID-19 quarantine. European Journal of Clinical Nutrition. Published online April 14, 2020. https://doi.org/10.1038/s41430-020-0635-2
17. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and death. Nutrients. Published online April 2, 2020. doi:10.3390/nu12040988
18. NIH COVID-19 Treatment Guidelines. Last updated July 30, 2020. https://covid19treatmentguidelines.nih.gov/introduction/
19. Freedberg DE, Conigiaro JC, Sobieszczyk ME, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. Posted May 8, 2020. Preprint: https://doi.org/10.1101/2020.05.01.20086694

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