Nebraska Medicine
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Revision Date: 10/20/2021

COVID-19 Antiviral and Pharmacotherapy Information

Supportive therapy is the cornerstone of treatment. *Recent IDSA and NIH guidelines reinforce this general approach to pharmacological treatment, with data for only a few specific therapies in certain circumstances[32,40]. The treatment framework below is adapted from the NIH, which is routinely updated at* www.covid19treatmentguidelines.nih.gov/therapeutic-management/.

Patient Profile	Recommendation
Not hospitalized, mild to moderate COVID-19	•Monoclonal antibodies (**Bam/Ete, Cas/Imdev, or Sotrovimab**) for patients that meet diagnostic and high-risk criteria for treatment or post-exposure prophylaxis •Consider use of **inhaled budesonide** in select patients in addition to, or in those refusing or not eligible for, monoclonal antibody therapy (see text for details) •Should **NOT** use **Dexamethasone, Remdesivir,** or **Baricitinib**
Hospitalized, but does Not require Supplemental Oxygen	•Consider clinical trial enrollment (SPESELPIS) •**Remdesivir** for patients at high-risk of COVID-19 progression (see text for additional details) •Should NOT use **Dexamethasone** or **Baricitinib**
Hospitalized and Requires Supplemental Oxygen	•Consider clinical trial enrollment (BET-B, BET-C, or NECTAR) • **SUPPLEMENTAL OXYGEN ≤5L/min:** •**Remdesivir** • **SUPPLEMENTAL OXYGEN >5L/min**: •**Remdesivir plus Dexamethasone** or **Remdesivir plus Baricitinib** (See text for additional details on patient criteria and adverse effects to guide choice)
Hospitalized and Progressive Respiratory Failure Requiring High Level Oxygen Delivery / Non-invasive Mechanical Ventilation	•**Remdesivir plus Dexamethasone plus Baricitinib** •As an alternative to baricitinib, consider addition of **Tocilizumab** (See text for additional details on anti-inflammatory combination therapy)
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	•**Remdesivir plus Dexamethasone plus Baricitinib** •As an alternative to baricitinib, consider addition of **Tocilizumab** (See text for additional details on anti-inflammatory combination therapy)

Therapies below have been tiered based on the available data, current availability, toxicity profile, and practical considerations specific to Nebraska Medicine. Updates are expected during this fluid situation.

Preferential:

» **IRB 555-20 A Trial of NT-I7 in COVID-19 (SPESELPIS)** (NCT04501796): E-mail Dr. Andre Kalil (akalil@unmc.edu) and Sheryl Houston (sheryl.houston@unmc.edu) for evaluation

- Study drug: NT-I7 (efineptakin alfa)
- Mechanism: Long-acting recombinant human IL-7
- Dosing: NT-I7 60mcg/kg, 120mcg/kg, or 240mcg/kg IM once
- Adverse Effects: Injection site reaction; lymphadenopathy; headache; dizziness; oropharyngeal pain; productive cough
- Inclusion Criteria: Age 19-75; lab-confirmed SARS-CoV-2 <5 days; O_2 sat >93% on RA, RR ≤20, and HR ≤100; ALC <1500
- Exclusion Criteria: Need for supplemental oxygen, noninvasive or mechanical ventilation, or ECMO; CRP >15 or D-dimer >0.75; eGFR <40 (including dialysis); AST/ALT >3x ULN; pregnancy/breastfeeding; use of systemic corticosteroids or immunosuppressants within 4 weeks prior to screening; HIV infection

» **IRB 535-21 - ACTIV-5/Big Effect Trial (BET-B) for the Treatment of COVID-19** (NCT04583969): E-mail Dr. Andre Kalil (akalil@unmc.edu) and LuAnn Larson (llarson@unmc.edu) for evaluation

- Study drug: Lenzilumab (or Placebo)
- Mechanism: mAb targeting soluble human GM-CSF, with potential immunomodulating activity. Upon administration, lenzilumab binds to and neutralizes GM-CSF
- Dosing:
  - Remdesivir 200mg IV once, then 100mg IV daily while hospitalized or up to 10 total days PLUS
  - Lenzilumab 600mg IV q8h x 3 doses
- Adverse Effects: Respiratory tract infection, headache, infusion reaction
- Inclusion Criteria: Age ≥18; hospitalized for COVID-19; lab-confirmed SARS-CoV-2 ≤14 days; requiring any supplemental oxygen, mechanical ventilation, or ECMO
- Exclusion Criteria: ALT/AST >5x ULN; eGFR <20; pregnancy/breastfeeding; anticipated discharge/transfer within 72 hours of enrollment; received ≥5 doses of remdesivir; received baricitinib, tocilizumab, or other immunosuppressants in 4 weeks prior to screening (e.g., baricitinib); known history of HIV, HBV, or untreated HCV infection

» **IRB 535-21 - ACTIV-5/Big Effect Trial (BET-C) for the Treatment of COVID-19** (NCT04988035): E-mail Dr. Andre Kalil (akalil@unmc.edu) and LuAnn Larson (llarson@unmc.edu) for evaluation

- Study drug: Danicopan (or Placebo)
- Mechanism: Enteral complement inhibitor; small molecule Factor D (FD) inhibitor. FD is one of nine serine proteases in the complement system.
- Dosing:
  - Remdesivir 200mg IV once, then 100mg IV daily while hospitalized or up to 10 total days PLUS
  - Danicopan PO, dosing varies according to age group: loading dose on D1, then 4x daily on D2-14 (while hospitalized), then 3x daily on D15-16, then then BID on D17-18 (days 15-18 doses may be given post-discharge)
- Adverse Effects: *N. meningitidis* infection; transaminitis
- Inclusion Criteria: Age ≥18; hospitalized for COVID-19; lab-confirmed SARS-CoV-2 ≤14 days; requiring any supplemental oxygen, mechanical ventilation, or ECMO
- Exclusion Criteria: ALT/AST >5x ULN; eGFR <15 (including dialysis); pregnancy/breastfeeding; anticipated discharge/transfer to another site within 72 hours of enrollment; received ≥5 doses of remdesivir; treatment with complement inhibitor within prior 8 weeks; history of *N. meningitidis* infection; liver cirrhosis
- Notes: Must have received meningococcal vaccination within 3yrs prior to starting study drug, or receive meningococcal prophylactic antibiotics before starting study drug through 2d after end of treatment

» **IRB 491-21 – Novel Experimental COVID-19 Therapies Affecting Host Response (NECTAR)** (NCT04924660): E-mail Dr. Aaron Barksdale (aaron.barksdale@unmc.edu) and Brooklin Zimmerman (brooklin.zimmerman@unmc.edu) for evaluation

- Study drug 1: TXA127 (or Placebo)
  - Mechanism: Synthetic formulation of angiotensin-(1-7)
  - Dosing: TXA127 0.5mg/kg IV daily for 5 days
  - Adverse Effects: headache; nausea; myalgia; fatigue; abdominal distension; flu-like symptoms; diarrhea; vomiting
- Study drug 2: TRV027 (or Placebo)
  - Mechanism: AT_1 receptor selective agonist
  - Dosing: TRV027 12mg/hr continuous IV infusion for 5 days

- Adverse Effects: fatigue; abdominal distension; headache; arthralgia; myoclonus; dizziness; hypotension
- Inclusion Criteria: Age ≥18; hospitalized for COVID-19; lab-confirmed SARS-CoV-2 ≤3 days; hypoxemia
- Exclusion Criteria: Prior allergic reaction to medication targeting RAAS system; COVID-19 symptom onset >14 days prior to randomization; hospitalized >72 hours prior to randomization; hemodynamic instability (e.g. MAP <65, norepinephrine ≥0.1mcg/kg/min); pregnancy/breastfeeding; ESRD/dialysis; renal artery stenosis; left ventricular outflow obstruction

» **Monoclonal Antibodies EUA – Bamlanivimab/Etesevimab[67,77], Casirivimab/Imdevimab[68,78], or Sotrovimab[95]**

- Dosing: Bamlanivimab/etesevimab 700mg/1400mg IV once; casirivimab/imdevimab 600mg/600mg IV or subq once; sotrovimab 500mg IV once
- Adverse Effects: Rare infusion-related reactions and mild hypersensitivity
- EUA Patient Criteria:
  - Treatment Indication
    - Outpatients with mild, symptomatic COVID-19, within 10 days of symptom onset
    - Not requiring supplemental oxygen for COVID-19 (or an increase from baseline in those already on supplemental oxygen)
    - Meets at least one of the CDC high-risk criteria
  - Post-Exposure Prophylaxis Indication (casirivimab/imdevimab only)
    - Exposed to an individual infected with SARS-CoV-2 consistent with CDC close contact criteria
    - Not fully vaccinated, or vaccinated but having an immunocompromising condition
    - Meets at least one of the CDC high-risk criteria
- Notes: All outpatients testing positive for SARS-CoV-2 at Nebraska Medicine will be screened automatically for a limited set of eligibility criteria and contacted prospectively if eligibility is met. Please refer to the detailed guidance document on the institutional monoclonal antibody therapy process for complete details on assessing/requesting this therapy for your patient. Benefit has been shown in preventing subsequent ED visits or hospitalization in populations at high-risk of progression. In phase 2-3 trials, the number-needed-to-treat was in the mid-teens for these agents. Cost: none, as product has been purchased by the US government, although patients may be charged an administration fee.

» **Remdesivir[39,66,79]**

- Dosing: 200mg IV once, then 100mg IV daily for 5 days of recommended therapy (discontinue earlier if ready for discharge). 10 days of therapy was studied, although no additional benefit has been identified from a longer course in most cases.
- Adverse Effects: Generally mild severity – GI intolerances, LFT abnormalities, infusion-related reactions
- Patient Criteria: PCR confirmed SARS-CoV-2 infection with symptoms starting ≤ 10 days ago or progressive COVID-19 disease; and one of: 1) requiring supplemental oxygen 2) SpO2 ≤ 94% on room air 3) infiltrates on chest imaging
  - Examples of patients with high-risk criteria that may benefit from early treatment before requiring oxygen include, but are not limited to: age ≥65, BMI ≥35, immunosuppression, or other chronic health conditions.
  - For children <12 years old and <40kg, EUA documentation requirements remain in place
- Notes: In patients hospitalized with prolonged symptoms of COVID-19, consider additional treatment with remdesivir (up to 10 days) if suspected active disease, i.e. clinical, radiologic, or microbiologic (low CT value) indicative of COVID-19 pneumonia. Cost: $3,744 per 5-day course AWP

» **Dexamethasone[60-61,90,92]**

- Dosing: 6mg PO or IV once daily for up to 10 days (discontinue prior to discharge or when recovered)
- Adverse Effects: Hyperglycemia, gastrointestinal bleeding, secondary infections, delirium, hypertension, fluid retention, insomnia, increased appetite
- Patient Criteria: Recommended for patients with COVID-19-related ARDS that are requiring mechanical ventilation. Consider in those with acute respiratory failure requiring increasing supplemental oxygen, *specifically >5L/min or F_iO_2 > 40%*. Use in non-oxygen requiring patients has been associated with worse clinical outcomes. Only those patients with acute hypoxemic respiratory failure due to COVID-19 (not due to chronic comorbidities) are expected to benefit. It has not been systematically studied with remdesivir, but they are regularly used together (ACTT-4 study was investigating this).
- Notes: The RECOVERY trial demonstrated that dexamethasone provided significant reductions in mortality, hospital discharge within 28 days, and progression to invasive mechanical ventilation or death. Subgroup analysis by level of respiratory support revealed that benefit was seen in patients receiving invasive mechanical ventilation or supplemental oxygen, but not in patients who were not receiving supplemental oxygen or respiratory support. Preliminary data from the COVID STEROID 2 trial indicates no additional survival benefit to higher doses of dexamethasone. More information on

steroids generally can be found below within the Drug Class Guidance section. Cost: $12 per 10-day course AWP.

» **Baricitinib Emergency Use Authorization (EUA)**[38-39,76]

- Mechanism: JAK and AAK1 inhibitor (anti-inflammatory agent) proposed for use to counter COVID-19 cytokine storm.
- Dosing: 4mg PO daily (adjusted for renal function) for up to 14 days until recovered or discharged (2mg/d if 2-8 years old)
- Adverse Effects: Long-term use for rheumatoid arthritis showed low rates of opportunistic infections including pneumonias and VTEs; short-term treatment of COVID-19 was very well-tolerated in both ACTT-2 and COV-BARRIER trials.
- EUA Criteria: Hospitalized patients requiring supplemental oxygen or respiratory support. *Use SmartPhrase in note before ordering: ".baricitinibEmergencyUse".*
  - Contraindications: eGFR <15 mL/min or on dialysis; neutropenia (ANC <500/mL); lymphopenia (ALC<200/mL); known active tuberculosis.
- Patient Criteria:
  - Consider as an option with remdesivir for patients on supplemental oxygen >5L/min, high-flow, or noninvasive ventilation, particularly for patients who cannot tolerate dexamethasone (for example, in patients with poorly controlled hyperglycemia, delirium, or gastrointestinal bleeding).
  - Recommended with remdesivir and dexamethasone for patients with progressive respiratory failure despite standard treatment. Tocilizumab is an alternative to baricitinib in triple therapy, and is preferred when baricitinib contraindications exist. In this case, the benefit of tocilizumab is only in combination with dexamethasone, not as a replacement to it. Baricitinib and tocilizumab should not be used at the same time.
  - If a patient has been on invasive mechanical ventilation for >72 hours prior to receipt of immunomodulatory therapy, the benefits and risks of adding baricitinib or tocilizumab are not known and are unlikely to favor supplemental treatment in most cases.
- Notes: Evaluated in combination with remdesivir in the NIH adaptive clinical trial ACTT-2. Compared to remdesivir alone, the combination resulted in a statistically significant reduction in median time to recovery of one-day overall and eight-days in the subset of patients on high-flow oxygen or non-invasive ventilation. Similar to dexamethasone, the largest improvement in clinical outcomes was seen in patients with severe disease. In the COV-BARRIER trial, in which baricitinib was added to a background of steroids (80%) and remdesivir (18%), the combination resulted in a statistically significant reduction in mortality. This was driven primarily by patients with a baseline high-flow oxygen requirement or requiring non-invasive ventilation. Cost: $2,500 per 14-day course AWP.

Situational: Efficacy unproven, and/or risk to benefit may favor use in select patients only

» **Inhaled Budesonide**[37,84-85,94]

- Dosing: 0.8mg inhaled BID for 14 days (only nebulized formulations are available in the U.S. – 0.5mg/2mL or 1mg/2mL)
- Adverse Effects: Oropharyngeal candidiasis and dysphonia with short-term use
- Patient Criteria: Consider use in patients that are ≥65yo, or ≥50yo with significant comorbidities, but who refuse or are ineligible for treatment with monoclonal antibodies. Monoclonal antibodies appear to be more efficacious in halting disease progression in this high-risk population, and should be the primary intervention pursued. Use of inhaled budesonide, potentially in addition to monoclonal antibody therapy, may be particularly considered in outpatients progressing between 7-14d following symptom onset. Efficacy for lower-risk patients has not been substantiated in a more comprehensive clinical trial, and is not recommended at this time.
- Notes: Observational data suggested lower rates of poor COVID-19 outcomes among patients with asthma and COPD, which led to the hypothesis that inhaled corticosteroid use may be responsible for this finding. However, a large observational study of chronic inhaled corticosteroid users did not substantiate an effect. A single open-label preliminary trial in early outpatient COVID-19 suggested benefit in reduced progression of disease or hospitalization. This small trial enrolled any adult patient with symptoms of 7d or less; a low-risk cohort for disease progression. The PRINCIPLE randomized, controlled trial was also open-label and enrolled a higher-risk cohort of patients (≥65yo or ≥50yo with comorbidities), allowing for treatment up to 14d after symptom onset. This cohort largely overlaps with those for whom monoclonal antibody therapy would be recommended. Progression of disease to hospitalization or death was reduced from 8.8% to 6.8% (a smaller decrease than that seen in monoclonal antibody trials) and patient self-reported time to recovery was reduced from 14.7 days to 11.8 days. Reduction in progression to hospitalization appeared driven by patients with symptoms of 7d or more, consistent with its anti-inflammatory mechanism of action. Therefore, may be beneficial in combination with monoclonal antibody therapy, particularly in patients towards the end of the EUA window for symptom onset (7-10d), where the inflammatory process assumes a more prominent role in disease progression. Although, the open-label nature of the studies to date without a placebo control likely introduces a high risk of bias. Short courses of budesonide are well-tolerated and risks well-understood.

» **Tocilizumab Emergency Use Authorization (EUA)**[15-16,29-30,48-49,62,73-75,100]

- Mechanism: IL-6 inhibitor for cytokine release syndrome (CRS) in oncology patients receiving CAR-T cell therapy
- Dosing: 8mg/kg IV once (max 800mg), or 12 mg/kg IV once for patients <30kg
- Adverse Effects: Neutropenia can be long lasting so risk of secondary infection is possible and has not been longitudinally evaluated in clinical trials. In one report, superinfections were identified in 54% of tocilizumab-treated patients compared to 24% of untreated COVID patients. In long-term use for RA, intestinal perforation has been reported.
- EUA Criteria: Hospitalized patients requiring supplemental oxygen or respiratory support and who are receiving or have received systemic corticosteroids. *Use SmartPhrase in note before ordering: ".tocilizumabEmergencyUse".*
    - Contraindications: neutropenia (ANC <1000/mL); thrombocytopenia (plts <50/mL); transaminitis (AST/ALT >10x ULN)
- Patient Criteria: Patients with progressive respiratory decline on high-flow oxygen, non-invasive ventilation, or recent mechanical ventilation despite therapy with remdesivir and dexamethasone can be considered for therapy. Tocilizumab is an alternative to baricitinib in triple therapy, and is preferred when baricitinib contraindications exist. In this case, the benefit of tocilizumab is only in combination with dexamethasone, not as a replacement to it. Baricitinib and tocilizumab should not be used at the same time.
    - If a patient has been on invasive mechanical ventilation for >72 hours prior to receipt of immunomodulatory therapy, the benefits and risks of adding baricitinib or tocilizumab are not known and are unlikely to favor supplemental treatment in most cases.
    - The half-life of tocilizumab is 13 days. Prolonged immunosuppression from tocilizumab can be associated with bacterial sepsis, fungal infection, and hospital-acquired pneumonia. Those at high-risk for, or with a suspected or proven bacterial infection, should not receive this therapy.
- Notes: Prior *in vitro* work in SARS indicated IL-6-mediated immune hyper-response as a potential cause of poor outcomes. A small, retrospective study suggested that elevated IL-6 levels may predict need for mechanical ventilation in COVID-19, although this lab value is not routinely available at hospitals to guide patient care. Cost of single dose: $5,000 AWP
    - Early clinical experience from treating COVID-19 in China and the US reported anecdotal benefit with tocilizumab; however, outcomes from randomized trials are conflicting, perhaps demonstrating improvement in need for mechanical ventilation but not consistently. They do not provide clarity on patient selection factors necessary for clear clinical decision-making overall but patients who are most severely have benefited to a greater extent. Over time, an increasing amount of patients have also been treated with corticosteroids, such as dexamethasone, which have previously shown benefit to patients with respiratory failure from COVID-19. The latest 4 large trials are below.
    - COVACTA was an industry-sponsored, randomized, placebo-controlled trial that failed to show a difference in clinical outcomes compared to placebo during Apr-May 2020, before glucocorticoids became standard care.
        - Of 438 patients evaluated, 38% were mechanically ventilated, 14% were on high-flow oxygen, 30% were on supplemental low-flow oxygen, and 31% did not require oxygen at baseline
        - Median CRP was 157 mcg/mL (15.7 mg/dL) in the tocilizumab group
        - Mortality rates in each arm were 19.7% vs. 19.4%
        - Glucocorticoids were used in 19.4% and 28.5% of patients
    - REMAP-CAP is an international open-label, adaptive platform trial. Tocilizumab (or sarilumab, another IL-6 inhibitor) were compared to standard of care, primarily from June-Nov 2020 when steroids became standard of care
        - At baseline, the 353 patients assigned tocilizumab were more critically ill than in previous trials
            - 29% of patients were on high-flow oxygen (≥30L/min with 40% FiO_2), 42% on non-invasive ventilation, 29% received invasive mechanical ventilation, and 18% were on vasopressors
        - For patients assigned tocilizumab, median CRP was 15 mg/dL (IQR 8.9-22.1)
        - The primary endpoint was the number of days patients were free of organ support at hospital day 21
        - Patients in the tocilizumab group had 10 fewer days of organ support (median 10 vs 0 days for placebo)
        - Mortality with tocilizumab was 28% vs 36% with placebo. The adjusted odds ratio for in-hospital survival was 1.64 (1.14-2.35) in favor of tocilizumab.
        - Benefit of IL-6 antagonists was greater in those receiving glucocorticoids
        - ~80% received corticosteroids and 33% received remdesivir
    - RECOVERY is an adaptive, randomized, open-label platform trial of hospitalized patients in the UK. For the tocilizumab portion of the study, patients were included with CRP >7.5 mg/dL and O_2 sat <92%.
        - Median CRP was 14.3mg/dL (IQR 10.7-20.4) for the 2022 patients allocated tocilizumab
        - 14% were on mechanical ventilation, 41% received non-invasive respiratory support, and 45% were receiving no respiratory support other than oxygen

- The primary endpoint was 28-day mortality, which was lower in the tocilizumab group: 29% to 33%
- 82% of patients were on corticosteroids, which appeared to have a significant impact on the survival benefit of patients receiving tocilizumab. No patients received remdesivir.
- Although this is by far the largest study on the drug, its open-label nature without a placebo control opens it up to a high risk of bias.

○ REMDACTA is a randomized, double-blind, placebo-controlled trial that failed to show a difference in clinical outcomes in the background of near universal (88%) dexamethasone use and initiation mainly in patients requiring high-flow noninvasive ventilation (≈80%). This trial was very similar to RECOVERY in terms of design and patient clinical status, although it did not use biomarkers for inclusion, the double-blind nature of REMDACTA helps to limit some biases inherent to RECOVERY, and REMDACTA utilized remdesivir as a standard-of-care in both groups (which may indicate that tocilizumab provides less additive benefit when this is the case).

Not Recommended (alphabetical order): Risk/benefit ratio does not favor use

» **Azithromycin**[24,26,36]
- No activity for SARS-CoV-2. Studies of combination therapy with hydroxychloroquine do not suggest added benefit with azithromycin combination therapy, particularly given study limitations and concern for excess toxicity and antibiotic overuse.

» **Colchicine**[81-82]
- ColCORONA outpatient trial demonstrated minimal benefit of colchicine in mitigating COVID-19 progression, with the number-needed-to-treat much larger than the number-needed-to-harm. The RECOVERY trial arm with colchicine was closed early, as no efficacy was demonstrated in hospitalized patients also receiving concomitant dexamethasone. Toxicity can occur at standard doses, particularly in the presence of existing hepatic/renal disease or interacting medications.

» **Convalescent Plasma Emergency Use Authorization (EUA)**[51-53,80,91]
- Early evidence suggested use for patients administered therapy as early in the disease process as possible, or for those with impaired humoral immunity. However, results from the RECOVERY randomized trial did not demonstrate an impact on mortality, disease progression, or time to discharge in hospitalized patients. Additionally, results from the SIREN-C3PO study also demonstrated lack of benefit in early initiation for high-risk outpatients. Data for monoclonal antibody therapies are superior to convalescent plasma in comparable circumstances and should be used preferentially.

» **Darunavir/cobicistat**[10-11]
- Available data have not demonstrated efficacy in the treatment of COVID-19 of any severity, although the medication does appear to be well tolerated for the short durations utilized.

» **Fluvoxamine**[86-88]
- An SSRI antidepressant with potent affinity for the σ-1 receptor, which regulates cytokine production and inflammatory response. One preliminary randomized controlled trial and one larger open-label prospective cohort both demonstrated reduction of need for hospitalization and time to symptom resolution in early outpatient COVID-19. The TOGETHER randomized, placebo-controlled trial released preliminary results consistent with the two earlier studies, demonstrating a 30% risk reduction in progression to hospitalization (NNT=24). However, 25% of patients had adverse effects and did not complete the prescribed 100mg BID for 10d. An apparently efficacious, inexpensive, and oral option for early COVID-19; awaiting peer review of recent data to solidify a recommendation. Multiple large nationwide randomized controlled trials (STOP COVID 2, COVID-OUT, and ACTIV-6) continue to investigate this therapy for early, mild COVID-19 (at a reduced dose of 50mg BID).

» **Hydroxychloroquine**[1-4,24-28,33-36,44-46,54-58]
- There were multiple uncontrolled or non-peer-reviewed early clinical reports describing use, with one research group responsible for most of the positive clinical reports. However, there are now multiple clinical trials within various clinical severity and geographic contexts that have demonstrated no benefit in the treatment of COVID-19 disease.

» **Interferons**[8-9,98]
- Typically used in combination with ribavirin, interferons have been studied for patients with other coronaviruses, with mixed results. Evaluated in addition to remdesivir in the ACTT-3 RCT, which demonstrated no additive benefit for the addition of interferon. Interferon's long-term adverse effect profile is generally unfavorable, and this was confirmed in ACTT-3 even for

short-term treatment of COVID-19, with double the rate of adverse events despite receiving only four doses of interferon.

» **Ivermectin**[31,42-44,83,99]
- A single *in vitro* study showed inhibition of SARS-CoV-2, however, concentrations used appear to have been far in excess of those achieved in humans with standard doses. It is unlikely that any dose which has thus far been studied in humans may achieve adequate lung concentrations to inhibit SARS-CoV-2. There have been multiple small, underpowered, or non-peer-reviewed clinical reports describing positive efficacy, most of which have incomplete information and significant methodological limitations. There have also been a few better-designed trials completed that have either demonstrated no benefit, or if finding a clinical benefit, have been retracted due to falsification of data. The CDC has issued a Health Advisory warning against the use of ivermectin for COVID-19 at this time, citing lack of quality evidence and a 3-fold increase in poison control calls due to adverse events, which have also been well documented in the literature. There remain a couple of well-designed, large, nationwide randomized controlled trials (COVID-OUT and ACTIV-6) that continue to investigate this therapy for early, mild COVID-19. Use of ivermectin should currently remain within this context given uncertain clinical benefit, particularly considering the presence of other therapeutics with well-defined (monoclonal antibodies) or more clinically promising (inhaled budesonide, fluvoxamine, molnupiravir) efficacy for early outpatient COVID-19.

» **Lopinavir/ritonavir**[13-14,18,44,47,59]
- Multiple *in vitro* studies suggesting activity, however, two clinical trials did not demonstrate benefit in either hospitalized or mild/moderate disease patients, or demonstrate an antiviral effect. A third very large clinical trial (RECOVERY) has also now concluded there to be no mortality or other clinical benefit in hospitalized patients.

» **Molnupiravir**[96-97]
- An oral ribonucleoside analogue that is integrated into the transcribing RNA and allows ongoing replication, but leads to an unrecoverable number of errors in future replication cycles. Molnupiravir is currently still under investigation in early outpatient COVID-19 for patients with ≤5 days of symptoms and having at least one high-risk criteria. Preliminary results of the phase 3 MOVe-OUT trial have been released, demonstrating a statistically significant reduction in patients progressing to hospitalization or death from 14.1% (an unusually high percentage for a cohort of this risk level) down to 7.3%. Adverse effects appear to very rarely lead to discontinuation. Results of the complete trial will be discussed at an upcoming FDA advisory committee meeting. Molnupiravir is also currently being studied for use as post-exposure prophylaxis.

» **Nitazoxanide**[12]
- Some *in vitro* studies have demonstrated potency against SARS-CoV-2, though clinical use against other coronaviruses has not demonstrated benefit. Poorly tolerated formulation; safety profile is relatively benign.

» **Oseltamivir**
- Coronaviruses do not utilize neuraminidase for the budding stage of reproduction and therefore no activity is expected.

» **Ribavirin (oral)**[7-9]
- Typically used in combination with an interferon, ribavirin has been studied for patients with other coronaviruses, with mixed results. Additionally, its adverse effect profile can be significant (anemia), particularly at the dosages for which it has been tested for MERS (~800-3600mg/day).

» **Zinc**[89]
- Varied formulations and dosages of elemental zinc have historically suggested limited efficacy in shortening symptoms due to common cold coronaviruses. There have been a number of small, uncontrolled, or non-peer-reviewed early clinical reports describing use. However, when tested in a small randomized clinical trial for outpatient COVID-19, zinc with or without concomitant high-dose vitamin C did not limit symptom duration, and the trial was terminated for futility.

Drug Class Guidance (alphabetical order)

» **Angiotensin/RAS Blocking Agents (ACEi/ARBs)**[17,40,50]
- Do not discontinue these therapies for COVID-19 disease. Multiple recent retrospective studies now support the earlier conclusions of professional societies in cardiology and nephrology that suggestions to discontinue ACEi/ARB therapy to decrease risk for more severe COVID-19 disease appear not to be well supported. Conversely, these agents should not be initiated solely for treatment of COVID-19 disease.

» **Anticoagulants**[40,41,63,65,69-71,93]

- Published guidelines from all relevant associations recommend that COVID-19 inpatients receive pharmacologic VTE prophylaxis (unless contraindicated). Either a low-molecular-weight heparin or fondaparinux can be used to reduce administration frequency, though heparin may be preferred in ICU patients due to its shorter half-life. Currently, the role of empiric therapeutically dosed anticoagulation is unknown, and it is ideal to enroll patients in randomized trials rather than empirically using therapeutic anticoagulation (see below discussion).
- Results from REMAP-CAP, ACTIV-4a, & ATTACC demonstrate that in non-critically ill patients an initial strategy of therapeutic anticoagulation with heparin increased survival to hospital discharge while also reducing the need for organ support (cardiovascular or respiratory) compared to standard prophylactically-dosed anticoagulation. Guidelines currently suggest continuing to weigh thrombotic versus bleeding risks in this population to guide clinical decision-making. Results of the above mentioned trials in critically ill patients noted no reduction in need for organ support or mortality, and enrollment was halted early in this arm. Similar results have been demonstrated in the INSPIRATION trial and other observational data. As a result, in the absence of other indications for therapeutic anticoagulation, use of empiric therapeutic anticoagulation in critically ill patients is discouraged in this time.
- Identification and treatment of the underlying cause(s) of COVID-19 associated coagulopathy should continue to be the focus of treatment efforts. Upon discharge, all COVID-19 patients should be educated on signs and symptoms of VTE. Due to results of the ACTION trial, extended thromboprophylaxis beyond discharge is not currently recommended in the absence of other indications.

» **Ibuprofen/NSAIDs**[22-23,32,40]

- Do not discontinue these therapies for COVID-19 disease. Acetaminophen and NSAIDs are both reasonable options for fever reduction in COVID-19 and may be selected in a patient-specific manner. Although there has been theoretical concern raised for NSAIDs worsening outcomes, no data currently exist to support this. WHO has revised their early statements and issued a clarification consistent with the above recommendation. NIH guidelines similarly recommend that patients taking NSAIDs continue this therapy and that antipyretics be selected in a patient-specific manner without regard for COVID-19 status.

» **Inhaled Pulmonary Vasodilators**[19-21,40,64]

- Limited *in vitro* evidence suggests nitric oxide may inhibit coronaviruses, and clinical experience has shown that inhaled nitric oxide can reduce mean pulmonary artery pressure and improve oxygenation in patients with non-COVID-19 ARDS. Despite this, SCCM guidelines recommend against use of nitric oxide given an unfavorable risk/benefit ratio for ARDS. NIH guidelines recommend inhaled pulmonary vasodilators only in mechanically ventilated COVID-19 patients with hypoxemia refractory to optimized therapy. If rapid improvement in oxygenation is not seen, therapy should be tapered off. Nitric oxide and others in its class (e.g., iloprost) are being investigated in clinical trials, and agents in this group are still recommended in the presence of clinical factors where they would routinely be considered for critical care.

» **Steroids**[5,6,19,32]

- Initially CDC, WHO, and SCCM did not recommend steroid therapy for COVID-19 outside of a specific alternative indication, such as sepsis, ARDS, or COPD. Based on recent evidence, however, WHO, NIH, SCCM, and IDSA all now recommend the use of glucocorticoids (e.g., dexamethasone) in patients with severe COVID-19 disease requiring supplemental oxygen or mechanical ventilation, but against using them in COVID-19 patients without hypoxemia requiring supplemental oxygen. More specific information regarding dexamethasone use can be found in its standalone section above.

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