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COVID-19 Antiviral and Pharmacotherapy Recommendations

Supportive therapy is the cornerstone of treatment. *No antiviral therapy option can currently be recommended in addition to supportive care, nor should any be considered comparatively superior for SARS-CoV-2 given the available data. It is also unclear at this time whether multidrug regimens provide any additional benefit in the treatment of COVID-19. Given the current lack of data over monotherapy regimens and the added toxicity of multidrug regimens, it is very unlikely that multidrug combinations will produce a favorable risk/benefit ratio.*

Antiviral therapy should only be considered in patients with confirmed infection. Therapies below have been tiered based on the available data, current availability, toxicity profile, and practical considerations specific to the Nebraska Medical Center. Updates are expected during this fluid situation.

Preferential (clinical trial enrollment):

» **Remdesivir Clinical Trial** (NCT04280705) – E-mail Andre Kalil (akalil@unmc.edu) and LuAnn Larson (llarson@unmc.edu) for evaluation
- Inclusion Criteria: Age ≥18, PCR confirmed SARS-CoV-2 infection within past 3 days, one of: 1) infiltrates on chest imaging 2) requiring supplemental oxygen or mechanical ventilation 3) respiratory exam findings and $SpO_2 \leq 94\%$
- Exclusion Criteria: AST or ALT >5x ULN, eGFR<50 or on dialysis, pregnancy or breast feeding, anticipated discharge within 3 days

Situational (alphabetical order): Risk/benefit ratio may favor use in selected patients. ID consultation required for use.

» **Hydroxychloroquine**[1-4,11]
- Dosing: 400mg BID x2 doses, then 200mg PO BID. Preferentially give with food.
- Duration: 5-10 days. Up to 20 total days of therapy have been reported in manuscripts.
- Adverse Effects: Generally of mild severity - GI intolerances, cytopenias, QT prolongation, headaches, dizziness
- Notes: Potent *in vitro* inhibitor of SARS-CoV-2 with early clinical reports of efficacy. Being investigated for and may be considered in all stages of disease severity. Use with caution in pediatrics. Impact of immunosuppressive effects is unknown.

» **Lopinavir/ritonavir**[13-14]
- Dosing: 400/100mg (2 tabs) BID
- Duration: 5-10 days. Up to 14 total days of therapy have been reported, but most patients have adverse effects requiring early termination.
- Adverse Effects: Occur in most patients and can be moderate/severe – GI intolerances, hepatitis, and LFT abnormalities
- Notes: Multiple *in vitro* studies suggesting activity, however early clinical reports are inconclusive. Being investigated in multiple clinical trials. Many clinically significant drug-drug interactions. Limited supply and adverse effects more substantial.

» **Remdesivir Compassionate Use** - ID Consult team will evaluate; do not begin the eIND process. If a possible candidate, the eIND process will be initiated through the UNMC Clinical Research Center (llarson@unmc.edu).
- Inclusion Criteria: Inpatient status, PCR confirmed SARS-CoV-2 infection, mechanical ventilation
  Exclusion Criteria: AST or ALT >5x ULN, eGFR<30 or on dialysis, evidence of multi-system organ failure, requiring vasopressors, concurrent receipt of any other antiviral therapies for SARS-CoV-2 (prior therapy is OK)

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

» **Angiotensin/RAS Blocking Agents (ACEi/ARBs)**[17]
- Multiple professional societies in cardiology and nephrology have reviewed the current data and conclude that the evidence suggesting discontinuation of ACEi/ARB therapy to decrease risk for more severe COVID-19 disease does not support discontinuing these therapies for this purpose.

» **Darunavir/cobisistat**[10]
- No *in vitro* or clinical data yet exist to support this use, though a clinical trial has been registered in China.

» **Interferons**[8-9]
- Typically used in combination with ribavirin, interferons have been studied for patients with other coronaviruses, with mixed results. Their adverse effect profiles are also generally unfavorable.

» **Nitazoxanide**[11-12]

- 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).

» **Steroids**[5,6]

- CDC and WHO do not recommend steroid therapy for COVID-19 outside of a specific alternative indication, such as sepsis. Systematic reviews in other coronavirus and respiratory viral infections have demonstrated no survival benefit and possible harm.

» **Tocilizumab**[15-16]

- IL-6 inhibitor; IV formulation. Prior *in vitro* work in SARS indicated IL-6-mediated immune hyper-response as a potential cause of poor outcomes. Preliminary clinical experience from China in COVID-19 reported benefit, however neutropenia can be long-lasting so risk of secondary infection is possible and unquantified.

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