Transplant Infectious Disease

TID Evidence Review for Inpatient Treatment Options for COVID-19

The listed agents represent potential treatments for inpatient cases of COVID-19 largely based on limited evidence. Careful clinical consideration should be applied when deciding to use the agents listed in this select evidence review. This document should not be used as empiric or definitive treatment guidelines. Evidence is continuing to evolve, as such this document will be updated accordingly.

AGENTS	PLACE IN THERAPY	DRUG INTERACTIONS	CONTRAINDICATIONS/ADVERSE EVENTS
Remdesivir (GS-5734)			
Antiviral with activity against Ebola, MERS, SARS *Prodrug nucleotide analog of adenosine triphosphate; incorporates into nascent viral RNA chains and results in premature termination.* Gilead	Investigational agent Emergency Use Authorization (EUA) available in US with limited supply. **FDA EUA Fact Sheet for Providers** Expanded Access via Gilead: Critically-ill patients with severe COVID-19, requiring mechanical ventilation, not on vasopressors at time of initiation	Avoid co-administration with: • Hydroxychloroquine – potential for reduced antiviral activity of remdesivir	**AE:** Abnormal LFTs, hepatotoxicity, abnormal INR, PT & PTT, reversible kidney injury, nausea, vomiting, diarrhea, headache, rash **Contraindications/Precautions:** Monitor for hepatotoxicity, monitor for nephrotoxicity as IV formulation contains cyclodextrin **FDA MedWatch Adverse Event Reporting for patients receiving EUA remdesivir**

Evidence

- Preliminary results from double-blind RCT comparing remdesivir (n=538) versus placebo (n=521) in hospitalized patients with COVID-19 and at least one of the following criteria: infiltrates on chest imaging, SpO2 ≤94% on room air, or supplemental oxygen requirement including mechanical ventilation. Pts were excluded if eGFR < 30ml/min, LFTs > 5x ULN, pregnant, or breastfeeding. Among 1063 patients, those treated with remdesivir had a shortened median time to recovery (11d v 15d) compared with placebo. Significant clinical status improvement, measured by 8-point ordinal scale, was seen with remdesivir compared to placebo (59.2% v 49.5%, OR 1.5). No significant difference was found for mortality at 14 days although it was numerically lower with remdesivir (7.1% v 11.9%). Serious adverse events were experienced in 21.1% of patients receiving remdesivir compared to 27.0% in those receiving placebo. Common adverse events in remdesivir treated patients were anemia or decreased hemoglobin (7.9%), AKI, reduced eGFR or CrCl (7.4%), pyrexia (3.3%), hyperglycemia (4.1%), and LFT increases (4.1%). Full data analysis pending further enrollment. (Beigel)
- Randomized open-label, phase 3 trial of 397 hospitalized patients with COVID-19 who received remdesivir for a duration of 5 days v 10 days in 55 hospitals across US, Europe, and Asia. Patients had SpO2 ≤94% on room air, infiltrates on chest imaging, and a positive SARS-CoV-2 PCR within 4 days of enrollment. Patients on mechanical ventilation were excluded. Supportive care was also administered. At baseline patients in 10-day group had significantly worse clinical status (p=0.02) compared to 5-day group. Patients were treated for a median duration of 5 days and 9 days in each group. At day 14, clinical improvement by 2 points, based on 7-point ordinal scale, occurred in 64% of patients treated for 5 days and 54% in those who received 10 days of remdesivir. Median duration of hospitalization among those discharged on or before day 14 was shorter in 5 day group compared to 10 day group (7d v 8d) with more patients being discharged in 5 day group (60% v 52%). Mortality was numerically lower in 5 day group (8% v 11%). Common adverse events were nausea (9%), worsening respiratory failure (8%), elevated ALT (7%), and constipation (7%). (Goldman)
- RCT of 237 hospitalized patients in Hubei, China with severe COVID-19 randomized 2:1 to remdesivir v placebo for up to 10 days. Study was underpowered but found no statistically significant difference in time to clinical improvement with remdesivir (21d) v placebo (23d) nor difference in duration of oxygen support, length of hospitalization, rate of discharge, nor death. No major difference in adverse reactions among groups. (Wang)

Clinical Trials

- Expanded Access: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection (US). NCT04323761
- Adaptive COVID-19 Treatment Trial (US). NCT04280705
- Expanded Access Remdesivir (RDV; GS-5734™). NCT04302766
- Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment (US). NCT04292730
- Study to Evaluate the Safety and Antiviral Activity of Remdesivir in Participants with Severe Coronavirus Disease (COVID-19) (US). NCT04292899

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- Goldman JD et al. NEJM. 27 May 2020. DOI: 10.1056/NEJMoa2015301
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Hydroxychloroquine (HCQ)			
Antimalarial *Increases pH of acidic intracellular vesicles that may lead to inhibition of endosome-mediated fusion, viral entry and pH dependent steps in viral replication. Anti-inflammatory and immunomodulatory properties that may inhibits release of inflammatory cytokines INFγ, IL-6, IL-1, TNF-α* HCQ: Hydroxyl analog of chloroquine. Similar activity and properties to chloroquine w/ ↓tox	**FDA EUA no longer available (US)** **Not recommended for COVID-19 due to lack of definitive evidence differentiating outcomes benefit with HCQ compared to supportive care and increased risk of adverse events** Not recommended outside of clinical trials, due to concerns about safety and efficacy FDA cautions against use for COVID-19 outside of hospital setting or clinical trial	Drug-drug interaction checker available here Avoid co-administration with: • Remdesivir – potential to reduce antiviral activity of remdesivir Caution used for co-administration with: • Tacrolimus & Sirolimus – potential to increase tacrolimus & sirolimus plasma conc due to moderate P-gp inhibition; potential risk for QT prolongation • Cyclosporine – potential to increase cyclosporine plasma conc • Posaconazole & Voriconazole – potential to increase HCQ plasma conc & increase risk of QT prolongation due to CYP3A4 inhibition • Trimethoprim/sulfamethoxazole – potential for increased HCQ plasma conc similar to effect of chloroquine due to MATE1 inhibition & potential for enhanced hypoglycemic effect • Lopinavir/ritonavir – potential to increase HCQ plasma conc & risk of QT prolongation	**Avoid use with concurrent azithromycin (esp in pts with acute renal failure) due to QTc prolongation and risk of cardiac arrhythmias (Chorin, NIH Guidelines)** For patients with underlying CV disease or on concurrent QT prolonging medications, obtain baseline EKG and monitor QTc. Avoid use if baseline QTc $\geq$ 500ms or in pts with known congenital QT prolongation. Maintain electrolytes (K>4mEq/L, Mg>2mg/dl) while on therapy (Roden) **AE:** QT prolongation, nausea, vomiting, cardiomyopathy, pancytopenia, hepatotoxicity, irreversible retinopathy, extrapyramidal reaction, pruritus **Contraindications/Precautions:** Caution in pts with QT prolongation, underlying cardiac disease, seizure history, severe hypoglycemia, proximal myopathy or neuromyopathy, retinal toxicity, GI disorders, hepatic impairment, G6PD deficiency

Evidence

- Randomized, double-blind, placebo-controlled trial of hydroxychloroquine post-exposure prophylaxis among 821 asymptomatic patients who were not hospitalized and reported to be at high-risk exposure to a confirmed COVID-19 contact. Pts were enrolled within 4 days following potential exposure and received HCQ 800mg once followed by 600mg once 6-8 hours later, then 600mg daily for 4 additional days or placebo. Primary outcome of incidence of lab-confirmed COVID-19 or clinically-suspected COVID-19 within 14 days did not differ significantly among those receiving HCQ v placebo (11.8% v 14.3%). Side effects were more common with HCQ than placebo (40.1% v 16.8%) without any reports of serious adverse events. (Boulware)
- Randomized, parallel-group trial to evaluate the efficacy of HCQ (400mg/day; 200mg BID x 5 days) v standard treatment (supportive care=control) in 31/62 patients with mild COVID-19 illness (excluded severe/critically ill) in Wuhan. Time to clinical recovery (TTCR) in days, clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment. Fever recovery time (3.2d vs. 2.2d, p=0.0008) and duration of cough (3.1d vs. 2d, p=0.0016) significantly shortened in HCQ versus control group, respectively; per chest CT, pneumonia improved 25/31 (80.6%) in HCQ vs. 17/31 (54.8%) in control group, p=0.047. Severe illness progressed in 4 of 62 patients (all controls). Mild adverse reactions (HCQ): rash, headache. (Chen Z)
- Pre-print information: Non-randomized propensity-matched comparative study of pts receiving HCQ 600mg daily within 48hrs of hosp (n=84) v those who did not (control, n=97) combined with standard of care. Among 181 pts, all of whom had bilateral PNA and required supplemental oxygen, no difference found in the composite outcome of transfer to ICU within 7 days or all-cause mortality (HCQ 20.2% v control 22.1%). ARDS developed within 7 days in 27.7% of pts treated with HCQ v 24.1% in controls. 9.5% of pts in HCQ group experienced EKG changes requiring therapy discontinuation, with a median d/c time of 4 days. Authors stated findings do not support use of HCQ in COVID PNA. (Mahévas)
- Pre-print information: Multicenter, open-label RCT of 150 pts hospitalized with COVID-19 who received HCQ 1,200mg daily x 3 days followed by 800mg daily + SOC (n=75) v SOC alone (control, n=75). 28-day negative conversion rates of SARS-CoV-2 was not different between HCQ + SOC v controls (85.4% v 81.3%, median time to negative conversion 8 v 7 days) nor were differences in negative conversion rates at days 4, 7, 10, 14, 21, including in a sub-analysis of pts who received HCQ within 7 days of symptom onset v those with initiation beyond 7 days. No difference in 28-day symptom alleviation (59.9% v 66.6%), however in a post-hoc analysis in which confounding use of other antiviral agents were removed, HCQ was associated with an improved rate of symptom alleviation, more rapid normalization of CRP, and a trend towards more rapid recovery of lymphopenia. AE rate of 30% in HCQ (10% diarrhea) v 8.8% in controls. (Tang)
- Pre-print information: Retrospective review of 84 adult pts with COVID-19 in US treated with HCQ and azithro combination therapy, which found a significant association with QTc prolongation (30% of pts with increase >40ms, 11% of pts with increase to >500ms), placing these pts at higher risk for arrhythmias, although no cases of torsades reported. Maximal QTc increase was noted on treatment days 3-4. Acute renal failure was noted to be a significant predictor of severe QTc prolongation, but baseline QTc and QTc >460ms did not predict QTc prolongation. Concurrent amiodarone use associated w/ risk. Authors recommend repeat monitoring of QTc for pts receiving HCQ/Azithro combo. (Chorin)
- Pre-print information: Retrospective review of 368 adult pts with COVID-19 at VAMC treated with HCQ alone (n=97), HCQ+Azithro (n=113), or controls receiving no HCQ (n=158). Higher mortality reported with HCQ alone (27.8%) compared to HCQ+Azithro (22.1%) & controls (11.4%) w/ similar rates of risk of mech ventilation (adjusted HR 1.43 HCQ alone v HR 0.43 HCQ+Azithro compared to controls). Emphasize need for results from ongoing RCT prior to recommended use of HCQ. (Magagnoli)

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AGENTS	PLACE IN THERAPY	DRUG INTERACTIONS	CONTRAINDICATIONS/ADVERSE EVENTS
Lopinavir/Ritonavir (Kaletra®)			
Antiretroviral *HIV protease inhibitor that may provide activity against 3CL protease enzyme of SARS-CoV-2 to prevent cleavage of large polyproteins during viral replication*	Limited availability and current level of evidence (CAO, NEJM 2020) does not support current use of lopinavir/ritonavir for COVID-19	Drug-drug interaction checker available here – Major CYP450 substrate (3A4), inhibitor (3A4, 2D6), inducer (2C19, 2C9, 1A2, 2B6), and transporter inhibitor Avoid co-administration with: • Sirolimus & Everolimus – potential to increase sirolimus & everolimus plasma conc due to CYP3A & P-gp inhibition Caution used for co-administration with: • Tacrolimus – potential to increase tacrolimus plasma conc due to CYP & P-gp induction • Cyclosporine – potential to increase cyclosporine plasma conc due to CYP3A4 inhibition • Mycophenolate – potential to alter mycophenolate plasma conc due to interference with glucoronidation • Voriconazole – potential to decrease voriconazole plasma conc due to CYP induction • Posaconazole – potential to increase ritonavir plasma conc due to CYP3A inhibition • Methylprednisolone & prednisone– potential to increase methylprednisolone & prednisone plasma conc due to CYP3A4 inhibition • Atovaquone – potential to decrease atovaquone plasma conc due to glucoronidation induction • Hydroxychloroquine – potential to increase HCQ plasma conc & risk of QT prolongation	**AE**: nausea, vomiting, diarrhea abdominal pain, dyspepsia, dysgeusia, hepatotoxicity, pancreatitis, diabetes, QT prolongation, torsades de pointes, dyslipidemia, peripheral lipoatrophy, and visceral adiposity **Contraindications/Precautions**: Contraindicated with co-administration of potent CYP3A inducers, and in patients who demonstrated hypersensitivity to any of its ingredients. Major CYP450 substrate (3A4), inhibitor (3A4, 2D6), inducer (2C19, 2C9, 1A2, 2B6), and transporter inhibitor

Evidence

- Press Release – RECOVERY: Randomized, controlled trial of 1596 hospitalized patients who received lopinavir-ritonavir compared with 3376 patients who received usual care alone demonstrated no significant difference in the primary end point of 28-day mortality (22.1% with lopinavir-ritonavir v 21.3% usual care, RR 1.04, p=0.58). 70% of patients required supplemental oxygen, 4% required mechanical ventilation, however mortality was similar among subgroups, and no evidence to support benefit on the risk of progression to mechanical ventilation or length of hospitalization. (RECOVERY)
- Randomized, controlled, open-label trial of 199 severely-ill hospitalized patients with confirmed SARS-CoV-2 comparing lopinavir/ritonavir with standard of care (n=99) versus SOC alone (n=100) for 14 days, with a 13 day median time between symptom onset and randomization. Primary endpoint of time to clinical improvement or live hospital discharge was not significantly different (16d v 16d), although lopinavir/ritonavir led to a median time to clinical improvement 1 day shorter than SOC (15d v 16d) in mITT group, however treatment within 12 days was not found to be associated with a shorter time to clinical improvement. 28-day mortality in lopinavir/ritonavir treated patients was numerically lower (19.2% v 25.0%) in mITT analysis, with shorter ICU stay (6d v 11d), and fewer instances of mechanical ventilation. Percentage of patients with clinical improvement at day 14 was higher in lopinavir/ritonavir treated group (45.5% v 30.0%), but had similar percentage of patients with detectable viral RNA to SOC group. Lopinavir/ritonavir was more frequently associated with GI-related AE, and was stopped early in 13 pts due to adverse events. Systemic steroids were given in both groups (33.0% v 35.7%). (Cao)
- Retrospective, multicenter cohort study of 191 COVID-19 confirmed patients in Wuhan, China, with 41 (21%) patients receiving lopinavir/ritonavir. 29 of these patients were discharged and found to have a median duration of viral shedding of 22 days with no observable difference in duration of viral shedding among survivors who did and did not receive lopinavir/ritonavir. Receipt of lopinavir/ritonavir was not significantly different amongst survivors and non-survivors (22% v 21%). (Zhou)

References

- Press Release – Statement from chief investigators of the randomized evaluation of COVID-19 therapy (RECOVERY) trial on lopinavir-ritonavir. Univ of Oxford. 29 June 2020.
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- Zhou F et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. DOI: https://doi.org/10.1016/S0140-6736(20)30566-3

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Favipravir (T-705, Avigan®)			
Antiviral *Purine nucleoside analog that competitively inhibits RNA-dependent RNA polymerase resulting in chain termination thus preventing viral replication. Activity against influenza A and B, Ebola, and SARS-CoV-2 in vitro*	Investigational – not commercially available in US	Mild CYP2C8 inhibitor	**AE:** AST/ALT elevations, GI toxicity, hyperuricemia, neutropenia **Contraindications/Precautions:** teratogenic, avoid use in pregnancy

Evidence

- Randomized, open-label, clinical trial of 240 patients to evaluate favipiravir versus umifenovir (Arbidol) in COVID-19 patients at 3 hospitals in Wuhan, China. The primary outcome was clinical recovery on day 7, and the secondary outcomes were duration of fever, cough relief time, oxygen therapy, and MV rate. 116 patients were assigned to favipiravir (1600 mg BID on day1, followed by 600 mg BID), and 120 patients to umifenovir (200 mg TID). The rate of clinical recovery on day 7 was 61.21% (71/116) in the favipiravir group and 51.67% (62/120) in the umifenovir group (P=0.0199). The duration of fever and time to cough relief was significantly shorter in the favipiravir group (both p<0.001). However, there was no difference in supplemental oxygen therapy use and MV rate. GI symptoms, and elevated uric acid was more common with favipiravir. (Chang Chen)
- Open-label, controlled study of 80 COVID-19 patients to compare favipiravir (Day 1: 1600 mg BID; Days 2–14: 600 mg BID) with lopinavir/ritonavir (Days 1–14: 400 mg/100 mg BID). Patients had mild to moderate COVID-19 and were enrolled within 7 days from disease onset. Both groups were treated with added interferon-α by aerosol inhalation (5 million units twice daily). Outcomes were changes in CT, viral clearance, and drug safety. There were 35 patients in the favipiravir arm and 45 patients in the lopinavir/ritonavir arm. Time to viral clearance was shorter in the favipiravir group (4 days v 11 days, P<0.001), and CT imaging showed significant improvement with favipiravir (91.4% v 62.2%, P=0.004). Adverse reactions were less common in the favipiravir group compared to lopinavir/ritonavir (11.4% v 55.6%, p<0.01). (Cai)

Clinical Trials

- Study of the use of favipravir in hospitalized subjects with COVID-19 (US). NCT04358549
- Favipravir v hydroxychloroquine, azithromycin, zinc v standard of care (PIONEER) (UK). NCT04373733
- Efficacy and safety of favipravir in management of COVID-19 (Egypt). NCT04349241
- Favipravir combined with tocilizumab in the treatment of COVID-19 (China). NCT04310228

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