STRAC ID Leads Outpatient Strategies for COVID-19 Infection

Updated: January 28, 2021

- This is a summary of recommendations from STRAC ID Leads for outpatient management of COVID-19.
- There are no oral FDA-approved or authorized therapies for COVID-19.
- NIH and Infectious Diseases Society of America (IDSA) guidelines do not recommend non-FDA approved therapies for COVID-19 outside of a clinical trial.

Recommended by ID Leads

- Isolation – Persons diagnosed with COVID-19 should isolate at home
  - For mild to moderate disease, CDC recommends discontinuing isolation 10 days after the onset of symptoms and resolution of fever for at least 24 hours without the use of fever-reducing medicatins.
  - For asymptomatic persons, isolation for 10 days after the first positive test for SARS-CoV-2 is recommended.

  https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/isolation.html

- General Recommendations
  - Nutrition/hydration
  - Adequate sleep
  - Stop/limit smoking and vaping
  - Limit alcohol use
  - Acetaminophen or ibuprofen for fever

- Equipment
  - Thermometer
  - Pulse oximeter
  - Home blood pressure cuff

- Warning Signals Warranting Presentation to Health Care Setting for Evaluation
  - Oxygen saturation <94% at rest
  - Significant desaturation into 85% range upon walking
  - Persistent shortness of breath
  - Persistent fever
  - Decrease in mental status (e.g., confusion, lethargy)
  - Significant decrease in blood pressure

- Monoclonal Antibodies – Consider if patient meets criteria and is within 5 days of symptom onset
    - FDA authorized (under EUA):
        - Bamlanivimab (Lilly)
        - Casirivimab and imdevimab (Regeneron)
    - Inclusion criteria for monoclonal antibody use
        - Have had a positive direct viral test for SARS-CoV-2
        - Have had ≤ 5 days of symptoms (up to 10 days)
        - 12 years of age and older
        - Weigh at least 40 kilograms (about 88 pounds)

          AND
        - At high risk for progressing to severe COVID-19 and/or hospitalization (see definition below)
    - Must be administered IV over 1 hour with 1 hour of monitoring after infusion
    - Available at STRAC regional infusion center (RIC)
    - Side effects include infusion-related reactions such as fever, chills, flushing, hives, itching, anaphylaxis

    - **High risk for progressing to severe COVID-19 and/or hospitalization is defined as patients who meet at least one of the following criteria**:
        - Have a body mass index (BMI) ≥35
        - Have chronic kidney disease
        - Have diabetes
        - Have immunosuppressive disease
        - Are currently receiving immunosuppressive treatment
        - Are ≥65 years of age
        - Are ≥55 years of age AND have
            - Cardiovascular disease, or
            - Hypertension, or
            - Chronic obstructive pulmonary disease/other chronic respiratory disease.
        - Are 12 – 17 years of age AND have
            - BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, or
            - Sickle cell disease, or
            - Congenital or acquired heart disease, or
            - Neurodevelopmental disorders, for example, cerebral palsy, or
            - A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), or

- Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

https://www.fda.gov/media/143605/download
https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19
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Often Recommended by ID Leads

- Zinc lozenges
  - Antiviral activity
  - Can decrease duration/severity of common cold
  - Well-tolerated
  - High doses over long term – GI side effects, copper deficiency

  Prasad AS, Fitzgerald JT, Bao B, Beck FWJ, Chandrasekar PH. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. Ann Intern Med 2000;133:245-252.

- Vitamin D
  - Important for immune function and an Immune modulator
  - Vitamin D deficiency associated with worse outcomes
  - Consider especially for those at risk for deficiency
    - Elderly
    - Persons with melanin-rich skin
    - Persons with no or limited sun exposure
  - Dose of 2000 IU daily

  Mitchell F. Vitamin-D and COVID-19: do deficient risk a poorer outcome? The Lancet Diabetes and Endocrinology. 8(7):570.
  Jain A, Chaurasia, Sengar NS, Singh M, Mahor S, Narain. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Nature Research 2020;10:20191.

- Melatonin
  - Antioxidant and anti-inflammatory
  - Production decreased in older adults
  - Good safety profile
  - Reasonable dose is 3 mg nightly which is easily found in tablet form
  - If a smaller dose is needed due to morning grogginess, use the liquid form at 0.3 mg nightly

  Hardeland R. Melatonin and inflammation: story of a double-edged blade. J Pineal Res. 2018;65(4):e12525.

Silvestri M, Rossi GA. Melatonin: its possible role in the management of viral infections: a brief review. Ital J Pediatr. 2013;39:61.

Sometimes Recommended by ID Leads

- Famotidine
  - Histamine-2 receptor antagonist may modulate cytokine storm
  - Positive preliminary studies warrant further investigation
  - Good safety profile

  Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. Am J Gastroenterol 2020

- Self-proning
  - May be used in cooperative patients who have mild desaturation and are comfortable in prone position
  - Benefit usually noticed within 5-10 minutes
  - Usual interval 30-120 minutes
  - Sequence: prone, left lateral decubitus, right lateral decubitis, upright sitting
  - Only maintain if comfortable for patient
  - Avoid with pregnancy, spinal instability, face or neck trauma, hemoptysis

  Telias I, Katira BH, Brochard L. Is the prone position helpful during spontaneous breathing in patients with COVID-10? Jour Amer Med Assoc 2020;323:22:2265-2267.

No Recommendation

- Aspirin (ASA)
  - Preliminary observational study showed less complications in hospitalized patients who had received ASA within 24 hours of admission or 7 days prior to admission
  - Risk of bleeding
  - Avoid in children due to Reye's Syndrome

  Chow JH, Khanna, AK, Kethireddy, S, et al. Aspirin Use is Associated with Decreased Mechanical Ventilation, ICU Admission, and In-Hospital Mortality in Hospitalized Patients with COVID-19 Anesthesia & Analgesia Pub ahead of print: Oct. 21, 2020

- Ivermectin
  - Preliminary positive study in hospitalized patients
  - Good safety profile
  - Animal preparations should not be used in humans

  Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter J. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019. Chest: Oct. 12, 2020.
  - Additional information:

https://blogs.jwatch.org/hiv-id-observations/index.php/ivermectin-for-covid-19-breakthrough-treatment-or-hydroxychloroquine-redux/2021/01/04/

- Interim meta-analysis for all-cause mortality
- https://www.youtube.com/watch?v=yOAh7GtvcOs&feature=youtu.be
- Mortality risk ratio 0.17, (CI 0.08, 0.35), an 83% reduction
- Other endpoints (time to viral clearance, clinical recovery, hospital LOS) also favorable
- Limitations – incomplete data, open label format, differences in dosing, publication bias
- Some concerns about neurotoxicity in inflammatory phase (due to decrease in BBB)
- Results from more RCTs expected soon
- NIH guidelines still recommend against use outside a clinical trial https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/ivermectin/
- Our sources indicate that ivermectin is scarce at the current time
- Use of veterinary ivermectin is not recommended.

- Fluvoxamine
  - SSRI that is an immunomodulator
  - Potential mechanisms
  - Sigma-1 activation – reduces cytokine production
  - Inhibits sphingomyelinase, relevant for viral entry
  - Inhibits hyperactivation of platelets and mast cells
  - Inhibits metabolism of melatonin
  - Good safety profile
  - Inexpensive and widely available

  - Positive Phase 2 study in outpatients
  - Lenze EJ, Mattar C, Zorumski CF et al. Fluvoxamine vs. placebo and clinical deterioration with symptomatic COVID-19. JAMA Published online November 12, 2020.
  - STOP COVID Trial (Phase 2 trial) Lenze et al. JAMA 2020
  - Primary endpoint – clinical deterioration, N=152 outpatients
  - 0% (0/80) in fluvoxamine group vs 8.3% (6/72) in the placebo group. 5/6 to hospital; 4 hospitalized
  - P=0.009
  - SAEs – 1 in fluvoxamine group (hospitalization for dehydration) vs. 6 in placebo group

  - Phase 3 trial underway. Pts can be referred to trial https://stopcovidtrial.wustl.edu/

- Nasal irrigation with 1% povidone-iodine
  - Iodine should not be used in thyroid conditions or pregnancy
  - User must be competent in using irrigation device, including proper cleaning
  - Farrell NF et al. Benefits and safety of nasal saline irrigations in a pandemic—washing COVID-19 away. JAMA Otolaryngology-Head & Neck Surgery. 2020;146;787

- Probiotic *Lactobacillus rhamnosus*
  - Some evidence to suggest immunomodulatory effect in sepsis
  - Clinical trial ongoing in COVID-19

  https://sites.duke.edu/protectehc/about-our-study/

Not Recommended Until More Information is Available

- Colchicine
  - Preliminary positive study in hospitalized patients
  - Side effects: GI (diarrhea, nausea/vomiting, abdominal pain), muscle weakness, numbness/tingling, allergic reaction

  Deftereos SG, Giannopoulos G, Vrachatis DA et al. Effect of colchicine vs. standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease. JAMA Network Open 2020:3(6):e2013136

  - Additional Information:
    - COLCORONA Study
    - https://www.medrxiv.org/content/10.1101/2021.01.26.21250494v1.full.pdf
    - Dose 0.5 mg BID x 3 days and once daily thereafter for total of 30 days
    - Study in non-hospitalized pts. Primary endpoint death or hospitalization
    - COVID dx by PCR or clinical criteria, N=4488
    - Death or hospitalization decreased 1% (4.7% vs 5.8%; OR 0.79, p 0.08)
    - PCR confirmed Covid, N=4159
    - Death or hospitalization decreased 1.4% (4.6% vs 6.0%, p 0.04)
    - Diarrhea more common in the colchicine group (13.7% vs 7.3%, p 0.0001)
    - Pulmonary embolism more common in the colchicine group 0.5% vs. 0.1%, **11 vs 2 pts**, p 0.01
    - Generic colchicine no longer available; based on our sources 30 days of colchicine costs ~$250

Not Recommended

- Corticosteroids – not recommended in outpatients
  - RECOVERY trial showed benefit for those requiring supplemental oxygen.
  - Pts who did not require oxygen had worse clinical outcomes

  The Recovery Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. New Eng J Med NEJMoa2021436, 2020. doi:10.1056/NEJMoa2021436.

- Hydroxychloroquine
  - Multiple well-conducted studies show negative results
  - Side effects – GI and prolonged QT interval

  Saag MS. Misguided use of hydroxychloroquine for COVID-19. Jour Amer Med Assoc Published online November 9, 2020

- Azithromycin and Doxycycline
  - Studies largely done with hydroxychloroquine
  - Well-conducted trials have been negative
  - Unnecessary use contributes to antimicrobial resistance
  - Side effects – prolonged QT interval, GI, *C. difficile* colitis

- Vitamin C
  - Antioxidant and anti-inflammatory
  - Studied in sepsis with variable outcomes
  - Few safety concerns
  - COVID-19 studies have been IV doses in hospitalized patients
  - Clinical trials ongoing

NIH Guidelines https://www.covid19treatmentguidelines.nih.gov/

IDSA Guidelines https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

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