STRAC ID Leads Outpatient Strategies for COVID-19 Infection

Updated: August 4, 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 authorized or 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 medications.
    - For severe disease (requiring hospitalization), CDC recommends discontinuing isolation 20 days after the onset of symptoms and resolution of fever for at least 24 hours without the use of fever-reducing medications; for immunosuppressed persons and those requiring intubation isolation should be continued for 28 days.
    - 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
  - FDA authorized (under EUA) https://www.fda.gov/media/145611/download
    - Casirivimab and imdevimab (REGEN-COV, Regeneron)
  - **Treatment** (within 10 days of onset)
    - Mild to moderate COVID-19 disease
    - in adult and pediatric patients (12 years of age and older weighing at least 40 kg)
    - with positive results of direct SARS-CoV-2 viral testing,
    - who are at high risk for progression to severe COVID-19, including hospitalization or death
  - Limitations of Authorized Use
    - ***Not*** authorized for use in patients who:
      - Are hospitalized due to COVID-19
      - Require oxygen therapy due to COVID-19
      - 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
    - Monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.
  - Criteria for identifying high risk individuals for monoclonal antibody administration:

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m2 ,
- or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy)
- Or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19)

- Other factors may place individual patients at high risk for progression to severe COVID-19 and the EUA is not limited to the medical conditions or factors listed above.

Not Recommended

- Oral corticosteroids – not recommended in outpatients not on oxygen for COVID-19
  - RECOVERY trial showed benefit for hospitalized pts requiring supplemental oxygen.
  - Hospitalized pts who did not require oxygen had worse clinical outcomes on steroids

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

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
  - Vitamin D supplementation can protect against acute (non-COVID) respiratory infection
  - Supplementation in hospitalized COVID-19 pts – no difference in LOS, intubation, death
  - 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. 2020;8(7):570. https://www.thelancet.com/journals/landia/article/PIIS2213-8587%2820%2930183-2/fulltext

  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. https://www.covid19treatmentguidelines.nih.gov/therapies/supplements/vitamin-d/

- 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.
Cross KM et al. Melatonin in early treatment for COVID-19: A narrative review of current evidence and possible efficacy. Endocrine Practice 2021
https://doi.org/10.1016/j.eprac.2021.06.001

Sometimes Recommended by ID Leads

- 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
  - Lenze EJ, Mattar C, Zorumski CF et al. Fluvoxamine vs. placebo and clinical deterioration with symptomatic COVID-19. JAMA Published online November 12, 2020.
    - Positive Phase 2 study in outpatients; Dose 100 mg TID
    - 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
  - Seftel D, Boulware D. Prospective cohort of fluvoxamine for early treatment of coronavirus disease 19. Open Forum ID 2021;8(2) ofab050 https://doi.org/10.1093/ofid/ofab050 1 Feb 2021
    - Dose 50 mg twice daily
    - 0/65 pts on fluvoxamine hospitalized; 0/65 residual sx
    - 6/48 (12/5%) on observation hospitalized; 29/48 (60%) residual sx
  - Phase 3 trial underway. Pts can be referred to trial https://stopcovidtrial.wustl.edu/ Dose 100 mg twice daily

- Inhaled budesonide
  - Ramakrishnan S et al. Inhaled budesonide in the treatment of early COVID-19: a phase 2, open label, RCT. Lancet Respiratory Medicine 2021;9(7):763-772. April 09, 2021 DOI:https://doi.org/10.1016/S2213-2600(21)00160-0
  - Small study, n=146
  - Early administration of inhaled budesonide reduced the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19.

- Famotidine
  - Histamine-2 receptor antagonist may modulate cytokine storm
  - Positive preliminary studies warrant further investigation
  - Good safety profile
  - Would not exceed approved dose of 40 mg daily

  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

- Ivermectin
  - Recent meta-analysis showed improved mortality but two large studies in analysis had flawed data, and without them, no benefit
  - Good safety profile
  - Some concerns about neurotoxicity in inflammatory phase (due to decrease in BBB)
  - 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.
  Hill A et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. Open Forum ID ofab358 https://doi.org/10.1093/ofid/ofab358 6 July 2021

- 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

- 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

- 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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