Integrated Care Partners

Outpatient Treatment Resources for Mild COVID-19 Cases

1. Clinical presentation

- Frequently reported s/sx of pts admitted to hospital at illness onset:
  - Fever: 77 – 98%
    - Fever in Guan et al. study was present in **44%** of patients on admission, but in **89%** during hospitalization
    - Absence of fever does *not* exclude COVID
  - Cough: 46 – 82%
  - Myalgia/fatigue: 11 – 52%
  - Shortness of breath: 3 – 31%
  - Gastrointestinal symptoms: up to 10%
    - Can precede the development of fever and dyspnea (Wang et al)
  - Less commonly reported symptoms:
    - Sore throat
    - Cough with sputum production and/or hemoptysis

Symptoms near the time of presentation in various cohorts

	Guan et al. NEJM (largest cohort)	Shi et al Lancet	Yang et al. Lancet (critically ill pts)	Chen et al.	Huang et al.	Xu et al. BMJ
Constitutional						
Fever	473/1081 (43%)	18/21 (86%)	46/52 (88%)	82/99 (83%)	40/41 (98%)	48/62 (77%)
Myalgia	164/1081 (15%)		6/52 (12%)	11/99 (11%)		
Headache	150/1081 (14%)	2/21 (10%)	3/52 (6%)	8/99 (8%)	2/38 (8%)	21/62 (34%)
Upper respiratory						
Rhinorrhea	53/1081 (5%)	5/21 (24%)	3/52 (6%)	4/99 (4%)		
Sore throat	153/1081 (14%)			5/99 (5%)		
Lower respiratory						
Dyspnea	205/1081 (19%)	9/21 (43%)	33/52 (64%)	31/99 (31%)	22/40 (55%)	2/62 (3%)
Chest tightness		5/21 (24%)				
Cough	745/1081 (68%)	15/21 (71%)	40/52 (77%)	81/99 (82%)	31/41 (76%)	50/62 (81%)
Sputum	370/1081 (34%)	3/21 (14%)			11/39 (28%)	35/62 (56%)
Hemoptysis	10/1081 (1%)				2/39 (5%)	2/62 (3%)
Gastrointestinal						
Nausea/Vomiting	55/1081 (5%)	2/21 (10%)	2/52 (6%)	1/99 (1%)		
Diarrhea	42/1081 (4%)	1/21 (5%)		2/99 (2%)	1/38 (3%)	3/62 (8%)

-The Internet Book of Critical Care, by @PulmCrit

2. Who is eligible for treatment at home and management of their contacts?

- Home care for patients with mild symptoms and management of their contacts (updated by WHO on 3/17/20)
  - **https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts**

Created by Christina Polomoff, PharmD; Sean Jeffery, PharmD; Krystal Scinto and Nancy Scarpelli, UCONN Pharmacy Students; Naomi Nomizu, MD

Integrated Care Partners

3. Treatment options for symptom management of mild cases

- Patients with mild disease do not require hospital interventions; but isolation is necessary to contain virus transmission and will depend on national strategy and resources.
- Symptom management for COVID-19 can be based on symptom management for influenza. **Tamiflu does *not* work for COVID**

    - Fever and Pain:
        - Acetaminophen may be preferable over NSAIDs until more data is available
    - Dry Cough:
        - To suppress cough, use products containing dextromethorphan (e.g. Robitussin DM, Delsym, Mucinex DM, Tussin DM – alcohol free)
    - Productive Cough:
        - To loosen phlegm use products containing guaifenesin (e.g. Robitussin, Mucinex)
    - Shortness of Breath:
        - Albuterol with a spacer

- **Do *not* routinely give systemic corticosteroids** for treatment of viral pneumonia outside of clinical trials. A systematic review of observational studies of corticosteroids administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance).
    - Given the lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason. Other reasons may include: exacerbation of asthma or COPD, septic shock, and risk and benefit analysis needs to be conducted for individual patients.

- **Controversy with NSAIDs**
    - Controversy started with a tweet by the French health minister warned people not to take NSAIDs because some French patients experienced serious side effects
    - He cited *The Lancet Respiratory Medicine* **correspondence article**, “Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?” published on March 11, 2020:
        - This article suggests patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection and therefore should be monitored for ACE2-modulating medications, such as ACEi or ARBs.

        - *The European Society of Cardiology* states, “speculation about the safety of ACEi or ARB treatment in relation to COVID-19 does not have a sound scientific basis or evidence to support it.”

- **France advises that ibuprofen and thiazolidinediones can increase ACE2**
- WHO statements:
    - 3/16/20: Avoid ibuprofen
    - 3/18/20: At present, based on currently available information, **WHO does not recommend against the use of ibuprofen**. We are also consulting with physicians treating COVID-19 patients and are not aware of reports of any negative effects of ibuprofen, beyond the usual known side effects that limit its use in certain populations. WHO is not aware of published clinical or population-based data on this topic.
- **FDA statement on 3/19/20**:
    - **"At this time, FDA is not aware of scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening COVID-19 symptoms.** The agency is investigating this issue further and will communicate publicly when more information is available."

- **Bottom line:**
    - If possible, recommend acetaminophen over NSAIDs
    - Continue ACEi/ARB in patients who are currently taking.

4. **General treatment guidelines for symptom management of Severe Acute Respiratory Infection when COVID is suspected**

    - WHO Guidelines: ***https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected*** – see pg. 4

Integrated Care Partners

5. **Emerging anti-viral treatments being studied - reserved for the most vulnerable hospitalized patients**

- **Chloroquine and hydroxychloroquine (Plaquenil)**
    - In vitro and animal data
        - Chloroquine: Wang et al. 2020: can inhibit COVID with 50% inhibitory concentration of 1 uM, implying therapeutic levels can be achieved in humans
        - Hydroxychloroquine: Yalo et al. 2020: hydroxychloroquine was much more potent than chloroquine at inhibition of COVID-19 in cell lines.
    - Human data
        - Gautret et al. 2020: Hydroxychloroquine and azithromycin
            - **Study drug**:
                - Hydroxychloroquine 300 mg TID
                - Azithromycin 500 mg once followed by 250 mg daily for four days was added depending on clinical presentation
            - **Inclusion criteria**: age >12 years, PCR documented SARS-CoV-2 carriage in nasopharyngeal sample at admission
            - **Exclusion criteria**: known allergy to the drug, or had another contraindication including retinopathy, G6PD deficiency and QT prolongation, breastfeeding and pregnant patients
            - Viral load in nasopharyngeal swabs was tested daily in a hospital
            - **End point**: presence and absence of virus at Day 6-post inclusion
            - **Results**: 20 patients were treated, 16 control patients
                - Tx group showed significant reduction of viral carriage at Day 6-post inclusion, and lower average carrying duration
                - The addition of azithromycin was significantly more efficient for viral elimination
    - **Contraindications/Precautions**
        - Prolonged QT, epilepsy, porphyria, myasthenia gravis, retinal pathology
    - **Serious ADE** - generally from prolonged use (chloroquine is more toxic)
        - Torsade de pointes, cardiomyopathy, bone marrow suppression, hypoglycemia
- **Remdesivir**
    - Experimental antiviral being tested as a potential treatment
    - Not commercially available – only for compassionate use at present
- **Lopinavir/ritonavir**
    - Data suggests lopinavir/ritonavir should not be used for monotherapy
    - May be effective when used in combination with other antiviral agents

- **Tocilizumab (Actemra)**
    - A recombinant humanized monoclonal antibody which binds to interleukin-6 receptor and blocks it from functioning
    - Mechanistically would be expected to benefit patients with COVID-19 who develop a cytokine storm
    - Case series from China (Xu et al.)

6. Where can I find information about potential drug interactions with experimental COVID-19 treatments?

- Liverpool COVID-19 Drug Interactions Database http://www.covid19-druginteractions.org/

7. Is there a risk associated with using nebulizers vs. metered-dose inhalers (MDIs)?

- The Canadian Medical Association Journal posted an article: **"RE: Transmission of Corona Virus by Nebulizer- a serious, underappreciated risk!"** on March 3, 2020 which states, "nebulizer therapy in patients with pandemic COVID-19 infection has the potential to transmit potentially viable COVID-19 to susceptible bystander hosts."

8. Drug Shortages

- FDA is monitoring the drug supply chain and is in contact with > 180 manufacturers of human drugs. FDA will alert public of supply disruptions
    - Link: **FDA Drug Shortages Database**
- The American Pharmacists Association recommends:
    - Patients talk to their local pharmacist if concerned about medication supplies. Hoarding or stockpiling is not necessary, it could lead to drug shortage.
    - If patients' medication supplies are low, they can check their Rx benefit coverage with insurance company to determine coverage for early refill or supply limits. Many payors have relaxed their early fill policies

9. What clinical trials are available?

- New possible treatments are evolving every day. Use **clinicaltrials.gov website** for most up-to-date information.

Integrated Care Partners

Potential Outpatient Orders:

OTC Products for adult patients to purchase

Fever:

- Acetaminophen 1000mg (two 500mg tablets) three times daily until fever/pain resolves

Cough: Purchase a product containing dextromethorphan

- Robitussin DM liquid: follow directions on bottle
- Mucinex DM: follow directions on box
- Tussin DM for alcohol free version

Rx's for adult symptomatic relief

Shortness of Breath:

- Albuterol generic inhaler or formulary alternative: 2 puffs q4-6 PRN SOB
- Albuterol nebulizer as alternative (see risk above)

Cough: if OTC agents not effective

- Tessalon Perles: 100 – 200 mg PO TID PRN cough
- Codeine 10mg / guaifenesin 100mg syrup per 5 mL: 10 mL PO q4h PRN cough

Antiviral: data still evolving

- Azithromycin (Zithromax Z-Pak): 500 mg on day 1, then 250 mg on days 2-5
    - May potentially have beneficial anti-viral properties and/or immunomodulatory properties
    - This may be useful for community acquired pneumonia and COPD exacerbation
- We are discouraging outpatient providers from prescribing other therapies such as chloroquine, hydroxychloroquine, Remdesivir, lopinavir/ritonavir
    - Reserved for the most vulnerable hospitalized patients and these medications are infectious disease provider-restricted in HHC inpatient facilities

Useful links:

https://www.who.int/
https://www.cdc.gov/coronavirus/2019-ncov/index.html
https://emcrit.org/ibcc/covid19/
https://www.idstewardship.com/coronavirus-covid-19-resources-pharmacists/
https://covid-19.uwmedicine.org/Pages/default.aspx
COVID-19 Clinical Trials- https://clinicaltrials.gov/ct2/results?cond=%22wuhan+coronavirus%22

Created by Christina Polomoff, PharmD; Sean Jeffery, PharmD; Krystal Scinto and Nancy Scarpelli, UCONN Pharmacy Students; Naomi Nomizu, MD

Table 2. Clinical syndromes associated with COVID-19

Mild illness	Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea, nausea and vomiting *(3, 11-13).* The elderly and immunosuppressed may present with atypical symptoms. Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events, such as e.g. dyspnea, fever, GI-symptoms or fatigue, may overlap with COVID-19 symptoms.
Pneumonia	**Adult** with pneumonia but no signs of severe pneumonia and no need for supplemental oxygen. **Child** with non-severe pneumonia who has cough or difficulty breathing + fast breathing: fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40, and no signs of severe pneumonia.
Severe pneumonia	**Adolescent or adult:** fever or suspected respiratory infection, plus one of: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO_2 ≤ 93% on room air (adapted from *14)*. **Child** with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO_2 < 90%; severe respiratory distress (e.g. grunting, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions *(15).* Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 *(16).* While the diagnosis is made on clinical grounds; chest imaging may identify or exclude some pulmonary complications.
Acute respiratory distress syndrome *(17-19)*	**Onset:** within 1 week of a known clinical insult or new or worsening respiratory symptoms. **Chest imaging** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates**: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present. **Oxygenation impairment in adults** *(17, 19)*: • Mild ARDS: 200 mmHg < PaO_2/FiO_2[a] ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O, or non-ventilated) • Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg (with PEEP ≥ 5 cmH_2O, or non-ventilated) • Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O, or non-ventilated) • When PaO_2 is not available, SpO_2/FiO_2 ≤ 315 suggests ARDS (including in non-ventilated patients). **Oxygenation impairment in children:** note OI = Oxygenation Index and OSI = Oxygenation Index using SpO_2. Use PaO_2-based metric when available. If PaO_2 not available, wean FiO_2 to maintain SpO_2 ≤ 97% to calculate OSI or SpO_2/FiO_2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH_2O via full face mask: PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤ 264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3.
Sepsis *(5, 6)*	**Adults:** life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection.[b] Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine *(5, 20)* output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia. **Children:** suspected or proven infection and ≥ 2 aged based systemic inflammatory response syndrome criteria, of which one must be abnormal temperature or white blood cell count.
Septic shock *(5, 6)*	**Adults:** persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L. **Children:** any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental state; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulse; tachypnea; mottled or cool skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia *(21.)*.

[a] If altitude is higher than 1000 m, then correction factor should be calculated as follows: PaO_2/FiO_2 x barometric pressure/760.

[b] The SOFA score ranges from 0 to 24 and includes points related to six organ systems: respiratory (hypoxemia defined by low PaO_2/FiO_2); coagulation (low platelets); liver (high bilirubin); cardiovascular (hypotension); central nervous system (low level of consciousness defined by Glasgow Coma Scale); and renal (low urine output or high creatinine). Sepsis is defined by an increase in the sepsis-related SOFA score of ≥ 2 points. Assume the baseline score is 0 if data are not available *(22).*

Abbreviations: ARI acute respiratory infection; BP blood pressure; bpm beats/minute; CPAP continuous positive airway pressure; FiO_2 fraction of inspired oxygen; MAP mean arterial pressure; NIV non-invasive ventilation; OI Oxygenation Index; OSI Oxygenation Index using SpO_2; PaO_2 partial pressure of oxygen; PEEP positive end-expiratory pressure; SBP systolic blood pressure; SD standard deviation; SIRS systemic inflammatory response syndrome; SOFA sequential organ failure assessment; SpO_2 oxygen saturation.