Management of Ambulatory Patients with COVID-19

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Disclosures

• Nothing to disclose
Case (from Dr. Jon Iralu)

• 91 yo female American Indian presented with diarrhea and feverishness. She had no cough or dyspnea.
• Past medical history: bronchiectasis secondary to prior tuberculosis.
• Exam: appeared well; temperature 98 F; oxygen saturation 93%.
• Xpert positive for SARS-CoV-2 (result returned after she had gone home)
Management of Ambulatory Patients with COVID-19: Questions

• What testing should be done in someone with suspected COVID-19?
• When should you test and treat for influenza?
• When should someone come in for evaluation?
• Are there any specific treatments for mild or moderate COVID-19?
• What should be done about concomitant medications?
• How should you advise regarding isolation and protection of household contacts?
## COVID-19 Spectrum

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic/presymptomatic infection</td>
<td>Positive test for SARS-CoV-2 but no symptoms</td>
</tr>
<tr>
<td>Mild illness</td>
<td>Varied symptoms (eg, fever, cough, sore throat, taste/smell disturbance) but no shortness of breath or abnormal imaging</td>
</tr>
<tr>
<td>Moderate illness</td>
<td>SpO₂ &gt;94% &amp; lower respiratory disease (clinical or imaging findings)</td>
</tr>
<tr>
<td>Severe illness</td>
<td>SpO₂ &lt; 94%, PaO₂/FiO₂ &lt; 300, respiratory rate &gt;30/min, or lung infiltrates &gt; 50%</td>
</tr>
<tr>
<td>Critical illness</td>
<td>Respiratory failure, shock, and/or multiorgan dysfunction</td>
</tr>
</tbody>
</table>

Risk Factors for Severe COVID-19

- Older age
- Cancer
- Cardiovascular disease: heart failure, coronary artery disease, cardiomyopathy
- Chronic kidney disease
- Chronic obstructive pulmonary disease
- Immunocompromised: solid organ transplant
- Obesity (BMI of >=30)
- Pregnancy
- Sickle cell disease
- Smoking
- Type 2 diabetes mellitus

Possible risk factors include:
- Asthma (mod. to severe)
- Cerebrovascular disease
- Hypertension
- Liver disease
- Neurologic conditions, eg, dementia
- Other immunocompromised states
- Overweight
- Type 1 DM

Williamson EJ et al, Nature, 2020
What testing should be done?

- Patients with symptoms compatible with COVID-19 (or exposure) should have SARS CoV-2 testing.
- If clinical suspicion is high and first test is negative, repeat SARS CoV-2 testing.
Influenza-like Illness

• Fever and cough and/or sore throat
• COVID-19 and influenza (and other viral respiratory infections) cannot be reliably distinguished based on clinical criteria
• When influenza is circulating, in patients at high risk for complications of influenza, consider testing for SARS-CoV-2 and influenza A/B (multiplex tests available)
  • Potential for SARS CoV-2/influenza coinfection
• In patients at high risk for complications of influenza or worsening symptoms, consider empiric therapy
Examples of Adults at Risk for Severe Influenza

- Adults 65 years or older
- Pregnant women
- Nursing homes/long-term care facilities residents
- American Indians, including Alaska Natives

- Medical conditions, including
  - Chronic lung disease (asthma, COPD, CF)
  - Diabetes mellitus
  - Heart disease
  - Immunocompromised or receiving immunosuppressive treatments
  - Kidney disorders
  - Liver disorders
  - Neurologic/neurodevelopmental conditions
  - Obesity (extreme)
  - Sickle cell disease
Antiviral treatment for influenza

- Antiviral treatment recommended as soon as possible for any patient with suspected or confirmed influenza who:
  - Is hospitalized, or
  - has severe, complicated, or progressive illness, or
  - is at higher risk for influenza complications
- Don’t wait for lab testing, empiric treatment for priority groups
- For non-high-risk outpatients with suspected influenza – consider antiviral treatment based on clinical judgement; ideal if can be initiated within 48 hours of illness onset

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

NIH COVID-19 Treatment Guidelines
Slide courtesy of Dr. Jennifer Johnson, Brigham and Women’s Hospital
Antiviral agents for influenza

- **Zanamivir** (inhaled) – contraindicated in patients with underlying lung disease
- **Oseltamivir** 75mg BID x 5 d – [shorter time to resolution of symptoms]
  - usually covered by insurance, price ~ $35-100 @ Walmart
- **Baloxxavir** 40mg (< 80kg) or 80mg (> 80kg) x 1 – [CAPSTONE 2 = shorter time to resolution of symptoms and cessation of shedding]
  - Cost ~$150 @ Walmart
  - FDA approved for early treatment of uncomplicated influenza in outpatients
  - No published RCT data in hospitalized patients (for hospitalized influenza patients, CDC recommends oseltamivir)

Adapted from slide by Dr. Jennifer Johnson, Brigham and Women’s Hospital
Who should come in for evaluation?

• Patient with dyspnea, particularly if at rest or limiting daily activities
  • Typically occurs about 1 week after onset of symptoms
  • If home oximeter available, patient whose oxygen saturation drops below 95% (use on warm fingers, twice a day)
• Patient with severe or progressive symptoms (eg, confusion, lethargy, dizziness, falls, chest discomfort/tightness)
• Patient who does not clearly have a respiratory viral infection
• Patient without access to caregiver, food, assistance
• Low threshold for evaluation of people at high risk for severe COVID-19 or other processes (endocarditis, meningitis, etc)
In-person Evaluation

• Exam: look for tachypnea, hypoxemia, abnormal lung findings

• Testing for other pathogens (if not previously done)
  • Influenza, depending on season (multiplex assays detect SARS-CoV-2, influenza A and B)
  • Other viral respiratory pathogens
  • Throat and/or sputum culture; rapid strep antigen (if bacterial infection suspected)

• Chest imaging: X-ray, occasionally U/S
What about antibiotics?

• Empiric oral antibiotics for pneumonia?
  • Not for most patients; evaluation usually needed to diagnose bacterial pneumonia
  • If clinical or radiographic suspicion, then empiric therapy could be:
    • No comorbidities: amoxicillin or doxycycline x 5 days
    • Comorbidities: amox/clav + [doxy or azithro], or levofloxacin x 5 days

• Empiric oral antibiotics for Strep throat?
  • Not for most patients, throat swab for Strep rapid/culture usually needed
  • Could be appropriate if high-risk patient (known or likely exposure to GAS, recurrent Strep pharyngitis) and/or consistent clinical scenario
  • Penicillin or amoxicillin x 10 days (or cephalexin/cefadroxil)

Slide courtesy of Dr. Jennifer Johnson, Brigham and Women’s Hospital
https://academic.oup.com/cid/article/55/10/e86/321183
Case

• 40 woman without past medical history presents with dry cough x 2 days, close contact exposure to family member diagnosed with COVID-19.
  • CXR with patchy peripheral opacity in left mid to lower lung
  • Started on community acquired pneumonia (CAP) treatment (amoxicillin + azithromycin)
  • SARS CoV-2 PCR returns positive
  • Reasonable to stop antibiotics given diagnosis consistent with COVID-19 and nothing definitive pointing towards concurrent bacterial cause


Courtesy of Drs. Katharine Morley, Kevin Heaton, Jackie Chu
Treatment of Community-Acquired Pneumonia During the Coronavirus Disease 2019 (COVID-19) Pandemic

Joshua P. Metlay, MD, PhD, and Grant W. Waterer, MB, BS, PhD

The rapidly escalating coronavirus disease 2019 (COVID-19) pandemic has focused attention on the diagnosis and treatment of patients with acute respiratory infection in an unprecedented manner. Although most of the lung injury patients have been believed to be caused by the virus, concern over bacterial co-infection also informs current treatment approaches for patients with COVID-19-related pneumonia. As the cochairs of the recently released American Thoracic Society and Infectious Diseases Society of America Guideline for Treatment of Adults with Community-Acquired Pneumonia (CAP) (1), we offer our interpretation of the guideline as it applies to the management of patients with COVID-19 (Table).

1. **Empirical coverage for bacterial pathogens is recommended in patients with CAP without confirmed COVID-19 but is not required in all patients with confirmed COVID-19-related pneumonia.**

Community-acquired pneumonia is diagnosed in patients with signs and symptoms of respiratory infection (especially cough, sputum production, and fever) and radiographic evidence of lung involvement. The cause of CAP includes a range of bacteria and viruses, and with the introduction of the pneumococcal conjugate vaccine, however, a recent case series reported that serologic evidence of co-infection with bacterial pathogens (including chlamydia) was not uncommon among fatal cases of COVID-19 pneumonia (6).

2. Although data are limited, it is likely that the relevant bacterial pathogens in patients with COVID-19 and pneumonia are the same as in previous patients with CAP and therefore empirical antibiotic recommendations should be the same.

The bacterial pathogens responsible for CAP are reflective of the bacteria that often colonize the upper airway and opportunistically infect the lung during a respiratory illness. Therefore, we believe the same range of pathogens, including *Streptococcus pneumoniae, Haemophilus influenzae, Chlamydia pneumoniae*, and *Staphylococcus aureus*, should be considered in patients with COVID-19-related pneumonia. For low-risk inpatients (typically those on the general medical floors), the guideline recommends a β-lactam (for example, ampicillin-sulbactam, ceftriaxone, or cefotaxime) plus either a macrolide (azithromycin or clarithromycin) or doxycycline as combination therapies or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) as monotherapy. For high-
Case

• 40 woman without past medical history presents with dry cough x 1 week which initially improved but then worsened 2 days ago, now with return of fever and increase in sputum production

• CXR with focal consolidation in right middle lobe
  • Started on CAP treatment (amoxicillin-clavulanate + azithromycin)
  • SARS CoV-2 PCR returns positive

  • Might continue antibiotics given "second worsening”, focal consolidation


Courtesy of Drs. Katharine Morley, Kevin Heaton, Jackie Chu
Who should go to Emergency Department?

- Progressive dyspnea, weakness
- Confusion, lethargy, falls, chest pain suggestive of acute coronary syndrome, pulmonary embolism
- High respiratory rate, low oxygen saturation, low blood pressure
- Low threshold if older age and comorbidities (e.g. severe lung, heart, kidney disease, diabetes)
- Markedly abnormal CXR
- Patients with COVID-19 pneumonia can deteriorate rapidly: if discharged from clinic or ED, close follow-up critical
Management Across the COVID-19 Spectrum

<table>
<thead>
<tr>
<th>Features</th>
<th>Asymptomatic or Presymptomatic</th>
<th>Mild Illness</th>
<th>Moderate Illness</th>
<th>Severe Illness</th>
<th>Critical Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing</td>
<td>Positive SARS-CoV-2 test; no symptoms</td>
<td>Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea</td>
<td>Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%</td>
<td>Oxygen saturation &lt;94%; respiratory rate ≥30 breaths/min; lung infiltrates &gt;50%</td>
<td>Respiratory failure, shock, and multiorgan dysfunction or failure</td>
</tr>
<tr>
<td>Isolation</td>
<td>Screening testing; if patient has known exposure, diagnostic testing</td>
<td>Diagnostic testing</td>
<td>Diagnostic testing</td>
<td>Diagnostic testing</td>
<td>Diagnostic testing</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Proposed Disease Pathogenesis

- Viral replication
- Inflammation

Potential Treatment

- Antiviral therapy
- Antibody therapy
- Antiinflammatory therapy

Management Considerations

- Monitoring for symptoms
- Clinical monitoring and supportive care
- Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir
- Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)
- Critical care and specific therapy (dexamethasone, possibly remdesivir)

Gandhi RT, CID, 2020; Gandhi RT, Lynch J, del Rio C. NEJM 2020
Monoclonal Antibodies

• Monoclonal antibodies against SARS-CoV-2 being studied for treatment and prevention

• Target spike protein of SARS-CoV-2

• Emergency Use Authorizations for treatment of ambulatory patients with mild to moderate COVID-19 within 10 days of symptom onset:
  • Bamlanivimab (700 mg)
  • Casirivimab + Imdevimab (2400 mg)
In outpatients with mild to moderate disease (n=452), participants randomized to received iv infusion of placebo or one of three doses of a neutralizing antibody directed against SARS-CoV-2 spike protein (LY-CoV555)
LY-CoV555 (Bamlanivimab)

- At day 11, 2800 mg dose of antibody appeared to accelerate decline in viral load as compared to placebo
  - 3.4-fold lower in 2800 mg group than in the placebo group
  - Viral load decline did not differ significantly between other antibody doses and placebo
- In all 3 dose groups, there appeared to be a separation in virus level decay as compared to placebo

LY-CoV555 (Bamlanivimab)

- ED visit or hospitalization:
  - 1.6% in antibody group, 6.3% in placebo group
  - >65 yo, BMI >35: 4% in antibody group, 15% in placebo group

<table>
<thead>
<tr>
<th>Hospitalization/ED Visit: All Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>700 mg</td>
</tr>
<tr>
<td>2800 mg</td>
</tr>
<tr>
<td>7000 mg</td>
</tr>
<tr>
<td>Pooled antibody</td>
</tr>
</tbody>
</table>

- Median time to symptom improvement: 6 days with bamlanivimab; 8 days with placebo.
- Safety profile of bamlanivimab and placebo similar

Casirivimab/Imdevimab

• Two recombinant human mAbs: bind to non-overlapping epitopes of the SARS-CoV-2 spike protein receptor binding domain

• Phase 1/2 clinical trial in patients with mild to moderate COVID-19 (n=799)
  • Adults with 1 or more symptoms
  • Treatment initiated within 3 days of positive test (PCR or Ag)
  • Randomized 1:1:1 to receive C/I 1200/1200 mg (2400 mg); C/I 4000/4000 mg (8000 mg); or placebo
  • Median age: 42 years (7% >=65 years old)
  • 34% considered high risk
  • Symptoms: severe (31%); moderate (36%), mild (13%)

Boost immune responses

Boost immune responses

Casirivimab/Imdevimab

- Primary endpoint: time weighted average (TWA) change from baseline NP swab SARS CoV-2 level in patients with positive baseline PCR (n=665)
- Difference in TWA from day 1 to 7 in pooled C/I group: -0.36 log10 c/mL (p<0.0001)
- Largest reduction in VL in patients with high VL (-0.78 log10 c/mL) or who were seronegative at baseline (-0.69 log10 c/mL)

Casirivimab/Imdevimab

- Median time to symptom improvement: 5 days for participants who received C/I and 6 days for those who received placebo.

- Serious adverse event rate of C/I and placebo similar
  - 1 anaphylactic reaction
  - 4 infusion reactions in 8000 mg group; 1 in placebo gp

### Hospitalization/ED Visit: All Participants

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>231</td>
<td>10</td>
<td>4%</td>
</tr>
<tr>
<td>C/I 2400 mg</td>
<td>215</td>
<td>4</td>
<td>2%</td>
</tr>
<tr>
<td>C/I 8000 mg</td>
<td>219</td>
<td>4</td>
<td>2%</td>
</tr>
<tr>
<td>Pooled antibody</td>
<td>434</td>
<td>8</td>
<td>2%</td>
</tr>
</tbody>
</table>

### Hospitalization/ED Visit: Participants at Higher Risk of Hospitalization

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>78</td>
<td>7</td>
<td>9%</td>
</tr>
<tr>
<td>C/I 2400 mg</td>
<td>70</td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td>C/I 8000 mg</td>
<td>81</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Pooled antibody</td>
<td>151</td>
<td>4</td>
<td>3%</td>
</tr>
</tbody>
</table>

Expanded Use Authorization Criteria: Ambulatory Patients with Mild to Moderate COVID-19 at High Risk for Progression

- Body mass index (BMI) ≥35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥65 years of age
- ≥55 years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease
Expanded Use Authorization Criteria: Ambulatory Patients with Mild to Moderate COVID-19 at High Risk for Progression - 2

• 12 – 17 years of age
  • BMI 85th percentile for their age and gender
  • Sickle cell disease
  • Congenital or acquired heart disease
  • Neurodevelopmental disorders, eg cerebral palsy
  • Medical related technological dependence, for example tracheostomy, gastrostomy or positive pressure ventilation
  • Asthma, reactive airway or other chronic respiratory disease that requires daily medicine
Monoclonal Ab in Hospitalized Patients

• LY-CoV555 sub-study of ACTIV-3 trial closed after data suggested a lack of clinical benefit for LY-CoV555 in a hospitalized population

• EUA recommends against Casirivimab/Imdevimab in patients who are hospitalized for COVID-19 or who require oxygen therapy due to COVID-19
Monoclonal Antibodies: What do the Guidelines Say?

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA on 4/11/2020. Last updated, 12/2/2020

COVID-19 Guideline, Part 2: Infection Prevention
COVID-19 Guideline, Part 3: Diagnostics
COVID-19 Guideline, Part 4: Serology


Among ambulatory patients with COVID-19, the panel suggests against the routine use of bamlanivimab.

Remark: In patients at increased risk (as defined by FDA EUA) bamlanivimab is a reasonable treatment option if, after informed decision-making, the patient puts a high value on the uncertain benefits and a low value on uncertain adverse events.
Monoclonal Antibodies: What do the Guidelines Say?

• There are insufficient data to recommend either for or against use of bamlanivimab or casirivimab/imdevimab for treatment of outpatients with mild to moderate COVID-19.

• Bamlanivimab or casirivimab/imdevimab should not be considered the standard of care for treatment of patients with COVID-19.
Monoclonal Antibodies: My Take

• Monoclonal antibodies show promise but difficult to be certain as to magnitude of clinical benefit and which patients most likely to benefit
• More data from ongoing clinical trials needed; we continue to refer patients to those trials
• Monoclonal antibodies should not be used in patients hospitalized with COVID-19
• If monoclonal antibodies used under EUAs in high risk patients:
  • Logistical challenges in administering monoclonal antibodies to large number of people with mild to moderate COVID-19
  • Critical need to ensure equity in access
What about Concomitant Medications?

• ACE inhibitors
  • Because SARS-CoV-2 enters cells through ACE2, questions raised about ACE inhibitors or ARBs (which may increase ACE2 levels)
  • Large observational studies have not shown increased risk
  • Continue ACE inhibitors or ARBs if needed for other indications

• NSAIDs
  • Initial concern raised but results from cohort study and clinical experience reassuring that these drugs can be used

• Nebulized medications: avoid use in presence of others
COVID-19: Supportive Care

• Acetaminophen or NSAIDS
• Staying well hydrated (especially those having fever)
• Antitussives
• Rest but frequent repositioning, ambulation, advance activity as tolerated
Covid-19: Isolation

• PCR may remain positive for weeks to months
  • Duration of infectivity <=10 d after sx onset in pts with mild-to-moderate disease
  • <15-20 d in those with severe illness or immunocompromise

• Isolation can generally be discontinued 10 d after symptom onset and resolution of fever for at least 24 hours (without use of anti-pyretics) and improvement of other symptoms
Protecting Household Contacts

• If possible, separate bedroom & bathroom for person who is sick
• Keep people at higher risk separate from person who is sick
• Maintain 6 ft distance
• Open windows, turn on fans
• Sleep head to toe
• Physical divider to separate ill person’s bed
• Sick person should eat separately

Back to the Case

Case

• 91 yo female presented with diarrhea and feverishness.
• Past medical history: bronchiectasis
• Temperature 98 degrees F; oxygen saturation 93%
• Cepheid Xpert positive for SARS-CoV-2 after she goes home.

Follow-up (from Dr. Jon Iralu)

• Called 24 hours later: felt well; no fever, cough, dyspnea. Oxygen sat 94%
• Called a few days later: completely back to normal
Acknowledgments

• Jackie Chu
• Kevin Heaton
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• Tim Uyeki

• Efe Airewele
• Jon Iralu

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