

# (Still) Catching up with the Coronavirus

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# Disclosures

- No relevant financial disclosures
- I *will* be discussing off-label and investigational therapies

# Objectives

- Describe current known characteristics of the SARS-CoV-2 virus and findings of COVID-19 illness
- Outline recent trends in transmission and expectations for continued spread
- Apply available evidence to treat and control the spread of COVID-19

## First, a reminder...

- “Coronavirus” is a family of viruses
- “SARS-CoV-2” is the name of the virus causing the pandemic
- “COVID-19” is the name of the illness the virus causes
- (COVID = COronaVirus Disease)

## Where did it come from?

- SARS-CoV-2 is still thought to be most closely related to two bat coronaviruses. The pangolin (scaly anteater) is still a suspected intermediate host<sup>3</sup>
- Surprisingly, we still don't know the origin for sure, and it's still unclear exactly when and how SARS-CoV-2 made the leap to humans

## How is this continuing to spread?

- Our understanding of SARS-CoV-2 transmission is improving but still incomplete
- It's becoming clearer that respiratory droplets are a primary means of transmission between people
- Larger studies (25,000+ patients) are showing that rates of SARS-CoV-2 transmission correlate strongly with physical distancing measures (one meta-analysis recommended 1 m or more)\*
- Any type of face or eye protection significantly reduces transmission rates (N95 > surgical mask > other with a 7-34% reduction in risk)\*

\*Chu DK et al. The Lancet. 2020 Jun 1

## Some lingering uncertainties

- We have increasing evidence that SARS-CoV-2 can remain suspended in the air for hours (airborne spread). However, the observed effect of physical distancing argues against this contributing significantly to transmission.
- Although virus can consistently be recovered from the stool of infected patients, fecal-oral spread is not thought to play a major role in transmission

## A few things becoming clearer

- We have seen a number of cases of patients with persistently positive COVID-19 PCR tests continuing 6+ weeks beyond onset of illness.
- However, *9 days from onset of illness* is the longest anyone has been able to recover viable virus from infected patients.
- Asymptomatic patients infected with SARS-CoV-2 can definitely spread the virus within that first 9-day period of infection, but probably at a lower rate than symptomatic patients.

## Some things remain the same...

- R0, the reproduction number, is consistently estimated around 2.5
  - This is the number of susceptible people an infected individual is likely to infect
  - Seasonal flu has an R0 of about 1.3
- Viral shedding starts about 2 days prior to symptom onset and peaks around the time symptoms start, tapering off quickly within a week<sup>11</sup>
- The incubation period is within 14 days of exposure with a median of 4-5 days<sup>12,13</sup>

# Disease Presentation

- Fever is, by far, the most consistent feature in confirmed cases (98-99%), followed by dry cough (~60%), myalgias (35%) and dyspnea (30%)<sup>14</sup>
- Other symptoms observed with some frequency:<sup>14,15</sup>
  - Headache
  - Sore throat
  - Rhinorrhea
  - GI symptoms
  - Alterations of taste and smell
  - Thromboembolic events

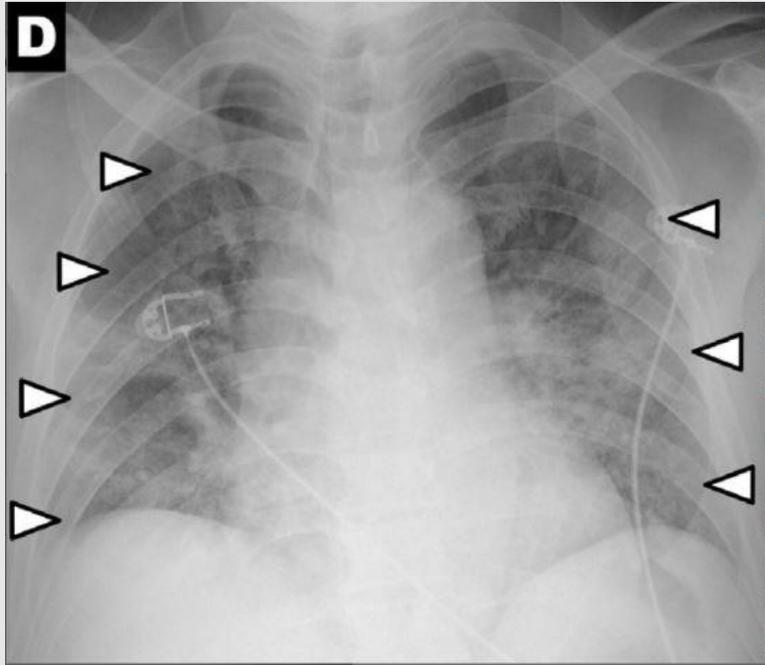
## A word on thromboembolic events

- COVID-19 appears to produce a hypercoagulable state
- Complications can range from DVT/PE to MI and stroke
- Microvascular complications can also occur (ex: “COVID toes”)

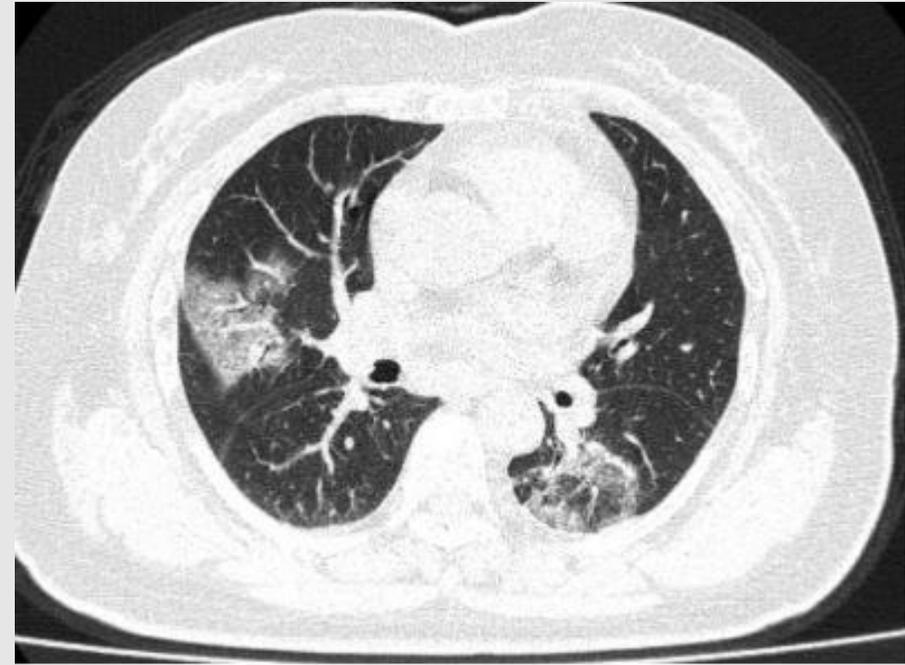


# Disease Presentation

- Radiographic findings



<https://pubs.rsna.org/doi/10.1148/radiol.2020201160>



<https://www.ajronline.org/doi/full/10.2214/AJR.20.22969>

# Diagnosis

- PCR
  - Nasopharyngeal swab (70-75% sensitive)
  - Oropharyngeal swab (~60% sensitive)
  - BAL (95% sensitive)
  - Oral rinse has been discussed but not widely implemented
- Viral culture is a bad idea...
- Serologic (antibody) tests are increasingly available, but...

# COVID-19 antibody testing

- These tests overall are *still* not ready for “prime time”
  - There are several different types of antibody produced in response to SARS-CoV-2 infection, and we aren't sure which one predicts immunity
  - Right now, we have dozens (maybe hundreds) of different antibody tests from different laboratories, and no one has coalesced around a “gold standard” test
  - We aren't sure about the accuracy of each test or what the result means even if it's accurate – are you still infected? Immune? If so, for how long?
  - There's a lot of work left to be done in this area

# The Challenge of Testing

- The situation is gradually improving – multiple smaller labs are creating their own tests and getting them certified
- We still don't quite have the capacity for widespread (universal) testing
- Generally, testing is still reserved for hospitalized/institutionalized patients, high-risk patients and healthcare workers
- Given the poor sensitivity of many PCR tests, many experts advocate for presumptive diagnosis

## Disease Progression

- In symptomatic infected people, symptoms progress over the first week
- If patients are going to go on to develop severe symptoms (ARDS), they tend to worsen abruptly at the end of this week<sup>14</sup>
- About 80% of symptomatic infections are mild (i.e. not requiring hospitalization)<sup>16</sup>
- Most of the remaining 20% consist of patients over 50 with comorbidities

## Risk factors for severe disease

- Increasing age appears to have the greatest impact on rates of severe disease and mortality
  - Studies have consistently reported mortality rates well under 1% below age 50
  - After that, mortality increases significantly, from 1-2% in the 50-59 group up to 15+% in patients over 80<sup>17</sup>
  - Keep in mind that these are generally rates among *hospitalized* patients and do not account for a number of mild or even asymptomatic cases in the community

## More risk factors for severe disease

- Underlying lung disease (COPD, asthma)
- Diabetes
- Hypertension
- Cardiovascular disease
- Chronic kidney disease
- Underlying malignancy
- Y chromosome<sup>17</sup>

## About that ACE2 thing...

- SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) for cell entry<sup>18</sup>
- Treatment with ACE inhibitors and ARBs results in upregulation and increased expression of ACE2<sup>19</sup>
- However, increasing data do not show worse outcomes for patients taking ACE inhibitors or ARBs, and the broad recommendation is to continue these unless an infected patient is hypotensive

# Predicting who will progress

- Multiple laboratory abnormalities have been associated with worse outcomes in the setting of COVID-19:<sup>14</sup>
  - Lymphopenia
  - Elevated D-dimer
  - Elevated LDH
  - Elevated troponin
  - Elevated CK
  - Elevated PT
  - AKI
  - Elevated inflammatory markers (CRP, ferritin)

# Management

- Rapid isolation, testing and supportive care is still our best strategy
- We are still learning how effective many of the widely used treatments really are
- There is still uncertainty regarding how other drugs (NSAIDs, steroids) impact the clinical course of COVID-19
- We are still unsure how effective some of our current methods of PPE use really are

# Potential Treatments

- Remdesivir
  - A novel nucleotide analogue with *in vitro* activity against SARS-CoV-2 and related coronaviruses
  - Received an emergency use authorization from the FDA in May 2020
  - On 3/23, Gilead halted distribution through this program because they could not keep up with overwhelming demand. Production capacity has since increased, but the drug is still not widely available.
  - Subsequent randomized trials have shown promising results, and remdesivir is now generally recommended for hospitalized patients with severe COVID-19

# Potential Treatments

- Hydroxychloroquine +/- azithromycin
  - Both chloroquine and hydroxychloroquine inhibit SARS-CoV-2 *in vitro*<sup>20</sup>
  - Most people have heard about the French study<sup>21</sup>
    - 20 treated patients, 16 controls
    - Lots of methodological issues with this study
  - Larger, better-controlled studies have since shown little, if any, benefit, and some have actually shown harm\*

\*Mehra MR et al. Lancet. 2020

# Potential Treatments

- Tocilizumab (Actemra)
  - IL-6 receptor inhibitor previously used primarily to treat RA
  - Elevated IL-6 levels have been noted in a number of severely ill patients with COVID-19
  - Use is predicated on a “cytokine storm” hypothesis to explain delayed lung injury
  - Small studies have shown improvements in O2 requirements and mortality with no significant adverse events\*

\*Sciascia S et al. Clin Exp Rheumatol. 2020;38(3):529. Epub 2020 May 1.

# Potential Treatments

- Convalescent plasma
  - Makes sense – use potentially neutralizing antibodies from patients who have recovered from COVID-19 to treat sicker patients
  - Small case series have suggested improvement in patients with severe COVID-19 after convalescent plasma infusion
  - How do we identify appropriate donors? Confirm the presence of neutralizing antibodies?
  - Some are trying IVIG instead (maybe some cross-protection from previously circulating coronaviruses?)

## NSAIDs

- Early European and WHO recommendations to avoid NSAIDs in the setting of COVID-19 were based on a handful of reports of young adults receiving NSAIDs early in their courses and going on to develop severe disease
- Major healthcare agencies (WHO, CDC, NIH) now say it's OK to use NSAIDs when needed
- Use acetaminophen if you are concerned

# Glucocorticoids

- WHO and CDC recommend avoiding glucocorticoids in the setting of COVID-19 unless there are other indications like COPD or asthma exacerbation
- Glucocorticoid use was associated with delayed viral clearance in patients with MERS-CoV
- At this time, we have no outcomes data showing the impact of steroids on COVID-19

## How do patients fare?

- The largest cohort study of SARS-CoV-2 patients thus far (44k) defined severe disease as dyspnea, hypoxia or >50% lung involvement on imaging within 24-48 hours of presentation (14% of patients)<sup>24</sup>
- Critical illness (respiratory failure requiring intervention, shock, multiorgan dysfunction) was seen in 5%
- Overall case fatality rate was 2.3%
- No deaths reported among the non-critical cases
- Mortality has varied quite a bit from 0.7% in some parts of China to 7.2% in Italy. “Big picture” estimate is still around 1.4%<sup>17,25</sup>

## Comparative mortality

- How does this case fatality compare to other respiratory viruses?
  - Seasonal influenza = 0.1-0.2%
  - 1918 pandemic (Spanish) influenza = 2.5%
  - SARS-CoV-1 = ~10%
  - MERS-CoV = ~35%

## Recovery

- Studies thus far suggest that COVID-19 patients develop protective antibodies
- Macaques don't get it on re-challenge...<sup>26</sup>
- A couple of promising vaccines in trials in the US show protection at 30-45 days
- We don't know how long immunity lasts – other coronaviruses show waning immunity over months to a few years

## Can you get re-infected?

- Probably not – at least not right away
- A study out of South Korea performed viral culture on patients who were “re-positive” anywhere from 8 to 82 days after initial diagnosis\*
- None of these “re-positive” patients were found to have viable virus at the time of the second positive PCR

\*Korea Centers for Disease Control and Prevention

## Prevention

- SARS-CoV-2 is probably spread primarily by droplets (as opposed to airborne or contact spread)
- Standard droplet distance is 6 feet
- Current PPE guidelines now have some data behind them - droplet and contact precautions PLUS eye protection PLUS escalation to airborne precautions for aerosolizing procedures
- Universal masking in public probably has a significant impact on spread

## Prevention

- Limit contact with healthcare workers as much as possible
- Use dedicated equipment
- Telemedicine/telehealth interventions when possible
- Try to cohort positive and suspected positive COVID cases in the facility
- Negative pressure rooms are not mandatory

## Screening

- It's now commonplace to screen for common COVID-19 symptoms prior to entering a healthcare facility
- This will slow the entry of SARS-CoV-2 into an individual facility, but remember those asymptomatic shedders...
- Still not a lot of firm guidance on this issue from public health authorities
- It's a helpful step, but we need testing capacity to back it up

# Cleaning

- The good news – this virus isn't particularly hard to kill
- Most of our standard disinfection methods appear to be effective, including
  - Quaternary ammonium compounds (ex: Sani-Cloth)
  - UV light
  - Diluted bleach (4 teaspoons per quart of water, per CDC)
  - Ethanol (at least 60% and preferably 70%)

## When is it OK to discontinue PPE?

- CDC recommends stopping for patients who meet all of the following criteria:
  - No longer have fever for at least 72 hours in the absence of antipyretics
  - Respiratory symptoms improving
  - Two negative nasopharyngeal PCR swabs collected at least 24 hours apart
- If they are going home, you don't necessarily have to get someone off precautions prior to discharge

## Home care

- Preferred for all non-severe cases
- Entirely supportive – fluids, analgesics, antipyretics
- CDC guidelines for patients on home isolation:
  - Stay at home and try to maintain distance from other people and animals
  - Wear a facemask when in the same room or vehicle as another person or when presenting to a healthcare facility
  - Clean high-touch surfaces (doorknobs, countertops, toilets) frequently

# When can I leave my house?

- CDC says you can stop isolating when
  - At least 10 days have passed since symptoms first appeared AND
  - At least 72 hours have passed since meeting the symptom milestones outlined for the hospital
  - This applies to healthcare workers as well

## What comes next?

- Current goal is to slow the spread enough that we don't completely overwhelm our healthcare capacity
- We managed to interrupt the exponential growth phase for SARS-CoV-2 with social distancing measures
- Now, it's going to be trial-and-error for a while as different levels of government try different approaches. COVID-19 cases will increase again, but it remains to be seen how much.

## What can I do?

- Wear your mask
- Keep your distance when possible
- Wash your hands
- Follow CDC guidelines for isolating yourself if you have potentially consistent symptoms
- Don't panic – the overwhelming majority of us will survive this

## Recap of the new things

- No viable virus has been recovered beyond 9 days after onset of illness. Persistently positive patients are probably not infectious.
- You should be immune once you clear the virus – we just don't know for how long yet
- Hypercoagulability is an increasingly recognized complication of COVID-19
- We still have work to do on widespread PCR testing and even more so on antibody testing

# References

1. Chinese SARS Molecular Epidemiology Consortium. Molecular evolution of the SARS coronavirus during the course of the SARS epidemic in China. *Science*. 2004;303(5664):1666. Epub 2004 Jan 29.
2. Cotten M, Lam TT, Watson SJ et al. Full-genome deep sequencing and phylogenetic analysis of novel human betacoronavirus. *Emerg Infect Dis*. 2013;19(5):736.
3. Perlman S. Another Decade, Another Coronavirus. *N Engl J Med*. 2020;382(8):760. Epub 2020 Jan 24.
4. van Doremalen N, Bushmaker T, Morris DH et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med*. 2020;
5. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-2019). February 16-24, 2020. <http://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>
6. Ong SW, Tan YK, Chia PY et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. *Jama*. 2020 Mar 4.
7. Santarpia JL, Rivera DN, Herrera V et al. Transmission Potential of SARS-CoV-2 in Viral Shedding Observed at the University of Nebraska Medical Center. *medRxiv*. 2020 Jan 1.
8. Liu Y, Yan LM, Wan L et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis*. 2020;
9. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;
10. Hu Z, Song C, Xu C et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci*. 2020;

# References

11. He X, Lau EH, Wu P et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. medRxiv. 2020 Jan 1.
12. Li Q, Guan X, Wu P et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;
13. Guan WJ, Ni ZY, Hu Y et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;
14. Wang D, Hu B, Hu C et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;
15. Giacomelli A, Pezzati L, Conti F et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020
16. Surveillances V. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19)—China, 2020. China CDC Weekly. 2020;2(8):113-22.
17. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020 Mar 23.
18. Zhou P, Yang XL, Wang XG et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270. Epub 2020 Feb 3.
19. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virology 2020; published online
20. Yao X, Ye F, Zhang M et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;

# References

21. Gautret et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents* – In Press 17 March 2020  
DOI:10.1016/j.ijantimicag.2020.105949.
22. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020.
23. Cao B, Wang Y, Wen D et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020;
24. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;
25. Spychalski P, Błażyńska-Spychalska A, Kobiela J. Estimating case fatality rates of COVID-19. *Lancet Infect Dis* 2020.
26. Bao L, Deng W, Gao H, et al. Reinfection could not occur in SARS-CoV-2-infected rhesus macaques. Pre-print.  
<https://www.biorxiv.org/content/10.1101/2020.03.13.990226v1.full.pdf> (Accessed on March 26, 2020).