



TRENDS-in-MEDICINE

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by Lynne Peterson

SUMMARY

Among the interesting **new** and/or **reconfirmed** tidbits out of this Covid-19 session were:

- **Hypertension** is really common in critically ill Covid-19 patients, and an ACE2 inhibitor is a possible treatment.
- Time from **symptom onset to recovery** for mild cases is 2 weeks, but it is 3-6 weeks for severe cases.
- **Viral shedding** can occur 24-48 hours before symptoms appear but are greatest after symptoms start.
- No particular **signs or symptoms** can reliably discriminate Covid-19 from other respiratory viral illnesses (e.g., flu).
- **Treatment** is more likely to work than a vaccine. Any vaccine for SARS-CoV-2 is likely to be too late and not work for future coronavirus outbreaks. The NIAID/Moderna vaccine “is not the only one and may not be the best one.”
- The main cause of death from Covid-19 is **ARDS**, and survivors often get pulmonary fibrosis.
- **Immunity** after Covid-19 is uncommon but possible.
- There is no evidence of a SARS-CoV-2 **reservoir** in the body, but it is possible – and too early to know.

Trends-in-Medicine

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COVID-19 UPDATE

from the

CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (CROI)

March 10, 2020

While Covid-19 has led to the cancellation or postponement of all the major medical conferences in March, CROI found a third option – convert the conference to a virtual meeting, with the same lectures provided online to people who were registered (including press).

A special virtual session on Covid-19 at CROI was probably the very best briefing anyone in the U.S. has given since the beginning of the Covid-19 outbreak – caused by the SARS-CoV-2 (SARS2) virus.

The bottom line was that more people in the U.S. and worldwide are going to contract Covid-19. A vaccine is at least a year to a year and a half away – if one works at all – so a vaccine is likely to be too late for this outbreak. Even if a vaccine for SARS-CoV-2 is developed, it likely won't work for other coronaviruses, and additional (but different) coronavirus outbreaks are considered likely in the not too distant future. Thus, the focus needs to be on treatment, and there are a few potential treatments being studied beyond Gilead Sciences' remdesivir.

THE VIEW FROM CHINA:

Learning a lot, situation improving

The live presentation by Zunyou Wu, MD, PhD, chief epidemiologist with China's Center for Disease Control and Prevention (CDC) was very thorough. He outlined the timeline of the outbreak in China, from the first 3 patients to today. Among the comments of particular interest:

■ Transmission.

- Covid-19 was very contagious and spread very fast. It only took 30 days to spread across the country.
- The majority of cases (69%) were imported from Hubei province or close contacts (15%), “which suggests low levels of community transmission outside Hubei.” Only 16% had no known exposure history.
- 1%-5% of 38,000 close contacts developed Covid-19. Transmission is driven by family clusters.

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- Secondary household attack rates were ~10% early in the outbreak but fell to 3% with faster isolation.
- Transmission in *closed settings* (e.g., nursing homes, prisons) is happening but is not a major driver in China.
- Transmission in *schools* has not been observed – maybe because schools were closed during most of the outbreak.

■ Patient profiles.

- There was no meaningful difference between males and females getting infected.
- 94% of people infected were age 20-79.
- The most common symptoms were fever, dry cough, and fatigue, but a high number of cases had hypertension, diabetes, respiratory disease, or lung disease. **Hypertension** was particularly common in the critical patients.
- Average time from exposure to symptom onset is 5-6 days. Time from symptom onset to recovery for *mild* cases is 2 weeks, but it is 3-6 weeks for *severe* cases.
- Truly asymptomatic infection is unknown without serology but appears rare (<1%). About 75% of “asymptomatic cases at the time of diagnosis soon progress to disease.”
- Children tend to have milder disease than adults.

■ Viral shedding.

- This is highest early in the course of disease and can occur in the 24-48 hours before symptom onset.
- Virus can be isolated from stool, but there is no evidence of fecal-to-oral transmission.
- Virus shedding usually continues for 7-12 days in mild/moderate cases and >2 weeks in severe cases.
- Patients who recover can be PCR positive after symptoms resolve.

■ Treatment.

- There is no treatment, no vaccine, and no measure to control it.
- Nationwide 1.4 billion people in China underwent 10 days of at-home isolation. In Hubei province 59.2 million people are quarantined, “and **this will continue for a while.**”

Separately from this, it was reported that China is now dismantling one or more of its “pop-up” coronavirus hospitals.

THE U.S. CDC PERSPECTIVE: *Stuck in wash-your-hands mode*

John Brooks, MD, chief medical officer, Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention (CDC), gave a very basic talk, and his closing comment summed up his presentation pretty well: **“Remember, there is plenty of soap.”**

Other than that, the comments that stood out were:

- Most patients eventually develop a fever, but in one report only 44% initially had a fever.
- **No particular signs or symptoms can reliably discriminate Covid-19 from other respiratory viral illnesses** such as the flu.
- “Most people will recover spontaneously with supportive care.”
- He made special note of “what appears to be very little Covid-19 in children...Data [published last week] show children are less susceptible. If true, the data likely represent under-reporting of children.” He said this could occur either because they have milder illness or if they come to care, it is not recognized.
- **“Viral shedding is greatest at the time symptoms start...** There is no data regarding the duration of replication-competent virus shedding.”
- “Our best estimate...is, all things considered, the case fatality rate is 0.5%-3.5%. By comparison, flu is 0.1%... meaning Covid-19 could be 5 to 35 times more deadly.”
- Right now most parts of the U.S. are in containment mode, with cases climbing, but some are close to mitigation status, if not already there.

A VIROLOGIST’S VIEW: *Treatment more likely to work than a vaccine*

Ralph Baric, PhD, an epidemiologist from the University of North Carolina Chapel Hill, gave a very detailed and thorough explanation of the new coronaviruses (SARS, MERS, and SARS2). **He did not appear very optimistic about a vaccine.** Rather, his focus was more on treatment, and he pointed to three agents in particular: **Gilead Sciences’ remdesivir (GS-5734)**, **AbbVie’s Kaletra (lopinavir + ritonavir)**, and a ribonucleoside inhibitor being developed by George Painter III, PhD, an epidemiologist and CEO/director of Emory University’s Institute of Drug Development – **EIDD-1931**.

Among the interesting points Dr. Brooks made were:

■ **The virus.** SARS-CoV-2 is 78% identical to the previous SARS virus. A therapeutic for SARS will have little impact on SARS2.

■ **Transmission.**

- Human-to-human transmission is “rampant” worldwide.
- There is a large, large number of viral strains that have not been identified, so **future outbreaks are likely.**
- SARS2 changes the ways scientists think about zoonotic transfer (viral transfer from animals to humans) – a massive mutation process is not necessarily needed, which makes the transfer from animals to humans much easier and faster. “The major lesson is: Never underestimate the epidemic potential of an emerging virus.”
- “Superspreaders are common.”

■ **Impact on patients.**

- Mortality with Covid-19 is ~3.4%.
- The fatality rate for patients age ≥ 80 is 15%. He added, “Pretty much no one is dying under age 15.”
- **The main cause of death from Covid-19 is ARDS** (acute respiratory distress syndrome). If a patient gets ARDS, mortality is 30%, but even **if patients recover, they are likely to get pulmonary fibrosis!**
- Males develop more serious disease than females.

■ **Treatment/prevention.**

- With SARS2 the animal source is not known, and community spread is very common, which confounds quarantines and contact tracing. **“It is going to be very difficult to control the SARS2 outbreak.”**
- Because of the way different SARS-like viruses are likely to emerge, he was not optimistic about a vaccine.
- ✓ Vaccine efficacy can be reduced in older patients.

- ✓ There is evidence of Th2 immune pathology after vaccination.
- ✓ There is evidence (controversial) from primates and cell cultures of enhancing antibodies.
- ✓ The right adjuvant for SARS-CoV-2 is not known.
- **Gilead Sciences’ remdesivir** (GS-5734), which he has been studying, has shown efficacy in animals. Two trials are underway in China, and Gilead plans to start two U.S. trials soon. NIH is running a trial in repatriated Americans with Covid-19.
- **AbbVie’s Kaletra** is being tested with interferon-beta in China.
- **EIDD-1931**, which was developed at Emory University, is currently under FDA review, and a manuscript is also under review. He didn’t mention **EIDD-2801**, a modified version of EIDD-1931, that is also being developed at Emory. EIDD-1931 was for SARS and MERS, and EIDD-2801 is more specific for SARS-CoV-2.

THE NIH PERSPECTIVE:

*Supporting diagnostics, treatment,
and vaccine research*

Anthony Fauci, MD, PhD, director of the National Institute of Allergy and Infectious Diseases (NIAID) – who has become the “trusted” administration spokesperson on coronavirus – offered a few new tidbits, including:

■ **Diagnostics.**

- **NIH has been developing additional diagnostic tests** – both PCR and ELISA tests – for Covid-19.
- NIH-supported researchers in Hong Kong have developed a molecular diagnostic that they published on the World Health Organization (WHO) site and distributed reagents to 12 countries.

■ **Treatment.**

- In addition to studies of Gilead’s remdesivir and AbbVie’s Kaletra, Dr. Fauci said **chloroquine** may have utility for Covid-19. (It is listed on the WHO list of possible treatments.)
- As of March 3, 2020, there were 261 trials for Covid-19 listed in WHO’s International Clinical Trials Registry.

- **Vaccines.** NIAID is working on an mRNA vaccine with **Moderna** that is expected to start human trials in about 2 months, but Dr. Fauci said, “It is not the only one and may not be the best one...but it is a messenger RNA [vaccine].”

Comparison of Newly Discovered Coronaviruses

| Measurement | SARS | MERS | SARS2 |
|---------------------------------|-----------------------------------|-----------------------------------|--|
| Countries with cases | 29 | 27 | >100 |
| Mortality | 9.6% | ~34% | 3.4% overall ~14% critical patients |
| Reservoir (intermediate host) | Bats (palm civet) | Bats (dromedary camel) | Bats (likely zoonosis) |
| Incubation period | 2-7 days | 2-7 days | 2-14 days |
| Infectivity (rho) | 1.8-2.5 | 0.3-1.3 | ~3 |
| Superspreaders | Yes | Yes, common | Yes |
| Asymptomatic spread/mild spread | No | Rare | Yes/Yes |
| Transmission | Droplet/direct airborne/indirect? | Droplet/direct airborne/indirect? | Droplet/direct airborne/indirect/fecal |
| Attack rate | 10.3%-60% | 4%-20% | 20%-30% |

Dr. Fauci mentioned several other vaccines in development, including:

- CureVac and NIAID vaccine
- Johnson & Johnson – viral vector vaccine
- Jenner and NIAID – viral vector vaccine
- Codagenix – live attenuated vaccine
- Baylor University – recombinant protein vaccine
- Novavax – nanoparticle vaccine

QUESTIONS AND ANSWERS

Some unanswered questions have finally been answered. Viewers of this CROI session were allowed to email in questions, and Dr. Baric addressed those questions, including two from this reporter.

Will it be possible to develop serologic tests? **Yes.** Dr. Baric said, “The simple answer is Yes...A simple serologic test would be quite sensitive and specific.”

Does a person develop immunity after surviving Covid-19, and can a person who had Covid-19 get re-infected? **Uncommon but possible.** Dr. Baric said, “There are some sporadic reports of seroconversion with MERS and then return to baseline... including some RT-PCR-positive patients. The possibility for this happening is possible, though I don’t think it is frequent... There is also some evidence of chronically-infected MERS patients...though it is only a single one...With SARS2, there are sporadic reports in China of acute infection, with the patient released after it resolved, and then reportedly became infected again...but that was not published...It is an emerging story.”

What about reservoirs in the body? **No evidence but not impossible, too early to say.** Dr. Baric said, “At this time I’m not aware of any known reservoir for SARS or SARS2...Viral gene persistence can last quite a while in sputum...but whether that is associated with replication is not clear. Part of the problem is there were insufficient samples of SARS globally to follow sufficient cases for long-time persistence. Certainly, this outbreak is of sufficient scope to reveal those types of rare infection events...much like they did with Ebola.”

What happened to the (original) SARS virus? Is it circulating in a limited manner? **Biding time until it causes a new outbreak.** Dr. Baric said, “Most people who work with virus discovery... agree SARS and SARS2 are bad viruses...There are at least 200 bat species, and we only surveyed 75...So, most people think the original 2003 strain is still out there and waiting for its moment in time.”

What about ACE inhibitors? Are they a viable treatment option? Dr. Baric said, “ACE2 expression levels decrease with age...and it has been shown to play a protective role in ARDS ...There is probably a direct relationship of ACE2 expression ...and [coronaviruses]...However, there are certainly other factors that contribute, including immune senescence...There was a nice paper in 2013 or 2014 that demonstrated that **several ACE2 inhibitors had fairly good activity against SARS...So, I think it is a very good idea to go back and explore those drugs.**”

Is there airborne transmission of Covid-19 in addition to droplets? Dr. Baric said there was a report in 2003 of aerosolized feces with high concentrations of SARS that infected a large number of people in that high-rise community but also in a nearby high-rise community...So, there is an indication it could have airborne spread in the right circumstances...In general, the majority of data suggest it is droplet transmission and contact with fomites [objects that can carry the virus, such as clothes or utensils].”

Asked about the association between hypertension and Covid-19, Dr. Baric said, “I’ve thought it needed to be explored for quite a while.”