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AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists and pharmacy technicians will be able to:

- List developments related to treatments that are currently being investigated for COVID-19
- Recognize changes to the CDC's recommendations and risk criteria
- Describe non-pharmacologic interventions to reduce the spread of SARS-CoV-19

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this knowledge-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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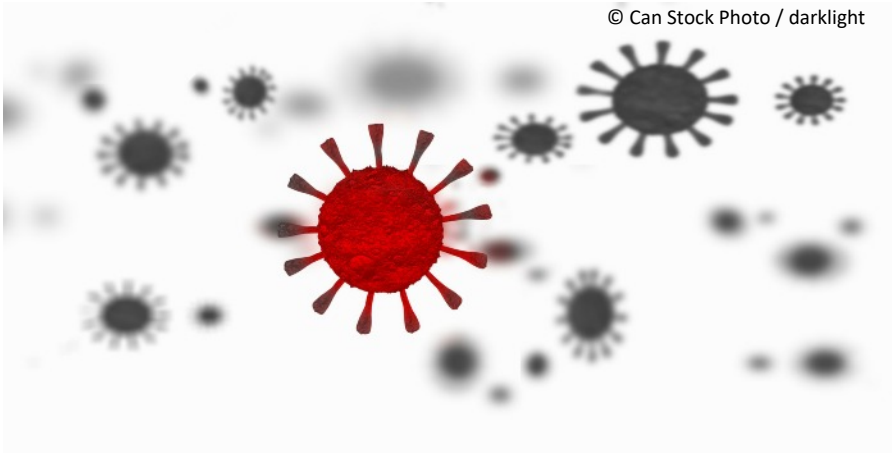
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UConn UPDATE #4: SARS-CoV-2 and COVID-19

ABSTRACT: UConn faculty assembled this homestudy in response to a high demand for reliable education on coronavirus. It answers questions submitted by our learners.

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INTRODUCTION

This is the fourth update to UConn's running series on SARS-COV-2 and COVID-19. In previous continuing education (CE) activities, we discussed the virus (SARS-CoV-2), the disease it causes (COVID-19), and frequently asked questions.

As noted in our learner survey issues on June 30, 2020, UConn School of Pharmacy was an early responder with continuing education for pharmacists and technicians. We issued frequent updates, but slowed our pace when other CE providers began to issue what appeared to be a tremendous amount of CE on this topic. In our survey, more than 70% of respondents said they were ready for another update from UConn. Here it is, and thank you for your feedback and support.

You can find links to UConn's previous CE activities on this topic at the end of this activity (page 10).

Could you provide additional details about the symptoms of the coronavirus, and especially the early symptoms?

The U.S. Centers for Disease Control and Prevention (CDC) recently added nausea, diarrhea, and congestion to its list of COVID-19 warning signs (see **Table 1**).[1] The CDC also notes that diarrhea and nausea are more common in younger patients. Some patients will describe congestion as a runny nose; patients' noses tend to run because the nasal cavity is rich in ACE2 and TMPRSS2 proteases, which facilitate SARS-CoV-2 binding, replication, and accumulation.[2] Since COVID-19 is thought of as a respiratory virus, clinicians may overlook gastrointestinal symptoms.

COVID-19 can manifest as mild to severe illness. Symptoms may appear two to 14 days after exposure to the virus.

Table 1. Updated List of Coronavirus Symptoms[1]

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- **Congestion or runny nose**
- **Nausea or vomiting**
- **Diarrhea**
- Progressive hypoxemia in many cases
- Respiratory failure that requires mechanical ventilation in some cases

Can you update the treatment guidelines? What's "out" and what's "in"?

Since the last update, considerable information has emerged about remdesivir use. In the last update, published data was limited to

- a case series of 61 patients who received the drug in the compassionate use program
- publication of a randomized placebo-controlled trial from China that was terminated early due to inability to recruit more patients, and
- a press release of the results of the NIH-sponsored ACTT-1 trial describing significant reductions in time to recovery and a trend towards lower mortality.

The full results of the ACTT-1 trial have been published.[3] The full publication and supplemental materials clarify which types of COVID-19 infected patients may benefit most from remdesivir. This is especially important given that limited quantities of the drug are available through the Emergency Use Authorization (EUA) program—not every COVID-19 infected patient admitted to a hospital will be able to access remdesivir.

Although the full cohort of patients who received remdesivir had significantly reduced times to clinical improvement compared to placebo-treated patients (11 days versus 15 days), the earlier hospitalized inpatients receive the drug in the course of their disease, the better the chance of a positive effect.[3] Patients who needed supplemental oxygen therapy seemed to have a greater response provided they were not receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). The latter two categories of patients derived no significant benefits from remdesivir. Importantly, analysis of remdesivir's effects based on onset of symptoms (fewer than or greater than 10 days duration) indicated that remdesivir was similarly effective in both patient groups. Finally, ACTT-1 data indicate that, for the most part, remdesivir is safe; serious adverse events were similar in remdesivir-treated and placebo-treated patients.[3]

Results from two additional trials illuminate clinical outcomes. Gilead sponsored a randomized, comparative trial to compare outcomes between adult patients treated with remdesivir for five or 10 days.[4] Inclusion criteria were similar to the ACTT-1 trial, but this trial excluded patients receiving mechanical ventilation or ECMO at randomization. The study compared a 5-day group (200 patients who received remdesivir 200 mg once daily followed by remdesivir 100 mg for 4 days) with a 10-day group (197 patients who received remdesivir 200 mg once daily followed by remdesivir 100 mg once daily for 9 days). All participants also received standard of care. At day 14, observed rates were 65% and 54% for clinical improvement, 70% and 59% for clinical recovery, and 8% and 11% for mortality, for the 5- and 10-day treatment groups respectively. The lack of a placebo group was a study limitation, but outcomes in both groups were generally comparable to those in the ACTT-1 trial.[4]

Gilead also has issued a press release describing the results of the SIMPLE trial.[5] This open-label trial compared 5- and 10-day courses of remdesivir added to usual care to usual care alone. Patients were considered to have moderate COVID-19 pneumonia (lung findings but no reduced oxygenation) and were inpatients. The primary endpoint was the clinical status as assessed by a 7-point ordinal score at Day 11. Patients who received five days of treatment were 65% more likely to have clinical improvement compared with those in the standard of care group (OR 1.65 [95% CI 1.09-2.48]; p=0.017). Interestingly, patients who received 10 days of therapy had a numerically lower likelihood of clinical improvement that did not reach statistical significance (OR 1.31 [95% CI 0.88-1.95]; p=0.18). The results from these two trials indicate that five days of remdesivir should be sufficient for most hospitalized patients (other than those who are mechanically ventilated).[5] Again, this finding is important in the context of the ongoing pandemic since drug quantities are limited.

The U.S. has expended all donated remdesivir allocations for the EUA. On June 29, 2020, Gilead announced that it will charge all governments of developed countries $2,340 for a 5-day course including the United States Department of Health and Human Services (HHS) and Veterans Administration systems. All other private U.S. insurers and Medicare and Medicaid, will pay $3,120.[6] HHS secured more than 500,000 treatment courses for patients who are hospitalized in the United States.[7] AmerisourceBergen will allocate the drug in a process similar to that used to distribute donated supplies for the EUA.[7] More details can be found on the HHS website at https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Pages/factsheet.aspx. At $3,120 for 5-days and roughly $6,000 for 10-days,[8] no evidence indicates the added expense is worth it. No data shows that remdesivir will increase the numbers of patients who survive an episode of COVID-19 infection yet.

Dexamethasone / Corticosteroids

Mounting evidence indicates a hallmark of earlier-stage COVID-19 infection may be prolific viral replication and low inflammation, while later-stage infection may have a significant hyperinflammatory component. Since the last update, numerous researchers have investigated corticosteroids' potential in treating COVID-19 infection. Researchers are conducting the prospective, randomized, controlled, open-label RECOVERY trial at more than 175 National Health Service hospitals in the United Kingdom. Its goal is to evaluate the possible effectiveness of a variety of investigational COVID-19 therapies added to standard care. One arm of this trial evaluated dexamethasone (6 mg once daily for up to 10 days) in inpatients with COVID-19 infection. On June 8, 2020, this trial's Data Monitoring Committee/Trial Steering committee halted enrollment after recruitment of 2,104 patients into the dexamethasone arm (a sufficient number of patients to establish whether the drug had meaningful benefit).[9]

The trial results have been released as a preliminary manuscript, meaning it has not been peer-reviewed.[10] Overall 28-day mortality was 21.6% in dexamethasone-treated patients compared to 24.6% in patients who received usual care (age-adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; P<0.001). In contrast to the results from the ACTT-1 remdesivir trial, patients who received mechanical ventilation responded most profoundly to dexamethasone; mortality was only 29% vs. 40.7% of usual care group (RR 0.65 [95% CI 0.51 to 0.82]; p<0.001). Importantly, patients not receiving any respiratory support (including supplemental oxygen) seemed to be at potential risk of harm; mortality in dexamethasone-treated patients was 17% vs. 13.2% in the usual care group (RR 1.22 [95% CI 0.93 to 1.61]; p=0.14).[10]

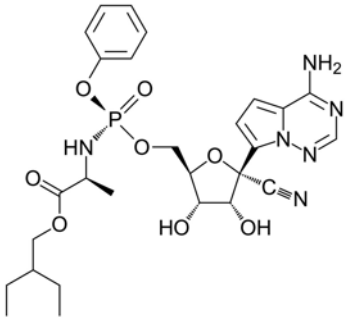
Application of Remdesivir and Dexamethasone Trial Results to Clinical Care

In summary, Dr. Aeschilmann indicates that based on the available evidence (which continues to evolve; more trials are ongoing), a reasonable strategy to manage patients admitted for hospital care of COVID-19 infection follows:

- Patients who do not need supplemental or invasive oxygen therapy: Consider initiation of remdesivir (duration of therapy = five days). Avoid use of dexamethasone and/or other corticosteroids.
- Patients who need non-invasive supplemental oxygen therapy: Consider initiation of both dexamethasone and remdesivir therapy (five days). It is important to note no controlled data establish this combination's safety or efficacy.
- Patients who need invasive oxygen therapy (mechanical ventilation or ECMO): Consider starting dexamethasone. Remdesivir appears to have little to no benefits in this patient group.

Hydroxychloroquine

Many professional societies have independently examined available chloroquine and hydroxychloroquine studies and saw no evidence of benefits. We discussed these drugs and their risks in previous updates. A National Institutes of Health panel that included representatives from 14 national professional societies and government agencies found insufficient evidence to recommend for or against using hydroxychloroquine for the treatment of COVID-19.[11] The best clinical trial to date was stopped early because of a lack of benefit.[12] This should be the end of the story about the use of hydroxychloroquine for treating hospitalized patients with mild to moderate disease severity, but patients will continue to inquire about chloroquine and hydroxychloroquine. Let patients know that these drugs may harm them, their loved ones, and their communities.[13] This does not mean that hydroxychloroquine might not work in prophylaxis or that the combination of hydroxychloroquine with zinc might not be effective, but they are only speculative treatments at this point.



Remdesivir

$C_{27}H_{35}N_6O_8P$

Where are we on a vaccine?

Many vaccines are in development, but each must meet statutory and regulatory requirements before approval. The FDA has issued a guidance document for interested companies.[14] On a global level, the WHO indicates that there are currently 18 vaccines in clinical trials and 132 vaccines in preclinical trials.[15] The U.S. government is choosing three vaccine candidates to fund for phase 3 trials under Operation Warp Speed: Moderna's mRNA-1273 in July, The University of Oxford and AstraZeneca's AZD1222 in August, and Pfizer and BioNTech's BNT162 in September. A sponsor would need to provide data from placebo-controlled trials indicating their vaccine is at least 50% effective against COVID-19 to be authorized for use, according to FDA guidance issued and effective June 30, 2020.[16] Although speculation about when a vaccine will be approved and available is robust, a prediction about an actual date is shear speculation. This might be a good topic for your next pharmacy contest—predicting such a date.

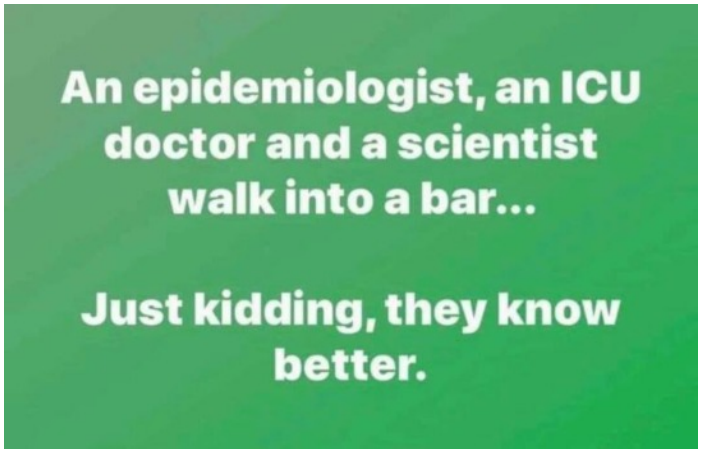
Under Operation Warp Speed, the US Government could fund bulk manufacturing of these candidate vaccines before they are approved. With this strategy, effective vaccines can be deployed more rapidly to populations at greatest risk, including populations with health disparities that have limited access to the healthcare system.[16] This is why assuring pharmacists are certified to administer COVID-19 vaccines in community settings is vital to public health.

What are the risk factors for transmission and have some people been infected twice?

People at greatest risk of infection are those who have had prolonged, unprotected close contact with a patient with symptomatic, confirmed COVID-19 and those who live in or have recently been to areas with sustained transmission. Contact indoors increases risk of transmission significantly and profoundly. Researchers have still been unable to pin down SARS-CoV-2 infection's precise immune cascade, including duration of immunity. They know that patients with MERS-CoV are unlikely to be re-infected shortly after they recover, but have not determined if this is the case for patients who contract and recover from SARS-CoV-2.[17]

Are there any updates concerning hypertension, diabetes, people who take ACE2 receptor inhibitors, or blood type?

Information on the association of blood type and coronavirus susceptibility remains limited. We discussed this subject and the theories behind it in UConn Update #2. Little additional information is available. Recently, researchers from a number of institutions in the northeast U.S. looked at ABO phenotype in critically ill patients with COVID-19. They found type A blood is a possible risk factor for COVID-19-related critical illness among



white patients, and that type O blood may be protective. However, the associations did not hold in people of color. This study is in pre-publication.[18]

Researchers have also linked susceptibility to a 3p21.31 and to rs657152 at locus 9q34.2 gene clusters in patients with COVID-19 with respiratory failure in Italy and Spain. It confirmed a potential involvement of the *ABO* blood-group system. Locus 9q34.2 coincided with the *ABO* blood group locus. Patients with type A blood were at higher risk for severe disease with acute respiratory syndrome than other blood types. Patients who had type O blood seemed less likely to experience severe disease.[19]

Although it feels like we've been dealing with coronavirus for a long time, it's been months, not years. Researchers are still examining the copious quantities of patient data to make connections between receptor sites, hypertension, diabetes, and other factors.

We thought that SARS-coronavirus-2 was a cold weather virus, but here we are in July and the virus is raging in the southern states. What do you know about that? And what data is available about infection rates after protests?

Direct sunlight and moister mucus membranes are somewhat protective against COVID-19 infection. Maximizing that protection requires being outdoors and staying at least three feet and optimally six feet away from others, and/or mutual wearing of masks or face shields.[20] If it is 90°F and sunny outside but 70° in the air-conditioned bar or restaurant and people are within three feet of each other, not wearing masks, all bets are off. Talking loudly, shouting, and/or singing along to music is a stupendous way to spread the virus. Being outside on a 68° night and closely packed together is also foolish. Risks will be accentuated in the late-autumn when we lose the sun's protective effect and have to deal with COVID-19 and seasonal influenza concurrently. If there was ever a time to encourage your patients to get their flu shot in August and September, this is it!

With regard to the widespread protests that occurred starting

at the end of May, the surge of new coronavirus cases that epidemiologists expected did not materialize. Yet. It appears that the confluence of social distancing, wearing masks, and being outside helped reduce coronavirus's spread. In many areas where protests occurred, infection rates were already falling, reducing the likelihood of exposure. It has also been shown that in communities that had large protests , the protests caused non-protesting community members to stay home, offsetting the impact of the protests on infection rates.[21] Additionally, protestors tend to be young; they may have symptomless infections, and their infections may have gone unnoticed. We may see a rise in infections among their parents and grandparents later.

Having said that, protesting in close proximity to others is becoming more dangerous. Our COVID-19 infection rates nationally were at their lowest levels since the peak at the end of May. Now, the number of infected people is rising at an exponential rate. This increases risk of contact with an infected person. Protests also appear to have become more crowded and less mobile starting around June 13, so the surprising lack of an earlier outbreak might not hold.

Be brave enough to publish association of post protest increase in infection rate in Blacks and Whites by zip code or county.

We aren't sure why publishing the data would be "brave." What we do know is that finding this data is like looking for a needle in a haystack; most data by zip code is maintained by the states (if at all). Epidemiologic investigations are ongoing and may clarify things better. Until then, we are still too close to the date range of the protests to sort things out with any kind of certainty. Interested readers will find our reference 21 edifying, and it is available online at no cost.

Are there medical issues for people who wear cloth masks all day? If so what?

We are unaware of any ongoing pandemics of hypoxia or hypercarbia related to mask wearing! Surgeons, sterile compounding/IV room pharmacists and technicians, and many lay people techs (THINK: people who work in hazardous waste, contractors exposed to dust, exterminators, and others) have worn masks for hours on end and we have identified no related reports of deaths. A 2013 study found that long-term use of N95s alone or with a mask overlay as an outer barrier created no significant physiologic burden for health care personnel over two work shifts.[22] Several other studies have reported similar results, noting that N95 and surgical masks increase the skin's temperature, sebum secretion, and pH. The more opaque the mask, the greater the likelihood of dermatitis or discomfort (i.e., N95s are more likely to cause discomfort than surgical masks or cloth masks).[23-25]

We could find no studies that specifically addressed the safety of cloth masks. Our collective experience tells us that less serious adverse effects include funny tan lines and foggy glasses.

What is your read on masks as opposed to face shields?

A systematic review identified 172 observational studies with no randomized controlled trials and 44 relevant comparative studies in healthcare and non-healthcare settings (N=25,697 patients).[26] They looked at masks, ocular covering (face shield or goggles), and social distancing. Reciprocal facemask use could reduce the odds of infection by 85% while ocular protection reduced infection by 78%. N95 masks showed a strong trend toward being more effective than surgical or cloth facemasks. The 95% confidence intervals between any type of mask and ocular protection overlapped, so the researchers could not conclude definitively that masks are more effective than ocular protection.[26]

Viral transmission with physical distancing of three feet or more was lower than with shorter separations (moderate certainty). Protection increased linearly as distance as lengthened (moderate certainty).[26] An editorial in the *Journal of the American Medical Association* cites data indicating that face shields in simulated environments have better than 90% effectiveness in reducing the inhalation of influenza virus droplets.[27] This suggests face shields may be more beneficial than cloth facemasks for wearers.

Dr. White's assessment is that facemasks and face shields seem to have similar efficacy. With a face shield, droplets would be propelled forward and impact the non-porous inner surface. Theoretically, the shield would not impede droplets that fall from the mouth. An advantage to face shields is that users can clean them more effectively than cloth masks to prevent cross contamination resulting from touch (although recent data suggests touch is not a major route of transmission). Researchers assume that people touch or readjust face shields less than facemasks, making readjustments on the forehead, not next to the mucus membranes where the risk of hand to nose/mouth contamination is greatest.[27] A non-porous shield that starts at the forehead and protrudes below the chin is likely to have superior efficacy when the impact on the wearer and those in contact are considered in aggregate. Similarly, greater protection from the respiratory route of transmission and superior protection via the ocular route would be expected. Neither method is as proven as social distancing.

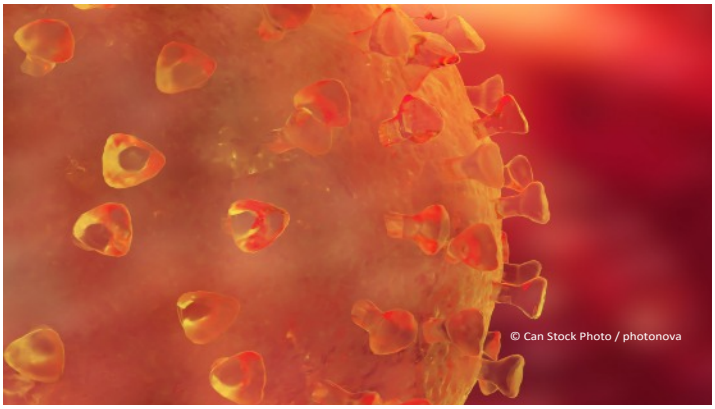


Table 2. A Comparison of LIMITED FACTS about Various Viral Pandemics[30-33]			
Viral Pandemic	**Dates**	**Number of Cases**	**Number of Deaths**
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	February 2020 - present	>12.2 million	>554,000
Ebola	December 2013 to March 2016	28,652	11,325
Severe Acute Respiratory Syndrome (SARS)	November 1, 2002 to July 31, 2003	8,422	774
Spanish Flu	April 1918 - Summer 1919	500 million	50 million
H1N1 Swine Flu	April 12, 2009 to April 10, 2010	60.8 million	151,700 to 575,400

Can you discuss coronavirus in comparison with Swine flu? Are their concerns about concurrent outbreaks?

This is a question we dreaded seeing. Comparing viral infections is like comparing that item that is part of the rose family and comes from trees that have pink blooms with another item that is laden with vitamin C and comes from trees that have white blooms—that is, apples and oranges. Just as apples and oranges are both fruits and share many overarching properties, SARS-CoV-2, Ebola, SARS-CoV, Spanish Flu, and swine flu (we've added a few for you) are all viruses and once you look at a number of factors, their differences make each unique.

We suspect numerous social media posts that compared various viral outbreaks prompted this question. Depending on the source, various actors have used the information to attempt to quell panic or increase concern. One very popular clip came from YouTube, and while the numbers that the original author used were correct, most people who shared the video shared only the first minute or two of the 10-minute video. Had people used Snopes, an Internet fact-checking resource, they would have seen the entire video and understood the numbers better. Find the Snopes analysis and the entire 10-minute video here: https://www.snopes.com/fact-check/coronavirus-graph-spreading-faster/.[28] And readers need to note that the author assembled this video in February 2020. **Table 2** shows current numbers. The original author, Cary Kaiming Huang of Abacaba Data Visualization Videos, is a masters student at Stanford and updates his videos periodically.[29]

When looking at these numbers, they're just numbers. They don't address many factors that we do not and will not know until the pandemic ends. We can see that over the course of a year, swine flu infected more than five times as many people as SARS-CoV-2 has to date and in the largest estimate, was associated with slightly more deaths than have already been attributed to COVID-19. With the recent up-tick in cases, it appears the number of COVID-19-associated deaths will continue to rise. However, to appreciate a pandemic's full impact, society needs to look at morbidity and tangential effects (e.g., increase in domestic violence, school closures, unemployment). We repeat what we said in previous updates: the difference between previous pandemics and this pandemic is that we have tools to reduce transmission.

And of course we have concerns about concurrent outbreaks, especially as many people have forgone routine healthcare and vaccinations during this pandemic. Please encourage your patients to be vaccinated. And remind them that social distancing and masks also reduce the spread of other viral infections spread via respiratory droplets.

Testing is very confusing right now. What is the latest information?

We are currently using two types of tests: viral and antibody.

Viral testing identifies current infection using nasal, saliva, or throat swabs. All current viral testing uses molecular antigen testing to detect SARS-CoV-2. Molecular RT-PCR or antigen testing (nasal, saliva, and throat swabs) are highly effective and rarely need to be repeated. They detect viral RNA or proteins on the virus's surface. COVID-19's incubation period is approximately 14 days with a median of four to five days. Patients usually develop symptoms in two to 14 days, at which point they consider being tested. A negative corona virus test indicates that on one day at one precise time, the individual was most probably not infected.[34,35]

Antibody testing identifies people who have had a past infection using a blood sample. Molecular antibody testing often needs a second blood draw for most accurate results. Antibody development may take days to weeks. Current tests look for IgM antibodies, which tend to develop earlier in an infection, and/or IgG antibodies, which are tend to develop later. Test results vary based on the test use, and can be same-day or take up to three days.

These tests are not completely accurate or reliable.

At this time, the government will pay for all viral tests under the Families First Coronavirus Response Act,[36] and insurers cover subsequent tests as needed. Specific insurance plans vary in their exact coverage. Some insurance companies cover testing and treatment fully, some cover testing for symptomatic patients, some require a physician referral, and others have different stipulations including "medical necessity."[37] Note that some laboratories are marketing these tests directly to patients, and you may field questions.

Table 3. Comparison of Symptom Rates between Children and Adults [38,39]		
Symptom	**Rate in Children**	**Rate in Adults**
Fever	56%-59%	71%
Cough	54%-56%	80%
Shortness of Breath	12%-13%	43%

Could you please discuss special concerns in children?

The literature about COVID19 in children is even more limited than it is for adults. We will share the little data we have. SARS-CoV2 seems to spare most children from significant disease. Those who are affected can have either acute COVID-19 or a delayed condition called multisystem inflammatory syndrome in children (MIS-C).

In children, acute COVID-19 has been associated with low hospitalization rates. Very few children have died. Similar to adults, pediatric patients who have chronic diseases are more likely to have COVID-19 requiring hospitalization. Data indicates that through April 2, 2020, 77% of hospitalized children had at least one comorbid chronic condition, compared to 12% of children who were not hospitalized. All children admitted to intensive care had at least one underlying condition.[38] A systematic review published on June 23, 2020 summarized data from published manuscripts that included pediatric patients with COVID-19 from January 24 through May 11, 2020.[39] The study included 131 studies including a total of 7,780 children (mean age 8.9 +/- 0.5 years) positive for COVID-19. Symptoms appear to occur less frequently in children than in adults (see **Table 3**).[38,39] Almost 20% of cases in children have been asymptomatic. The average duration of hospitalization was 11.6 days and only 3.3% of reported pediatric cases required critical care.[39]

As noted, children are more likely to do well with acute COVID-19 infection and the majority will only require supportive care. When therapy is needed, the therapies are generally similar to those used for adult patients with the exception that outside of the US, interferon usage is common (approximately 40% of children).[39] In the U.S., the FDA has even granted a specific EUA for remdesivir in pediatric patient. Similar to adult patients, children who have oxygenation on room air of less than 94% are defined as having severe disease.[40] Per the EUA, those who are 3.5 to 40 kg should only receive the lyophilized powder formulation as this contains less of the cyclodextran inactive component.[40]

Most pressing concern in children focuses on MIS-C presentation; some publications use the term pediatric multisystem inflammatory syndrome (PMIS) interchangeably. First reported in Europe in April 2020, these patients generally experienced a COVID-19 infection about one month before MIS-C dvelops.[41,42] It appears to share similar characteristics with Kawasaki Disease, toxic shock syndrome, and various inflammatory syndromes (e.g., macrophage activation syndromes).

Specifically, the CDC has defined the MIS-C classification as occurring in patients[41]

- younger than 21 years who present with fever for at least 24 hours with elevated inflammatory markers
- with severe illness involving more than one organ (i.e. cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic) and
- who do not meet criteria for another diagnosis and have evidence of COVID-19 (i.e., PCR, serology, antigen, or known exposure in the four weeks before MIS-C symptom onset).

Specifics regarding MIS-C presentations in the U.S. have recently been described. Specifically, between March 15 and May 20 (with the majority reported between April 16 and May 20), pediatric health centers reported 186 cases.[42] The median age of these children was 8.3 years (range 3.3-12.5 years) with 31% Hispanic/Latino, 25% Black non-Hispanic, followed by 19% White non-Hispanic. Two things heighten concern: 1) 73% were previously healthy, indicating risk factors are uncertain, and 2) 80% required intensive care admission, indicating a severe presentation. Further, 4% required extracorporeal membrane oxygenation support.[42]

MIS-C patients appear to present to the hospital after about four to six days of fever.[42-45] Unlike acute COVID-19, MIS-C appears to affect the heart. Patients presenting in shock, requiring vasoactive support.[42-45] Affected children also commonly have high inflammatory markers such as C-reactive protein (greater than 3 mg/dL some as high as 55.6 mg/dL), NT-proBNP (often >400-1000 ng/L), and ferritin (>500 ng/mL)]. Further, many have ventricular dysfunction and/or coronary abnormalities.[42-45] Intra-abdominal involvement and acute kidney injury have also been reported.[43]

Treatment for MIS-C is currently evolving. The majority of patients have required fluid resuscitation and inotropic support. Similar to Kawasaki Disease, which also affects the heart, clinicians used intravenous immune globulin in 97% of American pediatric patients who had at least two Kawasaki's disease–like features plus additional laboratory or echocardiographic findings between days six and eight. Other medications that were used in some patients included anticoagulants, corticosteroids, tocilizumab, siltuximab, and/or anakinra.[42] Many patients also received anticoagulation. Most children respond well to treatment with only a few deaths. Risk factors for MIS-C and long term effects are uncertain at this time.[42]

Please discuss alternative medicines, vitamins, and plant-based diets.

Let's put the bottom line right up front: like many treatments for COVID-19 proposed early in the pandemic, natural products have no proven benefit in treating or preventing coronavirus infection. While natural products may be available without a prescription, they confer some risk of toxicity. Pharmacists and pharmacy technicians should stay abreast of information on natural products as they may field questions from patients (and of course, family members); know three things: which products are being discussed, data and ongoing research, and potential toxicities.

Complementary and alternative (CAM) product researchers and proponents have proposed many natural products based on their mechanisms or *in vitro* data—in fact, most CAM data is *in vitro*. Clinical evidence in humans is lacking in COVID-19. People need to exercise caution until we have safety and efficacy evidence from human trials.[46] Since COVID-19' pathophysiology is unclear and evidence is scant, avoiding supplements is wise. They may cause more harm than benefit. Further studies are needed before educated healthcare professionals can recommend any supplements confidently for prevention or treatment for COVID-19.

The FDA and the Federal Trade Commission (FTC) issued several warnings to companies that falsely claimed their products could treat or prevent COVID-19. Among their actions were warning letters were to seven companies (Vital Silver, Quinessence Aromatherapy Ltd., Xephyr, LLC doing business as N-Ergetics, GuruNanda, LLC, Vivify Holistic Clinic, Herbal Amy LLC, and The Jim Bakker Show) for selling fraudulent products. These teas, essential oils, tinctures, and colloidal silver supplements are not FDA-approved, pose significant risk to patient and public health, and making claims of efficacy violates federal law. Using these products may delay proper diagnosis and treatment of COVID-19 and other potentially serious diseases and conditions.[47] Readers can find FDA resources for fraudulent COVID-19 products at https://www.fda.gov/drugs/drug-supply-chain-integrity/internet-pharmacy-warning-letters. **Table 4** (next page) lists CAM that is under study; it is not all-inclusive, but cover the most commonly researched products.

Neither the CDC nor the World Health Organization recommend diet as a prevention or cure for COVID-19, but both indicate that a nutritious diet can strengthen the immune system.[58,59] A healthy diet also improves many chronic conditions. Vitamin C, vitamin D, and zinc may bolster the immune system, and consuming these nutrients in food is the best way to obtain them.

- Foods containing vitamin C: fruits (citrus such as oranges and grapefruit including their juice, kiwifruit, strawberries, cantaloupe) and vegetables (red and green pepper, broccoli, baked potatoes, tomatoes)
- Foods containing vitamin D: low-fat milk, fortified milk alternatives, seafood
- Foods containing zinc: lean meat, seafood, legumes, nuts, seeds

Some functional food plants may enhance immune system, researchers postulate (but have not proven) that they may have antiviral activity against infection and possibly reduce other respiratory. Researchers propose that black pepper (*Piper nigrum*), curcumin, garlic (*Allium sativum*), ginger (*Zingiber officinale*), liquorice (*Glycyrrhiza glabra*), pomegranate (*Punica granatum*), tea (*Camellia sinensis*), and turmeric (*Curcuma longa*) might enhance humoral and cell-mediated immunity, and activate natural killer (NK) cells, macrophages, granulocytes, and complements.[60] Activation can enhance resistance to certain infections and produce molecules involved in immune response (interferon, cytokines, chemokines). Again, indiscriminate use can result in toxicity. Reference 60 includes a concise table that may be of interest to you.

Two reviews[61,62] suggest that a low purine diet that controls uric acid concentrations in the blood might be helpful. Purines fuel inosine monophosphate dehydrogenase, the enzyme that is essential for viral growth and differentiation. High uric acid concentrations, which can potentially stem from increased consumption of high purine foods, might encourage viral replication. Reducing consumptions of foods containing high purine concentrations (alcoholic beverages, sweetbreads, anchovies, sardines, liver, kidney, brains, herring, mackerel, scallops) or controlling consumption of food with moderate concentrations (beef, pork, poultry, fish/seafood, asparagus, cauliflower, spinach, mushrooms, peas, lentils, dried peas, oats, bran wheat, wheat germ) might be helpful.[61-63] Note that these articles are reviews, not studies.

(Text continues on page 10)

Table 4. CAM Products Currently Proposed or Advertised for COVID-19[48-57]			
Dietary or Natural Supplement	**Proposed Mechanism of Effect**	**Evidence?**	**Adverse & Toxic Effects***
Colloidal Silver	Antibacterial & antiviral mechanisms	Not considered safe or effective by FDA	Irreversible skin discoloration, risk of harm to major organs (liver, kidney, GI), severe neurologic effects (seizure, psychosis)
Echinacea purpura	Proposed immunomodulatory properties by means of enhancing innate immune system	Some evidence suggests production of pro-inflammatory cytokines IL-1, IL-6, TNF-a which would further promote lung injury by enhancing cytokine storm	Nausea and abdominal pain, severe allergic reactions such as rash
Elderberry (sambucus nigra)[1]	Modulation of inflammatory cytokines	Potential to reduce cold symptoms if taken in excess of 10 days prior to travel No data in COVID specific populations	GI (N/V/D), hypotension, tachycardia, hypotension, hypokalemia, cyanide toxicity if uncooked portions are consumed, caution in diabetic patients (interaction with glucose metabolism)[4]
Garlic extract (*Allium sativum*)	Immunomodulatory, presence of bioactive sulfur-containing compounds (sulfoxide, proteins, polyphenols), boost innate and specific cell immunity & enhance host resistance	No human efficacy data, in vitro and animal studies	Diarrhea, dizziness, nausea, vomiting, headache, flatulence (especially on empty stomach)
Licorice root *(Glycyrrhiza gabra)*	Immunomodulatory, contains glycyrrhizin (what causes its flavor); which is a compound found in 2002-2004 SARS to inhibit SARS-CoV in vitro	No human efficacy data published to date with licorice and SARS-CoV	Hypertension, hypokalemia-induced secondary disorders; low doses can cause complications in pregnant and breast-feeding children; can be toxic for people with cardiovascular and renal comorbidities, and chronic hypertension.
Vitamin C (ascorbic acid)	Free radical scavenger, decrease gene expression within proinflammatory cytokines, and enhance microbial killing	Use not supported by evidence in common cold (8% reduction in common cold duration)[7] Variable dose; high dose utilized in critically ill COVID patients not realistic for OTC	(With OTC preps) gastrointestinal (nausea, vomiting), abdominal cramping

CONCLUSION

COVID-19 has not been defeated. We are all still vulnerable, and some more vulnerable than others. We have learned tragically that nursing homes are particularly vulnerable. American health workers have more ventilators and more personal protective equipment than we did in the early pandemic. We have two modestly effective treatments available for some hospitalized patients based on infection and patient characteristics. What most people want—therapies that are game changers, magic bullets, and vaccines—are still research goals.

The best thing we can do is delay the number of people who contract coronavirus so we can treat them in health systems that are not overloaded and/or at a time when we have more—and more effective—therapies available.

UCONN's CORONAVIRUS SERIES

Interested individuals can find the original activity here: https://pharmacy.uconn.edu/wp-content/uploads/sites/2740/2020/03/CORONAVIRUS-MAR2020-FINAL.pdf.

And the first update here: https://pharmacy.uconn.edu/wp-content/uploads/sites/2740/2020/03/CORONAVIRUS-UPDATE-1-30MAR2020-FINAL.pdf

And the second update here: https://pharmacy.uconn.edu/wp-content/uploads/sites/2740/2020/04/CORONAVIRUS-UPDATE-2-13APR2020-FINAL-1.pdf

And the third update here: https://pharmacy.uconn.edu/wp-content/uploads/sites/2740/2020/05/CORONAVIRUS-UPDATE-3-FINAL.pdf

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