You Asked for It! CE

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 treatments that are currently being investigated for COVID-19
- Recognize issues of concern related to hydroxychloroquine
- Describe the science behind ABO blood groupings and human susceptibility to viruses

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 0.1 CEU (1 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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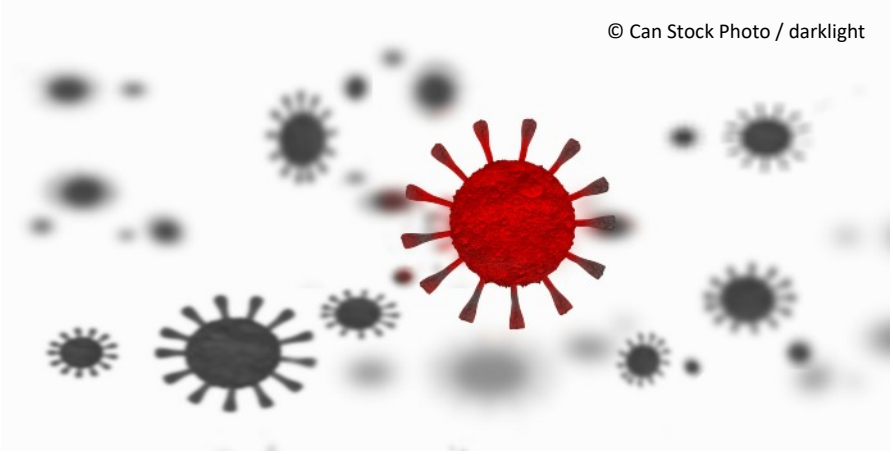

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UConn UPDATE #2: SARS-CoV-2 and COVID-19

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

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INTRODUCTION

This is UConn School of Pharmacy's second update to information related to SARS-CoV-2 viral infection 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 time passes and we advance into what we hope will be the peak of the pandemic, new questions arise. As we noted in previous CEs, the situation changes daily (and sometimes hourly), and misinformation is rampant.

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
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I know there are no FDA-approved treatments to lessen the severity or shorten the duration of the disease and people have been hearing about several potential treatments from uneducated people who have no idea what they are talking about. Maybe it would just be a curiosity, but a rundown of the treatment possibilities and their respective hypothetical mechanisms of action would satisfy that and give us a bit more information to help explain to patients why certain medications are being considered and why it's not yet a good idea to buy into any "cures."

At this time, clinicians are using a few medications in an attempt to treat COVID-19. **Table 1** (page 3) describes the medications clinicians are employing most often. Before reading the table, be sure to understand the following:

WHO should be treated for COVID-19?

Patients who contract COVID-19 and are well enough to stay at home and self-quarantine do not need treatment other than supportive care.

- Only hospitalized patients with confirmed SARS-CoV-2 are eligible for targeted pharmacologic treatment or investigational drugs.
- No medication has been identified as effective prophylaxis.

WHAT medications do experts suggest for treatment of COVID-19?

Short answer: Many have been suggested, none have been proven effective

Long answer: Clinicians, researchers, and various others have proposed many medications based on their mechanisms; they are mainly antivirals and immune modulating medications.

- Major professional societies such as Society of Critical Care Medicine and Infectious Diseases Society of America identify therapy recommendations as "weak" on their rating scales, or are unable to make a recommendation due to the lack of support from clinical evidence.[1,2]

WHY these medications?

SARS-CoV-2 is a single-stranded RNA beta coronavirus that expresses viral proteins to attach to host cells through certain enzymes and replicates by recruiting non-structural and accessory proteins[3-6]:

- Researchers believe antivirals may be helpful because they target common viruses with structures similar to SARS-CoV-2.
- Immunomodulatory medications will target nonstructural/accessory proteins (i.e., cytokines, specifically IL-6) that may be upregulated during virus replication to help the innate immune system.

WHERE can pharmacists obtain these medications?

- All medications used for treatment should be used in the **inpatient hospital** setting. They are reserved for the sickest patients, and they may also be used as part of a clinical trial.
- Some antivirals are available to be prescribed outpatient, but due to lack of evidence, outpatient use is not recommended. Outpatient supplies should be reserved for populations that have disease states in which these drugs are indicated (i.e., HIV/AIDs, rheumatoid arthritis, lupus)

WHEN will it be known if a treatment is effective?

Right now, clinical investigators have initiated hundreds of clinical trials to test and research proposed medications, but this takes time. We will probably not know for a while. So for now, care is multifactorial and depends heavily on supportive care.

Additional Investigational Therapies to Keep on Your Radar

You may have heard of other medications and strategies, such as remdesivir or convalescent plasma (discussed below). These investigational treatments are not commercially available. They are not recommended for routine use.

- Remdesivir: A broad-spectrum antiviral that has previously been evaluated for SARS, MERS and Ebola. According to experts, this is the most promising investigational therapy. However, it is not commercially available and its use is limited to select clinical sites employing Compassionate Use protocols.
- Convalescent plasma[16] (discussed below): Serum derived from blood from recovered, COVID-19 positive patients that may contain antibodies against the virus to administer to severely ill patients. Eleven clinical trials are underway.

For a comprehensive list of emerging therapies, visit *ASHP: Assessment of Evidence for COVID-19-Related Treatments*. It is updated almost daily.
https://www.ashp.org/-/media/8CA43C674C6D4335B6A19852843C4052.ashx

Another great resource is https://www.covid19-druginteractions.org/, from University of Liverpool, updated frequently.

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Table 1. Medications Being used for COVID-19 in Institutional Protocols[7-24]

	Hydroxychloroquine Sulfate (Plaquenil)	Lopinavir/Ritonavir (Kaletra)	Tocilizumab (Actemra)
Mechanism	Multiple mechanisms to inhibit viral replication + anti-inflammatory effects.	Antiretroviral nucleoside analogue (blocks RNA synthesis)	IL-6 inhibitor (immune modulating)
COVID Recommended Dose	Variable dose recommendations* Emergency Use Authorization: 800 mg day 1, 400 mg daily, for 4-7 days	400/100 mg PO BID x 10 days	4-8 mg/kg (max total dose 800 mg) once Dose may be repeated 12 hours later if inadequate response to first dose
Dosage Forms	□ Tablet □ Suspension can be made for nasogastric tube administration	□ Tablet (can be crushed, ~45% absorption through NG tube may require double dose or increased frequency) □ Oral solution	□ Intravenous □ Subcutaneous, prefilled syringe (Not recommended subcutaneously for the sickest patients, as absorption may be erratic and decreased. The SQ dosage form can be compounded and administered IV based on stability studies recently released by the manufacturer.)
Key COVID Points	□ Chloroquine not available in the US □ May see total daily dose split into q12h □ No dosage requirements recommended in renal or hepatic dysfunction, or obesity □ Cardiac monitoring	□ Generally not recommended for use (benefit not seen in clinical trials, low supply) □ Solution contains propylene glycol 15.3% and alcohol 42% v/v—PVC feeding tubes preferred.	□ Reserved for severe, refractory cases and clinical trial patients
Adverse Effects	□ QTc prolongation □ Cardiomyopathy □ Bone marrow suppression (thrombocytopenia, leukopenia) □ Hypoglycemia	□ GI effects (N/V/D) □ Transaminitits (ALT/AST) □ Hyperlipidemia □ Pancreatitis □ Hyperglycemia	□ Transaminitis (AST/ALT elevations) □ Elevated lipid levels (hypercholesterolemia) □ Neutropenia
Major Warnings/ Contraindications	□ Torsade de pointes □ Epilepsy □ Retinal pathology □ G6PD deficiency	MANY drug interactions—potent 3A4 inhibitor	□ **Boxed Warning**: Increased risk of opportunistic infections □ Serious adverse effects such as gastric perforation (not reported with one-time use)
Clinical Trials with Drug as Intervention**	77	15	20

*Emergency Use Authorization recommendation: for > 50 kg if clinical trial is not available/participation not feasible
400 mg BID day 1; 200 mg BID day 2-5
400 mg daily or twice daily for 5-10 days
600 mg BID day 1, 400 mg daily days 2-5
100-200 mg BID 5-14 days
200 mg TID for 10 days

**ClinicalTrials.gov as of 4/10/2020. Total COVID-19 clinical trials listed = 440

Note: Azithromycin may be administered if bacterial co-infection (i.e., community acquired pneumonia) is suspected in COVID-19 patients and atypical coverage is desired. Cardiac risk should be assessed as co-administration with hydroxychloroquine increases risk of QTc prolongation.

If you do another follow up, can you please address the issue of hydroxychloroquine being a film-coated tablet that you cannot crush or split. What do we do with patients who are NPO? What is the data regarding compounding a suspension?

We consulted our compounding faculty for this question, and they indicate that hydroxychloroquine has a coating because of its horrible, bitter taste. You can crush hydroxychloroquine tablets, and our faculty retrieved an old formula for a suspension which is easy to make (see **Table 2**).[25]

Table 2. Formula for Hydroxychloroquine Suspension[25]

- Gather 15 200 mg hydroxychloroquine tablets
- Rub them with a towel moistened with alcohol to remove their coating
- Ground the tablets to a fine powder, then levigate the powder to a paste with 15 mL Ora-Plus suspending agent
- Add 45 mL suspending agent and q.s. to 120 mL with water for irrigation
- DO NOT add sugar or artificial flavorings
- The resultant suspension will contain 25 mg/mL

(This came from a patient.) I have rheumatoid arthritis and I have been taking hydroxychloroquine for several years. Are pharmacies reserving a supply for patients like me?

It depends. We believe that pharmacies are being careful when they see prescriptions for hydroxychloroquine, and ensuring that they have an adequate supply for their known customers.

Many people in the pharmacy community have little exposure to or experience with hydroxychloroquine. The U.S. Food and Drug Administration (FDA) approved this drug in 1946, and it has three approved uses:

- Malaria
- Lupus erythematosus
- Rheumatoid arthritis

Those are the three traditional, FDA-approved uses. It is also often used off-label for Sjogren's syndrome. The FDA has authorized emergency use of hydroxychloroquine sulfate in hospitalized adult and adolescent patients weighing 50 kg (110 lbs) or more for suspected or laboratory confirmed COVID-19 infection due to the SARS-CoV-2 virus.[26] This is not a permanent approval, but a temporary emergency use authorization, and the authorization comes with narrowly defined restrictions:

- The patient must be hospitalized.
- The patient must not have access to a clinical trial, or be ineligible for a clinical trial.
- The drug must be administered orally.
- The optimal dosing is unknown, and the suggested dosing is 800 mg hydroxychloroquine on day 1 followed by 400 mg daily for four to seven days.
- Information on safety and effectiveness is lacking.

That said, pharmacy staff should not see or fill prescriptions for ambulatory patients who are community-based, nor should they see or fill prescriptions for prophylaxis. Regardless, most community pharmacies have received prescriptions from community-dwelling individuals. One pharmacist indicated that her pharmacy has received a number of prescriptions that prescribers have written for family members, the most noteworthy being for 1000 tablets.

As of April 9, 2020, At least 19 States have modified state laws to address prescriptions for hydroxychloroquine, chloroquine, and/or azithromycin directly. Guidance from Arkansas says, "Pharmacists and physicians must also consider that patients currently taking hydroxychloroquine for FDA-approved indications could be affected by this prescribing. Supplies of chloroquine and hydroxychloroquine should be monitored by pharmacists for medication availability."[27] In Ohio, the Emergency Rule for Dispensing Chloroquine and Hydroxychloroquine stipulates that the prescription needs a written diagnosis code; if written for COVID-19, the prescription must indicate the patient had a positive test; the supply cannot exceed 14 days; and no refills are permitted.[28] Pharmacy staff should be certain to check with their state pharmacy boards for guidance.

Pharmacists have many ways of dealing with situations like this, and the easiest is to quote guidance from your state if you have any. It may help to explain that the FDA only allows hydroxychloroquine under the circumstances described above, and that this drug has significant side effects and drug interactions. The oldest (and grumpiest) of our coauthors indicates that she would run out of patience if a patient pushed to have a prescription filled after she explained all this. While one can understand how people may wish to look out for their self-interests when they are frightened, she considers this fraud and abuse. (The world is very lucky that she does not work in a community pharmacy. And that's enough levity for this update.)

I'm also curious if it's true that the virus is more likely to be contracted by persons with type A blood?

First, some learners may need a refresher on the ABO blood group system, and the **Sidebar** on page 5 provides that for you.

Information suggesting that blood type may influence SARS-CoV-2 infection comes from a study that has been released (but not peer reviewed).[37] In that study, Chinese researchers compared the ABO blood group distribution in 2,173 patients with laboratory confirmed COVID-19. All patients had been hospitalized in Wuhan and Shenzhen, China. Their results suggest that individuals with blood group A seemed to have a higher risk for acquiring COVID-19 than individuals with non-A blood groups. Infection

risk seemed to be lowest in people with blood group O. This is the first observation of an association between the ABO blood type and COVID-19. It should be emphasized, however, that this is an early study with limitations. It would be premature to use this study to guide clinical practice at this time, but it should encourage further investigation of the relationship between the ABO blood group and COVID-19 susceptibility.

One might think, "Why did they even think to look at blood groups?" Researchers have known for quite some time that susceptibility to viral infection is related to ABO blood group in certain infections.[38]

Early studies of norovirus—a very contagious virus that causes diarrhea and vomiting—identified a startling fact: Some people could not be infected. These robust individuals typically clustered in families and lacked antibodies from a previous infection.[39] This finding suggested that a highly penetrant host-susceptibility allele influences resistance. Recent studies have confirmed this and linked susceptibility to blood group. People who have type O blood are more susceptible to norovirus infection, and those with type B blood are less susceptible, especially if the virus is from the gastrointestinal strain. It appears that histoblood-group antigens—complex human glycans expressed on surfaces of red blood cells, gut, respiratory epithelia, and biological secretions—are receptors or coreceptors. These antigens allow a productive norovirus infection in some, but not all, infections. Some people, however, may be resistant to one strain but may be susceptible to another.[40-42]

A more recent study looked at 41,033 apparently healthy blood donors to determine the frequency of hepatitis B, hepatitis C, syphilis, HIV, and malaria and see if ABO and Rh blood groups influenced infection.[43] These researchers looked at six years of data. This is what they found:

- Donors' ages ranged from 18-70 (mean age of 38±10.5years)
- 98.3% were males and 1.9% were females
- Group B positive was most common, followed by O positive
- Donors with group A blood were significantly more likely to contract HIV and hepatitis B
- No association between blood group O or any blood-transmitted infection were identified

These researchers concluded that blood group O may protect against blood-transmitted infection to some extent, while group A may increase susceptibility to hepatitis B and HIV.[43] However, other researchers have looked at this same issue, and found conflicting results.[44,45]

Let's return to SARS-CoV-2 and the pre-print study that looks at blood type and has not undergone peer review yet. These researchers determined that in their sample of people in China, blood group A was associated with an increased risk and blood

SIDEBAR: Blood Groups[29-36]

Karl Landsteiner discovered and elucidated the ABO blood types between 1901 and 1909, receiving the Nobel Prize in Physiology or Medicine in 1930 for his work. Most people know about ABO blood type because in human blood transfusions, it's critical to match the patient's A antigen in some cases. Mismatch can lead to potentially fatal adverse reactions, or an unwanted immune response to an organ transplant.

Healthcare providers use the ABO blood group system to identify the presence of one, both, or neither of the A and B antigens on erythrocytes (mature blood cells that contains hemoglobin to carry oxygen to tissues). The associated anti-A and anti-B antibodies are usually IgM antibodies, produced in the first years of life by sensitization to environmental substances such as food, bacteria, and viruses.

- Group A blood has only the A antigen on red cells (and B antibody in the plasma)
- Group B blood has only the B antigen on red cells (and A antibody in the plasma)
- Group AB has both A and B antigens on red cells (and neither A nor B antibody in the plasma)
- Group O blood has no A nor B antigens on red cells (but both A and B antibody are in the plasma)

Healthcare providers must also consider Rh factor, a protein that is present (+) or absent (–), creating the 8 most common blood types (A+, A-, B+, B-, O+, O-, AB+, AB-).

Readers should also note that the prevalence of certain blood types varies by country. This would be expected, as blood type is inherited. Several sources report that in Armenia, Cyprus, Malta, Norway, and Switzerland, more than 40% of the population has type A blood. In China, approximately half of the population has O+ blood, and 28% has A+ blood.

Statisticians and biologists have linked ABO blood groups with many chronic diseases such as preeclampsia (AB blood group seems to increase risk), coronary heart disease (type O lowers risk moderately), and cancer (type A may increase risk of gastric cancer, type B may increase risk for esophageal cancer), stomach ulcers (more common in group O individuals), type A may increase risk of breast cancer in Caucasians). Readers should note that while many of these studies are large, they tend to be conducted in homogeneous populations, and often, researchers don't consider confounding factors like diet, smoking, or comorbid conditions.

Blood types are not unique to humans, and other mammal's groupings may differ from those of humans. Rodents and apes (e.g., chimpanzees, bonobos, and gorillas) also have ABO blood types.

group O was associated with a decreased risk.[37] They report the increased risk of blood group A for COVID-19 with an odds ratio of 1.279. They also report a decreased risk in people with blood group O for COVID-19, with an odds ratio of 0.68. Readers should note that these researchers acknowledge limitations:

- Most of the patients came from one of three hospitals
- They had no information on control subjects' age and sex
- They could not determine infected individuals' chronic medical conditions—conditions that influence COVID-19's severity—and this could bias their conclusions

So it's not as simple as it seems. In this study, in this population, it appears that type A blood groups increase risk.[37] But we will need to look at many other layered factors that impact infection rates and may be linked to severe infection rates.

What else do I need to know about this pandemic?

News stations are quick to jump on any story that might hold promise, and of late, they seem to be focusing on the use of "convalescent plasma" to treat patients. The premise is that patients who have recovered from COVID-19 infection have developed COVID-19 specific antibodies, and mining those antibodies from their blood, then transferring them to other patients could treat the disease. This is called *passive antibody therapy*. The use of passive antibody therapy predates the discovery of effective antibiotics.[46,47]

Researchers began using passive antibody therapy in the late 1890s for several bacterial infections. At that time, they called it serum therapy. In its infancy, patients treated with serum therapy often developed hypersensitivity reactions or serum sickness, which we now know is a form of antibody-antigen complex disease. Remember, passive antibodies are derived from human blood, and thus are natural products that are produced *in vivo* or in live cell lines or systems. Over the next 40 years, researchers learned more about antibody purification, and they were able to produce purer and less toxic serums. Then, antibiotics became a proven, safer approach to bacterial infection.

Like all of the potential interventions, we've address here, we need more information about passive antibody therapy before we can make educated assessments. **Table 3** list passive antibody therapy's advantages and disadvantages.

CONCLUSION

Much remains unknown and unpredictable in this pandemic. Please know that we welcome your questions, and are monitoring the clinical literature constantly. Each time we hear another report of a "stunning breakthrough" or a "game-changer," a faculty member dives into the evidence to ensure we have a scientific understanding of its pros and cons. We also try to provide the historic background for why a particular approach may or may not work. We, too, are learning as we go, and we thank you for that.

We welcome your questions. Please submit questions or comments to jeannette.wick@uconn.com.

Table 3. Advantages and Disadvantages of Passive Antibody Therapy[46,47]

Advantages	Disadvantages

• Low toxicity
• High specificity (targets the microorganisim that causes the disease, and shouldn't affect the host)
• Antibodies can be immunomodulators, bridging the innate, acquired, cellular and humoral immune responses
• Potential synergy when combined with conventional antimicrobial chemotherapy
• Contributing role in vaccine development; effective serums suggest vaccines with similar actions
	• High specificity (>1 antibody preparation might be needed to target microorganisms with high antigenic variation). In other words, a single patient's antibodies might not be sufficient for SARS-CoV-2 viruses with antigenic variation
	• Potential contamination with infectious agents (e.g., prions, viruses)
	• Need to administer in routes other than the oral route
	• Efficacy decreases rapidly as the infection duration increases; may only be useful early in the diagnosis
	• High production, storage, and administration costs
	• **Administration amount is critical**
	  ◦ Administration of too little antibody can produce no therapeutic effect
	  ◦ Administration of too much antibody can produce PROZONE-like effects (antibody efficacy is lost and antibody administration can be detrimental to the host)

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