Southwestern Health Resources

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COVID-19 PHARMACY UPDATE

July 15, 2020

Disclaimer: We are getting frequent COVID-related questions about drug concerns and potential interactions. This information is as July 15, 2020. We will do our best to keep you up to date with this ever evolving situation. This is the most update information at the time of publication.

Note: There are no Food and Drug Administration (FDA) approved therapies for treatment or prevention of COVID-19. If at all possible, it is best to have patients enrolled in a clinical trial.

PRESS RELEASE: COMPARATIVE ANALYSIS SHOWS REMDESIVIR MORTALITY REDUCTION IN SEVERE COVID-19

Treatment with remdesivir was associated with an improvement in clinical recovery and a 62% reduction in the risk of mortality compared with standard of care in patients with severe COVID-19 – an important finding that requires confirmation in prospective clinical trials. This new data was presented at the Virtual COVID-19 Conference as part of the 23rd International AIDS conference.[1]

An analysis was conducted comparing outcomes from 312 patients treated with remdesivir plus standard of care in the phase 3 SIMPLE- Severe study[2] to a separate real-world retrospective cohort of 818 patients with similar baseline characteristics and disease severity who only received standard of care in the same time period. Results from the analysis showed that 74.4% of patients treated with remdesivir recovered (defined as an improvement in clinical status based on a 7-point ordinal scale) by day 14 compared with 59% of patients who only received standard of care. Additionally, the mortality rate at day 14 was found to be 7.6% for the remdesivir group and 12.5% for the standard of care group (adjusted odds ratio 0.38; 95% CI, 0.22-0.68; *P* =.001).

Clinical outcomes evaluating the safety and efficacy of remdesivir were also similar across different racial and ethnic patient populations. Rates of clinical improvement (defined as a ≥2-point improvement on a 7-point ordinal scale) at day 14 were 84% in Black patients (n=43), 76% in Hispanic White patients (n=17), 67% in Asian patients (n=18), 67% in non-Hispanic White patients (n=119) and 63% in patients who did not identify with any of these groups (n=32).

1. https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19
2. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe covid-19. N Engl J Med. 2020 May 27. PMID: 32459919 DOI: 10.1056/NEJMoa2015301

UPDATE: HYDROXYCHLOROQUINE WITH OR WITHOUT AZITHROMYCIN IN COVID-19

The data on hydroxychloroquine for the treatment of COVID-19 has been mixed. Most recently there has been a concern about hydroxychloroquine with azithromycin and potential for cardiac complications[1]. The newest study from Michigan shows a potential mortality benefit of hydroxychloroquine with or without azithromycin when used early in the hospitalization course[2].

Henry Ford Health System in Southwest Michigan conducted a study on COVID-related admissions from March 10, 2020 to May 2, 2020. There were four cohorts: hydroxychloroquine alone, azithromycin, hydroxychloroquine plus azithromycin, or other treatments. The combination of both hydroxychloroquine and azithromycin was only used in patients with severe COVID-19 and minimal cardiac risk factors. They used an EKG driven protocol for hydroxychloroquine and if QTc was greater than 500 ms, then hydroxychloroquine was reserved for those with severe disease and required telemetry and QTc monitoring. Adjunctive therapy was allowed in all four groups. The primary endpoint evaluated was inpatient hospital mortality.

At total of 2,541 patients were included in the study analysis. The median age was 64 years, 51% were male, 56% were African American, 52% had a BMI $\geq$ 30, and median inpatient length of stay was 6 days. Severity of disease on admission was assessed by highest mSOFA score and lowest O2 saturation. ICU admission and mechanical ventilation were also used to assess the severity of disease. The overall mortality of the study patients were 18.1%. 13.5% in the hydroxychloroquine group, 20.1% in the combination hydroxychloroquine and azithromycin group, 22.4% in azithromycin group, and 26.4% in the other treatments group. The primary causes of mortality in the 460 patients were respiratory failure (88%), cardiac arrest (4%), and other cardiopulmonary arrest and multi-organ failure (8%).

This study showed that hydroxychloroquine with or without azithromycin was associated with reduced mortality in hospitalized COVID-19 patients. Hydroxychoroquine alone was associated with a decreased mortality hazard ratio of 66% ($p<0.001$) and with azithromycin 77% ($P<0.001$). Age, white race, reduced O2 saturation level on admission, and ventilator use during admission were predictors of mortality.

They were able to propensity match 190 hydroxychloroquine patients with 190 patients not treated with hydroxychloroquine. For these two matched groups, the hydroxychloroquine group had a 51% decreased mortality hazard ratio. This survival benefit persisted up to 28 days from date of admission.

1. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; published online March 27. DOI:10.1001/jamacardio.2020.1017
2. Arshad S, Kilgore P, Chaudhry Z, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. International Journal of Infectious Disease 2020; published online July 1. https://doi.org/10.1016/j.ijid.2020.06.099

DOSE DEPENDENT INCREASED ODDS OF COVID-19 INFECTION WITH PROTON PUMP INHIBITOR (PPI) USE

Population survey data, from a pre-printed American Journal of Gastroenterology article, has been released noting increased odds of a positive COVID-19 test result in respondents who were taking PPIs. The online survey involved a total of 86,602 total respondents out of the 264,058 invited participants. Of those who responded, 53,130 reported having GI symptoms and were asked further questions regarding PPI and histamine 2 receptor antagonist (H2RA) use. PPI and H2RA frequency and duration of use were assessed. All survey respondents were also questioned about history of COVID-19. There were 3,386 respondents who reported having a positive COVID-19 test and follow-up disease symptom questions were asked.

After statistical analysis to try to control for confounders, daily PPI use was independently associated with increased odds of a positive COVID-19 test result (OR 2.15, 95% CI 1.9-2.44) as was twice daily PPI use (OR 3.67, 95% CI 2.93-4.60). H2RA "low dose" use was associated with a slight decrease in the odds of a positive COVID-19 test and no association was noted with "high dose" H2RA use; though dose definitions weren't specified. The study also noted increased odds of a positive COVID-19 result at all durations of PPI use: daily for $\leq$ 6 months (OR 3.25, 95% CI 2.81-3.77), daily > 6 months (OR 1.44, 95% CI 1.22-1.7), twice daily $\leq$ 6 months (OR 2.31, 95% CI 1.42-3.77) and twice daily > 6 months (OR 3.81, 95% CI 2.97-4.87). The analysis noted males, current smokers, non-Hispanic blacks, and Latinos also had a statistical increase in reporting a positive COVID-19 test; consistent with other research. Survey respondents with COVID-19 taking daily PPIs had lower odds of reporting GI related disease symptoms (OR 0.62, 95% CI 0.49-0.78) but this wasn't observed with BID use.

While this survey was designed as a prior evaluation of GI symptoms, PPI and H2RA use as well as COVID-19 incidence, symptoms and a statistical analysis were conducted to attempt to control for confounders; based on its design, there are still limitations and potential inherent bias. This association bears further scrutiny. However, an association is not causality and more robust clinical trial results will be needed to further evaluate the implications of this data. It does reinforce, once again, the importance of exercising principles of good clinical practice to ensure PPIs are used only in patients with an ongoing indication and at the lowest possible dose. It is also important to note that with the removal of ranitidine from the market and the evaluation of famotidine as a potential COVID-19 treatment option (see SWHR Pharmacy Updates from 4/30/2020 & 7/9/2020), famotidine shortages are being seen (see "Potential Shortages" section below).

1. CV Almario, WD Chey, BMR Speigel. Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors. Accepted for publication to Am J Gastroenterol. Available pre-print at https://journals.lww.com/ajg/Documents/AJG-20-1811_R1(PUBLISH%20AS%20WEBPART).pdf

UPDATE: MEDFORMIN ER RECALL

On July 18, Lupin Pharmaceuticals has updated its voluntary recall of metformin ER to include all batches of Metformin extended release tablets, 500mg and 1000mg. The company had previously voluntarily recalled one lot of its metformin extended release tablets, but has now-extended the recall to all lots. This is the latest in a growing number of metformin extended release recalls involving Granules, Amneal Pharmaceuticals, Apotex Corp, Teva Pharmaceuticals, Marksans Pharma Limited, In all cases, the potential contaminate has been N-Nitrosodimethylamine (NDMA), which is listed as a probable human carcinogen. NDMA is also found in the environment in water and foods, including meats, dairy products, and vegetables. At this time the only products being recalled are the **metformin extended release** products.

Please see previous SWHR Pharmacy Updates for information regarding the other recalls. If your patient is on metformin extended release, they can find the name of the manufacturer on their prescription label or they can call their dispensing pharmacy to see if their product was affected by this recall. There are other manufacturers of extended release metformin not impacted by the FDA notice so shortages may not occur. If the decision is made to change strengths/products, please be aware that some of extended release metformin products, like the extended release 1000 mg tablets, are exorbitantly expensive. The most affordable extended release products are generic Glucophage XR.

1. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/granules-pharmaceuticals-inc-issues-voluntary-nationwide-recall-metformin-hydrochloride-extended#:~:text=Granules%20Pharmaceuticals%2C%20Inc.%2C%20Chantilly,the%20Acceptable%20Daily%20Intake%20Limit.
2. https://www.fda.gov/news-events/press-announcements/fda-alerts-patients-and-health-care-professionals-nitrosamine-impurity-findings-certain-metformin

UPDATE: EXPANDED FDA/CDC WARNING ON METHANOL CONTAMINATED HAND SANITIZER

The Centers for Disease Control (CDC) has issued a health advisory warning in addition to the updates to the FDA warning as of 7/10/2020 just released on hand sanitizers containing methanol. To date the involved products are all imports from Mexico. They are labeled as containing ethanol (or ethyl alcohol) but have been found to be contaminated by methanol. Standard alcohol-based hand sanitizer is made using isopropyl alcohol or ethanol (ethyl alcohol), neither of which are toxic. However, ingestion of methanol containing products whether through the skin or orally can result in significant side effects including severe effects like permanent blindness and even death. Case reports of adverse effects have been reported to the FDA and in some cases hospitalizations and deaths have occurred. The risk is greatest in young children or anyone who might orally ingest one of these methanol containing products.

Anyone believed to have had a significant exposure should seek immediate medical attention. Anyone who suspects a quality issuE or identifies a case of someone believed to have adverse effects with hand sanitizer is encouraged to report it to the FDA on their MedWatch site at https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program.

The FDA first issued a warning of contaminated methanol in hand sanitizer from Eskbiochem SA de CV on June 12, 2020; and these products were voluntarily recalled. However, ongoing evaluation has revealed additional manufacturers' products with methanol contamination and the FDA warning has been expanded. Currently on Transliquid Technologies has joined Eskbiochem SA de CV in voluntarily recalling any of its products. The FDA currently recommends against using any products from these manufacturers AND against using any products with these names.

The following is a list of a growing number of new manufacturers and products currently involved in the warning/recall:

Manufacturer	Product(s)
4 E Global SAPI de CV	19 Blumen hand sanitizer products (See FDA site) KLAR AND DANVER Instant Hand Sanitizer (labeled with Greenbrier International Inc.) MODESA Instant Hand Sanitizer Moisturizers and Vitamin E The Honeykeeper Hand Sanitizer KLAR and DANVER INSTANT HAND SANTIZER Hello Kitty by Sanrio Hand Sanitizer Assured Instant Hand Sanitizer Vitamin E and Aloe Assured Instant Hand Sanitizer Aloe and Moisturizers
DDI Multinacional SA de CV	Earths Amenities Instant Unscented Hand Sanitizer with Aloe Vera Advanced Hand Sanitizer Agavespa Skincare Vidanos Easy Cleaning Rentals Hand Sanitizer Agavespa Skincare
Limpo Quimicos SA de CV	Andy's Best Andy's Gelclor NeoNatural Plus Advanced
Liqesa Exportacion or Liq-E-S.A. de CV	Optimus Lubricants Instant Hand Sanitizer **other products may be on the market but not listed as company is not registered with the FDA
Maquiladora Miniara, SA de CV	Shine and Clean Hand Sanitizer Selecto Hand Sanitizer
Mystic International SA de CV Transliquid Technologies	Mystic Shield Protection hand sanitizer

1. https://emergency.cdc.gov/han/2020/han00434.asp
2. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-methanol

Potential Drug Shortages

The Health Plan of Southwestern Health Resources, Care N' Care has been monitoring potential drug shortages related to COVID-19 in outpatient settings. Care N' Care is able to gather data from up-to-the-minute pharmacy claims as well as information coming into the call centers from its members and pharmacies. The shortages are confirmed through the American Society of Health-System Pharmacists (ASHP) website. Please note, these are for outpatient drugs obtained in a retail setting only. There were no reported drug shortages related to COVID-19 identified for the week of 7/10/2020 to 7/15/2020. The status for previously reported shortages are listed below:

- **Famotidine**
  No Change. See Newsletter dated 5/15/2020
- **Flovent HFA and Flovent Diskus Inhalation Powder**
  No Change. See Newsletter dated 4/22/2020
- **Albuterol Sulfate Metered Dose Inhalers**
  A shortage remains, however FDA has listed extended-dating for several lots of Ventolin HFA. These extended dates can be found at https://www.fda.gov/drugs/drugshortages/search-list-extended-use-dates-assist-drug-shortages.
- **Hydroxychloroquine/Chloroquine**
  No change. See Newsletter dated 4/3/2020
- **Hydrocortisone**
  No change. See Newsletter dated 4/3/2020

For additional information and updates on drug shortages please visit the American Society of Health-System Pharmacists website or the FDA website.

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