

COVID-19 (SARS-CoV-2) Pandemic

Medication Management Strategies

PREFACE

Current CMS State Operations Manual (SOM) requirements for skilled nursing facilities require a minimum monthly pharmacist Drug Regimen Review, or Medication Regimen Review (MRR), as indicated by the resident's condition (F756). This includes reporting of any medication "irregularities" in a written report to the director of nursing, attending physician and medical director. It is important to note that irregularities are broadly defined within the SOM as "use of a medication that is inconsistent with accepted standards of practice, not supported by medical evidence". Potential irregularities are further defined in the Unnecessary Drug Requirement (F758) which states that "Each resident's drug regimen must be free from unnecessary drugs".

The Centers for Medicare and Medicaid Services (CMS) has recently commented on Medication Regimen Review during this emergency and reinforced ASCP's communications regarding the necessity to continue, albeit providing it as safely as possible and generally off site from the skilled nursing centers.¹ Consultant pharmacists may be called upon to coordinate medication deprescribing with the facility medical director, director of nursing and attending physician under these circumstances. These pharmacist recommendations should not be construed as noting a 'medication irregularity' with the requirement of an individual report and response for each since it may delay necessary changes. However, the pharmacist should document these recommendations in the resident's medical record or in their consulting software to note the proposed intervention. Medication deprescribing in these circumstances may include reduction of 'non-critical' medications which do not constitute a medication 'irregularity' in the context of the SOM. Non-critical medications may be required to treat a medical condition at the time they were prescribed, but may become non-critical after assessment with the interdisciplinary team. A collaborative approach with the medical director, attending physician and director of nursing is needed and this may require line lists or blanket recommendations that are approved by the attending physician or medical director.

¹ www.ascp.com/disaster ASCP's Remote MRR and Restocking CMS Guidance

Listed below are several strategies that should be considered to ensure a resident-centered, interdisciplinary approach to pharmacists deprescribing recommendations.

- **Initial Consultant Pharmacist Approach:**

- Contact the Director of Nursing (DON) and Medical Director and discuss the facility's approach and interest to COVID-19 virus deprescribing efforts and offer assistance.
- Discuss monthly MRR recommendations versus deprescribing recommendations associated with the COVID-19 virus and how these will be reviewed and implemented at the facility level with the Medical Director and Attending Physician.

- **Interdisciplinary Options for Deprescribing Recommendations:**

- Pharmacist recommendations should be presented in a reportable format for the DON to discuss with the Medical Director or Attending Physician. These may not be construed as a medication irregularity unless the Pharmacist so deems them.
- The Medical Director or Attending Physician may decide to review the recommendations directly with the Pharmacist via a telehealth interaction or directly on the phone.
- Order changes should be communicated to the facility via the facility's normal process for medication order changes.
- Physician-Pharmacist collaborative practice agreements may be utilized in the states that allow them.

Below are some recommendations for Consultant Pharmacists based on frequently asked questions and issues dominating the clinical discussion for the COVID-19 virus:

Q1: WHAT IS THE CURRENT EVIDENCE AND MOST PRACTICAL APPROACH TO USING OF HYDROXYCHLOROQUINE AND/OR AZITHROMYCIN?

Anecdotal reports indicate mixed results with chloroquine and hydroxychloroquine. However, until such time as randomized placebo-controlled trial results are available and given the recent Food and Drug Administration (FDA) guidance and widely reported real world evidence of their effectiveness, these medications may be prescribed for COVID-19 virus positive or highly suspected individuals. State restrictions and the availability of these drugs will also dictate the use of these medications in treatment. Care should be maintained to ensure those individuals with existing needs for hydroxychloroquine maintain access and that these medications are used **only for COVID-19 virus positive** individuals or highly suspected residents in hospitals or long-term care settings where testing access and testing response time may be limited.

Chloroquine and hydroxychloroquine have been used to prevent and treat malaria for nearly 70 years. Hydroxychloroquine, considered to be safer and better tolerated than chloroquine, is also approved to treat rheumatoid arthritis and systemic lupus erythematosus. Research on the effect of these agents against the COVID-19 virus in vitro and mouse studies indicate effective antiviral activity when treatment is started early.² However, similar trials with the COVID-19 virus in humans have not been conducted. At this time, all evidence of efficacy and dosing recommendations come from anecdotal reports or poorly designed/underpowered trials.

Hydroxychloroquine:

- Doses and duration of hydroxychloroquine used in anecdotal reports and small studies:^{3,4,5}
 - o 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5, or
 - o 600 mg twice daily on day 1, then 400 mg once daily for 2-5, or
 - o 200 mg 3 times a day for 10 days
- Examples of efficacy claims:^{2,3}
 - o Chen Z et al: Use of hydroxychloroquine for the treatment of the COVID-19 virus lowers the time to clinical recovery and reduced the risk of other complications such as pneumonia
 - o Gautret P et al: Use of hydroxychloroquine reduced the viral load post therapy

² Keyaerts E, et al. Antiviral Activity of Chloroquine against Human Coronavirus OC43 Infection in Newborn Mice. *Antimicrobial Agents and Chemotherapy*, Aug. 2009, p. 3416–3421.

³ Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. <https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v2> (accessed 04/03/20)

⁴ Gautret p, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of Covid-19 : result of an open-label non – randomized clinical trial. <https://www.ncbi.nlm.nih.gov/pubmed/32205204> (accessed 04/03/20)

⁵ Hydroxychloroquine. In Lexi-drugs online [database on the Internet]. Hudson (OH): Lexicomp, Inc.; 2020 [updated 3 April 2020; cited 3 April 2020]. Available from: <http://online.lexi.com>. Subscription required to view.

- Notable adverse effects:⁶
 - o QTc prolongation present in short term use
 - o Baseline ECG for high risk patients and/or history of QTc prolongation
 - o 12 lead ECG, telemetry or smartphone-enabled mobile ECG device have been evaluated
 - o If QTc interval increases ≥ 60 ms from baseline, review benefits of therapy
 - o Additional adverse effects from long-term use, including blood dyscrasias and retinal damage are not expected for short-term treatment of the COVID-19 virus

Hydroxychloroquine + Azithromycin:

- Azithromycin Dose⁷
 - o 500 mg on day 1 and 250 mg on day 2-5 in conjunction with hydroxychloroquine
- Example of efficacy claims:⁸
 - o Gautret P et al: 6 patients received combination and viral load was reduced notably
 - o 700 residents in NY were treated with combination had high success rate

Additionally, many states are restricting the use of hydroxychloroquine and limiting prescription and dispensing to documented COVID-19 virus positive individuals. Typically, these restrictions are for 14 days of treatment and do not interrupt those patients that have been using hydroxychloroquine for lupus, rheumatoid arthritis or other reasons in established individuals. Each state is different, and the National Alliance of State Pharmacy Associations has a website for the latest changes in each state. www.NASPA.us

⁶ Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19 [published online ahead of print March 25, 2020]. *Mayo Clin Proc*. <https://doi.org/10.1016/j.mayocp.2020.03.024>.

⁷ Azithromycin. Lexi-drugs online [database on the Internet]. Hudson (OH): Lexicomp, Inc.; 2020 [updated 1 April 2020; cited 3 April 2020]. Available from: <http://online.lexi.com>. Subscription required to view.

⁸ Dr. Vladimir Zelenko has now treated 699 coronavirus patients with 100% success using Hydroxychloroquine Sulfate, Zinc and Z-Pak [UPDATES]. <https://techstartups.com/2020/03/28/dr-vladimir-zelenko-now-treated-699-coronavirus-patients-100-success-using-hydroxychloroquine-sulfate-zinc-z-pak-update/> (accessed 04/03/20)

Q2: WHAT IS THE CURRENT EVIDENCE AND MOST PRACTICAL APPROACH TO ASSESSING AND POTENTIALLY CHANGING NEBULIZED TREATMENTS TO OTHER INHALED TREATMENTS?

The association of COVID-19 virus spread with nebulizer use is controversial. While there are case reports^{9,10}, it is not possible to separate out droplets generated by the nebulizer itself from those generated by the patient.¹¹ Additionally, in clinical practice, patients being treated with nebulized bronchodilators are likely to have air flow obstruction due to asthma or COPD and are therefore more likely to be coughing and wheezing spontaneously.¹¹ Despite the controversy, several agencies recommend that **once a resident has a suspected or confirmed COVID-19 virus infection**, nebulizers should be converted to a metered dose inhaler (MDI) if appropriate and available. If nebulizer therapy is required to be continued, healthcare practitioners should utilize the highest level of personal protective equipment (PPE).^{12,13,14}

When alternate inhalation devices are employed, such as a metered-dose inhaler (MDI), dry-powder inhaler (DPI), or soft-mist inhaler (SMI), as a replacement for nebulizers, assess that the resident can comply with administration requirements. Many residents will not have good technique when using an DPI, MDI or SMI so it is important to assess resident capability before considering a change from a nebulizer to another inhalation device even in infected residents. If alternate inhalation devices are used, it is important with MDIs to use a holding chamber or “spacer” device to assure effective drug delivery. If nebulization is the best option, it is important to monitor the resident to prevent removal of mask or mouthpiece mid-treatment as this may increase droplet transmission and prevent the resident from receiving the full dose of medication.

GENERAL PRINCIPLES

1. **Switching from Nebulizers is for COVID-19 virus positive or High Suspicion of COVID-19 virus patients only (Evidence based and appropriately retains resources)**
2. **Use of MDIs MUST include a holding chamber or “spacer” device (evidence based)**

- Situations where continued nebulizer treatments may be necessary:
 - Comorbidities such as cognitive impairment, Parkinson’s Disease, or arthritis that interfere with or prevent the resident’s ability to appropriately use of other types of inhalation devices
 - Severe chronic obstructive pulmonary disease (COPD)
 - Unavailability of MDI albuterol

⁹ Yu IT, Li Y, Wong TW, Tam W, Chan AT, Lee JH, et al. Evidence of airborne transmission of severe acute respiratory syndrome virus. *N Engl J Med* 2004;**350**:1731–9.

¹⁰ Hugonnet S, Pittet D. Transmission of severe acute respiratory syndrome in critical care: do we need a change? *Am J Resp Crit Care Med* 2004;**169**:1177–8.

¹¹ Simonds AK, et al. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. *Health Technology Assessment* 2010; Vol. 14: No. 46, 131–172.

¹² Prevention and Control of Influenza during a Pandemic for All Healthcare Settings. Annex F. The Canadian Pandemic Influenza Plan for the Health Sector.

¹³ Interim U.S. Guidance for Risk Assessment and Public Health Management of Healthcare Personnel with Potential Exposure in a Healthcare Setting to Patients with Coronavirus Disease (COVID-19). March 7, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html> (Accessed 4/2/2020).

¹⁴ Tang JW, et al. Factors involved in the aerosol transmission of infection and control of ventilation in healthcare premises. *J Hosp Infect.* 2006 Oct;**64**(2):100-14. Epub 2006 Aug 17.

- Nursing staff should use a medical mask, gown, gloves, eye protection (goggles or face shield) during the inhalation administration using DPI, MDI, or SMI devices in COVID-19 virus suspected or confirmed cases.
- When administering nebulizer treatments is necessary in a COVID-19 virus suspected or confirmed patient, nursing staff should use the highest level of PPE, respirator N95 or FFP2 standard, or equivalent, gown, gloves, eye protection, apron, as recommended by the CDC or WHO ^{13,15}.
- When using MDIs, a spacer should be used. ^{16,17}
 - See manufacturer's recommendations for spacer cleaning
 - Important to let air dry to avoid chamber electrostatic charges that will alter medication delivery
- Inhaled corticosteroids are generally recommended to be avoided in patients with COPD due to increased risk of pneumonia. ¹⁸

Q3: SHOULD THE USE OF NON-STEROIDAL ANTI-INFLAMMATORY MEDICATIONS (NSAIDS) BE AVOIDED?

Currently, there is no scientific evidence connecting NSAID use with increasing risk of COVID-19 virus infection or worsening symptoms. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) all state that there is a lack of evidence for this connection. ^{19,20} NSAIDs increase the level of angiotensin converting enzyme 2 (ACE2), which has been hypothesized to facilitate infection with the COVID-19 virus. There is also a theoretical benefit to increasing ACE2 levels through mitigation of the progression of lung damage from the virus. Patients who require NSAIDs to treat chronic conditions should continue treatment. Patients who need acute pain or fever relief could use either acetaminophen or NSAIDs.

¹⁵ Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19). Interim Guidance. February 27, 2020.

https://apps.who.int/iris/bitstream/handle/10665/331215/WHO-2019-nCov-IPCPPE_use-2020.1-eng.pdf. (Accessed 4/3/20).

¹⁶ Revisiting the Need for MDI Common Canister Protocols During the COVID-19 Pandemic <https://www.ismp.org/resources/revisiting-need-mdi-common-canister-protocols-during-covid-19-pandemic> (Accessed 4/2/20).

¹⁷ Vincken W, et al. Spacer devices for inhaled therapy: why use them and how? *ERJ Open Res.* 2018 Apr; 4(20): 00065-2018. Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6004521/> (Accessed 4/7/20).

¹⁸ Grant J, et al. Inhaled Corticosteroids Increase Risk of Serious Pneumonia in Patients with COPD. *The Hospitalist.* 2014 June;2014(6).

¹⁹ <https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19>. Accessed 4/5/2020.

²⁰ <https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19>. Access 4/5/2020.

Q4: SHOULD ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI) AND ANGIOTENSIN RECEPTOR BLOCKERS (ARBs) BE AVOIDED IN PATIENTS SUSPECTED OF THE COVID-19 VIRUS?

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are increasingly being evaluated for their possible roles in both increasing susceptibility to the COVID-19 virus as well as a possible treatment option. Currently, there is no evidence that ACEI/ARB therapy increases the susceptibility to, or severity of, infection from the COVID-19 virus. A joint consensus statement from the American Heart Association (AHA), the American College of Cardiology (ACC) and the Heart Failure Society of America (HFSA) recommends “continuation of RAAS [Renin Angiotensin Aldosterone System] antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension or ischemic heart disease.”²¹

Angiotensin converting enzyme 2 (ACE2), is expressed in many cells, including the lung and cardiac cells, and exists as a counterbalance to angiotensin II.²² In animal studies, ACE2 expression may be increased in the presence of ACEI/ARB therapy, however, human data is limited and inconclusive.²³ The theoretical mechanism of increased risk of infection centers on the COVID-19 virus utilizing ACE2 receptors to gain entry into target cells.²⁴

Experimental data exists that demonstrates the downregulation of ACE2 (and resulting loss of counterbalance with angiotensin II) is associated with increased severity of lung damage.²⁵ As ACEI/ARB therapy may upregulate ACE2 expression, this may limit the profibrotic, vasoconstrictive and proinflammatory effects of angiotensin II.²⁶ Currently, a clinical trial utilizing losartan is underway to evaluate the therapeutic benefit in hospitalized and non-hospitalized COVID-19 virus patients.^{27,28}

Currently, guidance issued by the AHA/ACC/HFSA should be followed.^{29,30} The COVID-19 virus is associated with potential cardiac injuries and withdrawal of ACEI/ARB therapy could likely precipitate both short- and long-term harm. Further research is urgently needed to determine the possible roles of ACEI/ARB therapy in increasing the susceptibility to and reducing the severity of lung damage from the COVID-19 virus.

²¹ <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfssa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19>. Accessed 4/5/20.

²² Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11:875–879.

²³ Gu H, Xie Z, Li T, Zhang S, Lai C, Zhu P, Wang K, Han L, Duan Y, Zhao Z, et al. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. *Sci Rep*. 2016;6:19840.

²⁴ Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci*. 2020;63:364–374.

²⁵ Guo J, Huang Z, Lin L, Lv J. Coronavirus disease 2019 and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. *J Am Heart Assoc*. 2020;9:e016219.

²⁶ Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19 [published online ahead of print, 2020 Mar 30]. *N Engl J Med*. 2020;10.1056/NEJMSr2005760.

²⁷ <https://clinicaltrials.gov/ct2/show/NCT04312009>. Accessed 4/5/20.

²⁸ <https://clinicaltrials.gov/ct2/show/NCT04311177>. Accessed 4/5/20

²⁹ Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. Angiotensin-converting enzyme 2 and anti-hypertensives (angiotensin receptor blockers and angiotensin converting enzyme inhibitors) in coronavirus disease 2019 (COVID-19) [published online ahead of print March 30, 2020]. *Mayo Clin Proc*.

³⁰ Bavishi C, Maddox TM, Messerli FH. Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers. *JAMA Cardiol*. Published online April 03, 2020.

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More information on the COVID-19 Emergency can be found at www.ascp.com/disaster