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REVIEW

Treating COPD Patients with Inhaled Medications in the Era of COVID-19 and Beyond: Options and Rationales for Patients at Home

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Abstract: COVID-19 has affected millions of patients, caregivers, and clinicians around the world. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads via droplets and close contact from person to person, and there has been an increased concern regarding aerosol drug delivery due to the potential aerosolizing of viral particles. To date, little focus has been given to aerosol drug delivery to patients with COVID-19 treated at home to minimize their hospital utilization. Since most hospitals were stressed with multiple admissions and experienced restricted healthcare resources in the era of COVID-19 pandemic, treating patients with COPD at home became essential to minimize their hospital utilization. However, guidance on how to deliver aerosolized medications safely and effectively to this patient population treated at home is still lacking. In this paper, we provide some strategies and rationales for device and interface selection, delivery technique, and infection control for patients with COPD who are being treated at home in the era of COVID-19 and beyond.

Keywords: coronavirus, COVID-19, SARS-CoV-2, aerosols, nebulizers, inhalers, homecare, infection control

Video abstract

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Introduction

COVID-19 was caused by SARS-CoV-2, a novel coronavirus, that affected millions of people worldwide as this respiratory illness is transmitted from person to person via droplets and close contacts.[1] It has been known that respiratory viruses trigger COPD exacerbations and cause deterioration of the patients' symptoms.[2] While aerosolized medications are commonly used in the treatment of patients with COPD, there has been an increased concern regarding aerosol drug delivery to patients with COVID-19 due to the potential aerosolization of viral particles especially within the hospital setting. While hospitals were stressed with many patient admissions and there was so much discussion on the management of critically ill patients with the limited healthcare resources during the COVID-19 pandemic, little focus has been given to management strategies and guidance to clinicians and patients with chronic pulmonary diseases who are treated at home. Evidence based guidance on how to deliver aerosolized medications safely and effectively to this patient population treated at home is still lacking. The purpose of this review is to discuss some strategies and provide potential rationales for device selection, interface selection, delivery technique, and infection control for managing patients with COPD at home in the era of COVID-19 and beyond.

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Previous research reported that the severe acute respiratory syndrome (SARS) coronavirus and the middle east respiratory syndrome coronavirus (MERS-CoV) presented with similar clinical features and outcomes to that of COVID-19.[3] Due to the findings of previous research that revealed high-risk for MERS-CoV in asthma,[4] patients with chronic pulmonary diseases were also considered to be at an increased risk for COVID-19. However, this assumption has not been demonstrated in several reports and conflicting evidence exists on the risk and potential consequences of COVID-19 in this population.[5] Halpin et al demonstrated that the prevalence of asthma and COPD was lower in patients diagnosed with COVID-19.[6] The authors postulated that this may be due to the treatments used in chronic pulmonary diseases such as inhaled corticosteroids which may reduce not only the risk of infection but also the development of severe symptoms in COVID-19. Indeed, the Global Initiative for Asthma (GINA) and Global Initiative for Obstructive Lung Diseases (GOLD) strategies continue to recommend the use of prescribed inhaled medications in asthma and COPD to prevent worsening of disease symptoms and severity.[7,8] According to previous research, 40–60% of COPD exacerbations are due to viral infections.[2] Since having COPD is considered an underlying condition that may be associated with disease severity, it is vital to advise patients with COPD to continue taking their inhaled medications at home to control disease symptoms and prevent exacerbation of their disease.[9] However, patient outcomes from aerosol therapy depend on the compatibility of patient characteristics with the features of the aerosol device selected for the treatment.

Device Selection

Several factors affect device selection for inhaled medications. Of importance are patient characteristics such as age, degree of obstruction, physical and cognitive abilities, as well as patient preference. Furthermore, features of the aerosol device such as availability, cost, reimbursement, and convenience of use are crucial.[10–13] Aging decreases peak inspiratory flow rate (PIFR) and leads to an increased risk of ineffective inhalations with inhalers.[14,15] In addition, the patient error in the use of inhalers increases with the degree of airway obstruction.[14,16] Therefore, regular inhalers may not be appropriate for elderly patients with severe COPD. Many host factors increase the risk of critical errors during aerosol drug delivery with inhalers. These factors include impairment in manual dexterity, decreased respiratory muscle strength, impaired hearing, visual deficits, loss of physical strength in hand and finger muscles, cognitive dysfunction, and co-morbidities such as neuromuscular conditions. Inadequate hand strength may lead to an inability to use pressurized metered-dose inhalers (pMDIs). Furthermore, dry powder inhalers (DPIs) may not be ideal for this patient population due to impairment in manual dexterity and a low PIFR. Patients will have a hard time placing the unit dose medication into the reservoir of the device and use the unit-dose DPI effectively. While visual deficits may affect proper loading of the inhaler and the ability to see the dose counter, patients with hearing deficits may not apprehend the "click" sound indicating readiness to inhale through a DPI. Decreased respiratory muscle strength may also reduce the patient's ability to generate the minimum flow and volume needed to operate inhalers correctly.[17] Therefore, the patient's potential to understand how and when to use an aerosol device should be evaluated regularly to determine their cognitive ability. Failure on cognitive testing indicates that regular inhalers might be inappropriate for the patient.[17] Patient preference is linked to good inhalation techniques that improve patient adherence to the prescribed therapy.[18–20] Patients prefer an aerosol device that is small, portable, and easy to use. If an aerosol device has a short treatment time, requires less cleaning/maintenance, and is the least-out-of-pocket expense for the patient, it is considered convenient. Therefore, the preference of patients and the convenience of the device are other important factors that need to be considered in device selection. However, only 35 to 37% of healthcare providers considered the type of aerosol device to be highly important when prescribing inhaled drugs for newly diagnosed stable patients with COPD and those with post exacerbations.[21] Also, healthcare providers prioritize inhaled medication over the device when selecting treatments while showing limited attention to the proper use of aerosol devices.[21]

While it is important to avoid unnecessary aerosol therapy in patients with COPD who were tested positive for infectious diseases such as COVID-19, clinicians need to select the right device, the right interface, and the right medication for the right patient who needs to be treated with aerosolized medications in the era of COVID-19 and beyond. Therefore, clinicians should be trained in device selection, interface selection, delivery technique, device preparation, cleaning, and maintenance (Table 1). For instance, inhalers should be preferred over nebulizers to minimize aerosolization unless the patient cannot perform specific breathing techniques needed to use the prescribed inhaler effectively.[22,23] Effective aerosol therapy with pMDIs

Table 1 Options and Rationales for Aerosol Drug Delivery to Patients with COPD Who are Diagnosed with COVID-19 and Treated at Home

	Options	Rationales
Device Selection	• Prefer inhalers over nebulizers except for the following three conditions: (1) The patient cannot perform specific breathing techniques needed for inhalers, (2) The drug formulation is not available as inhalers, or (3) There is a shortage of inhalers.	• Exhaled air dispersion and virus transmission with inhalers may be lower than jet nebulizers due to their low emitted dose and less aerosol mass generation.
	• Do not use the dry powder inhalers (DPI) if the patient cannot generate a high inspiratory rate needed to use the device effectively or if the DPI causes airway irritation or cough during aerosol therapy.	• Coughing will increase exhaled air dispersion and virus transmission. Patients who cannot generate a high inspiratory flow rate will not disperse the drug particles and draw the drug from the device.
	• Prefer mesh nebulizers instead of jet nebulizers if you need to use a nebulizer when one of the three conditions listed above applies. Another option is to use breath actuated nebulizers that generate aerosols only in inspiration.	• Unlike mesh nebulizers, jet nebulizers release 2/3 of the aerosols generated by the device and disperse them to the environment due to the external gas flow needed for their operation.
Interface Selection	• Prefer a mouthpiece over a face mask to reduce fugitively emitted aerosol concentration.	• Unlike the face mask, the mouthpiece will not force aerosol out of the interface during therapy.
Device Preparation	• Wash your hands with soap and water for 20 seconds or use an alcohol-based hand sanitizer that contains at least %60 alcohol before and after aerosol therapy.	• Washing hands will help minimize the contamination of the aerosol device and medication during device preparation, cleaning and maintenance.
	• The risk of contamination during device preparation is lower with inhalers compared to jet nebulizers.	• Because the drug is enclosed, it is hard to contaminate the inhaler during device preparation, unlike jet nebulizer that has a high risk of transmission if patient's secretion drops in the nebulizer reservoir due to their open design.
	• Mesh nebulizers may be a good alternative for aerosol therapy if nebulizers need to be used COVID-19 positive patients with COPD.	• Since mesh nebulizers separate the medication from the patient interface through the mesh, it is hard to contaminate the mesh nebulizer with the patient's secretion.
Delivery Technique	• Use the pMDI with a valved holding chamber (VHC) that has a mouthpiece.	• Using a VHC with a mouthpiece will minimize the need for hand-breath coordination and oropharyngeal deposition.
	• Place a filter to the outlet of a nebulizer.	• The filter will capture exhaled droplets and reduce aerosol concentration in the environment.
	• Use the aerosol device based on the manufacturer's guidelines.	• Following the manufacturing guidelines will improve delivery technique, treatment efficiency and safety.
	• Administer aerosol therapy in a location such as outside on a patio, porch, or in a garage, where the air is not circulated into the house.	• It will minimize the dispersion of exhaled air in the house and the risk of virus transmission to family members.
Device Cleaning & Maintenance	• Replace disposable nebulizers once every 24 hours. • Clean reusable jet nebulizers with soap and water, rinse, disinfect, and air-dry after each therapy. • Clean mesh nebulizers based on the manufacturers' guidelines.	• Regular device cleaning and maintenance will help minimize device contamination and the risk of virus transmission.

requires optimum delivery technique by achieving good hand-breath coordination, actuating the pMDI at the beginning of inspiration, breathing slowly, and holding the breath at the end of inspiration.[10–12,24,25] Since patients were concerned about medication effectiveness but not with proper inhalation technique,[21,26] 92% of patients with COPD and asthma make at least one error in their inhalation technique.[27] In patients with poor technique, while using pMDIs, the use of valved-holding chambers should be encouraged. If patients are still unable to make the required steps for optimum technique with pMDIs, DPIs should be considered to deliver inhaled medications to patients who can achieve adequate inspiratory flow rate needed for the specific device.[9,22,23] Since each DPI requires a different inspiratory flow rate for optimum aerosol drug delivery,[28] evaluating patient ability and performance as well as patient education and follow-up is vital to achieving optimum disease management in COPD.[24]

Unfortunately, there was a shortage of inhalers during the COVID-19 pandemic in the United States.[29,30] When a drug formulation is not available as an inhaler or patients cannot perform the specific breathing techniques with inhalers, aerosolized medications can be delivered through nebulizers.[9,22,23] Different types of nebulizers are available and include: (1) Jet nebulizers, and (2) mesh nebulizers.[31] While jet nebulizers are less expensive than mesh nebulizers, two-third of the aerosols generated by the jet nebulizer are delivered to the environment[31–34] that may put other family members at risk of infection if the device is contaminated. In this case, using breath-actuated jet nebulizers could be a good option because they generate aerosols only during inspiration as opposed to conventional jet nebulizers that generate aerosols continuously during the entire breathing cycle.[35] Therefore, the release of exhaled aerosols into the environment with breath-actuated nebulizers is less than conventional nebulizers. Another alternative is to use the mesh nebulizer for aerosol therapy in the era of COVID-19. Since mesh nebulizers separate the medication from the patient interface through the mesh, the risk of device contamination in mesh nebulizers is lower than conventional jet nebulizers. Also, mesh nebulizers operate with electrical mains instead of external gas flow that contributes to the dispersion of patient-generated bioaerosol into the atmosphere.[23]

Interface Selection

Interface selection is as important as device selection in patients with COPD treated at home in the era of COVID-19. The right interface is the one that is tolerated and preferred by the patient. It is the interface that is used reliably during aerosol therapy. Therefore, clinicians should consider each interface that can be combined with the aerosol device selected for the patient's treatment. For instance, pMDIs are used with spacers or valved holding chambers (VHCs). Although spacers and VHCs are designed to improve the delivery efficiency of pMDIs, they differ in their design. VHCs have one-way valves that contain aerosol until the patient's inspiration, while spacers are simple tubes without valves and require some hand-breath coordination. Also, exhaling in the spacer after actuating the pMDI wastes most of the dose to the environment. Therefore, pMDIs should be combined with VHCs to decrease oropharyngeal deposition and the need for hand-breath coordination during aerosol therapy. Multiple actuations into the spacer or VHC will reduce drug delivery to patients with COPD.[36,37] Also, clinicians should be aware of the issue with the electrostatic charge of spacers and VHCs that will decrease inhaled dose by the patient. While one alternative is to wash spacers with detergent to eliminate electrostatic charge,[38–42] another option is to use a non-electrostatic spacer for aerosol therapy if possible.[43]

When a nebulizer is used for aerosol drug delivery for patients with COVID-19, a mouthpiece is preferred over a face mask because it will not force aerosol out of the interface in expiration and breath-hold.[22,23,44] Therefore, the mouthpiece has less fugitively emitted aerosol concentration compared to the face mask and attaching a filter to the exhalation port of the mouthpiece reduces the dispersion of exhaled bioaerosols to the environment.[45]

Delivery Technique

Aerosol delivery with inhalers requires several steps. For instance, shaking, priming, hand-breath coordination, and breath-hold are crucial for the effective use of pMDI during aerosol therapy.[46] While shaking and priming the pMDI before the treatment ensures a homogeneous mixture of the medication and proper filling of the metering chamber before actuation, it is also essential to coordinate pMDI actuation with inhalation, breath slowly, and hold the breath after inhalation. Common errors with the pMDI include inadequate shaking/priming, failure to coordinate pMDI actuation with inhalation, actuating pMDI during expiration, rapid inhalation after actuation, firing pMDI multiple times during single inhalation, actuating the pMDI into the mouth but inhaling through the nose, and inadequate or no breath-hold after inhalation.[36,46–50]

While DPIs eliminate some of these problems related to the delivery technique with pMDIs, they have their own challenges such as using the DPI in wrong orientation during device preparation or treatment, failure to pierce the blister package or capsule before inhalation, shaking the device, exhalation into the DPI, or inadequate inspiratory flow rate. Each DPI has a specific requirement for the inspiratory flow rate to draw the medication from the inhaler and to disaggregate the powder into small particles. Adequate inspiratory flow rate leads to better disaggregation and greater lung deposition with the DPI. However, elderly patients with COPD may not have the physical ability to generate the adequate inspiratory flow required by the DPI. Clinicians can determine the best inhaler for their patients by using a hand-held inspiratory flow meter such as In-Check-Dial (Clement Clarke International Ltd, UK) that simulates the resistance of common inhalers.[24,51,52] Such hand-held inspiratory flow meters could be used for inhaler selection and patient education on using the inhaler correctly.[51–55] Also, previous research showed that humidity from patient exhalation or in the ambient environment result in powder clumping and reduce the delivery efficiency of the DPI.[18,46]

The delivery technique with nebulizers is simple. Unlike pMDIs and DPIs, it does not require any specific breathing technique and only normal tidal breathing is adequate for effective aerosol delivery during the treatment with nebulizers.

Infection Control and Prevention

The transmission of COVID-19 is through droplets generated as bioaerosols that remain viable and infectious for hours. While larger aerosol particles fall to the ground, small ones remain in the air and spread with air currents. Also, it is difficult to differentiate bioaerosols from medical aerosols. Bioaerosols are generated by patients during talk, cough, sneeze, or sing. If a patient is diagnosed with COVID-19, his/her exhaled bioaerosols may contain the pathogen and play a prominent role in the spread of coronavirus. On the other hand, medical aerosols are produced by the aerosol device used during treatment. Also, medical aerosols that are not inhaled by the patient but pass into the atmosphere are defined as fugitive emissions. Although aerosol therapy generates fugitive emissions, they are medical aerosols generated by aerosol devices as opposed to bioaerosols produced by patients.[9,22,23] 50% of medical aerosols generated during aerosol therapy is fugitive emissions that have a particle size between 0.860 and 1.437 μm.[45,56–59] The quantity and characteristics of fugitive emissions are influenced by many factors such as flow rate, the type of aerosol device and interface used during therapy.[58,60,61] Temperature, air turbulence, and airflow rates as well as the size and layout of the room, affect the dispersion and decay of fugitive emissions. A retrospective study of a pooled analysis of risk with various aerosol-generating procedures showed that healthcare professionals had a significantly greater risk of infection with intubation and non-invasive manual ventilation than nebulizers.[62] A filter can be attached to the outlet of a nebulizer to capture exhaled aerosol droplets during aerosol therapy.[45,63,64] However, it is essential to note that the efficiency of these filters in the prevention of coronavirus transmission is not known due to the lack of clinical studies in this area of research.[22]

Since nebulizer contamination plays a vital role in the transmission of the virus and the risk of infection, cleaning nebulizers after each treatment and adhering to infection control procedures during aerosol therapy is essential in this global pandemic. While mesh nebulizers should be cleaned based on the manufacturer's guidelines, jet nebulizers should be rinsed, air-dried, and/or disinfected after each therapy.[65–67] Also, it is essential to keep in mind that the virus may persist in droplets in the air if a contaminated nebulizer is used for aerosol drug delivery to patients with COVID-19. Therefore, aerosol therapy should be administered in a location such as outside on a patio, porch, or in a garage, where the air is not circulated into the house, to minimize exposure to non-infected family members.[9] Exhaled air in the room should be replaced with fresh air from outside. Frequent airing and cross ventilation are just as effective as leaving the windows open. Air purifiers may reduce the concentration of aerosol particles in a room and have the same effect as ventilation with clean outside air. While three to six air changes per hour are commonly used in air purifiers, the higher exchange rate will reduce the existing particle concentration faster during this global pandemic. If the clean air delivery rate is 750 m^3/h, the infection risk/hour of time spent in a room with an infected person can be decreased to 10%.[68] Air purifiers should be placed in a location where they can freely draw the room air and distribute the purified air evenly throughout the room.[69] Therefore, they should not be placed behind furniture or under tables. Air purifiers have several disadvantages such as noise emissions of the fan, cost, and power consumption that may reduce their acceptance in daily life.[70] Also, changing the filter of air purifiers regularly is necessary to keep their efficiency. In the use of air purifiers, it is still essential to

keep using other protective measures such as wearing a mask, social distancing, and ventilation.

Patients should also stay isolated in one room and avoid not only shared space but also personal household items such as dishes, towels, or bedding as much as possible.[71] If shared spaces had to be used, they should stay at least 1 m away from others,[9,71,72] wear a face mask when near to family members, and change the face mask every day.[71] Keeping distance from other family members will help dilute exhaled bioaerosols containing the virus; therefore, the probability of disease transmission to other family members will decrease. The use of facemasks will decrease the concentration of exhaled bioaerosols in the room by filtering them during breathing, speaking, coughing, or sneezing. It is also important to note that using a face shield without a face mask is not effective in infection control because exhaled bioaerosols containing the pathogen flow unfiltered around the shield. Usually, face shields are used to prevent droplet infection via the mucous membranes of the eyes. Similarly, Plexiglas barriers that are designed for homecare are ineffective in preventing the spread of infected bioaerosols indoors because they serve as spit and splash protection against large particles. When coughing and sneezing, patients should also cover their nose and mouth with a tissue that needs to be thrown away immediately.[71,72] Cleaning often-touched surfaces in their separate room, washing hands with soap and water for 20 seconds and using an alcohol-based hand sanitizer that contains at least %60 alcohol are important to prevent the spread of infection.[71] Otherwise, poor compliance with infection control procedures and exposure to the virus will be an issue for uninfected family members. It is also essential to provide training to caregivers to decrease the risk of exposure to the virus while caring for someone with COVID-19. The World Health Organization have excellent guidelines on home care and infection control for patients with COVID-19.[71]

Due to a novel, highly transmissible virus, many countries have implemented infection control measures to isolate or quarantine individuals infected with or exposed to coronavirus. Also, policymakers placed regulations on social distancing and lockdowns to protect the most vulnerable. Patients and their caregivers should follow the doctor's recommendations about their treatments and home isolations. To improve the health and well-being of patients with COPD at home, telemedicine can be utilized for disease management, patient monitoring, and evaluation, as well as the training of patients and caregivers on optimum aerosol drug delivery and infection control in the era of COVID-19. Although telemedicine has faced some barriers such as cost, regulation, technological and equipment challenges in the past, advances in technology and recent healthcare reforms have reduced these barriers. Therefore, the prevalence of telemedicine is increasing in the era of COVID-19. While some studies on telemedicine show improvements in patient outcomes, satisfaction, hospital admission rates, anxiety, and depression in COPD,[73–83] others reported no significant improvements[82–86] The conflicting results on the previous studies may be due to the high variability of patients evaluated, the severity of the disease, the types of technology, and service lines used in these studies. According to previous research, telemedicine can reduce the number of visits to primary care and emergency departments,[73–76,81,87,88] provide better disease management[73,76,78,79,83,87] bolsters patient-clinician relationship,[77,85,89,90] and increase patient empowerment and engagement in COPD.[73,75,76,89,90] Also, it is useful in enhancing access to care during home isolations and lockdowns as well as in rural areas where access to care may be restricted. Previous research showed improvements in COPD and reductions in hospital admissions related to exacerbations due to additional services such as videoconferencing and phone support added to the traditional COPD management through telemedicine.[86,88] Also, while having access to a respiratory therapist or a nurse is a logical approach that should improve patient education and outcomes, it may increase the workload of clinicians and the cost of services provided to patients with COPD.[77–79,85,90,91] Other barriers of telemedicine include lack of standardization in services,[77,78,84,87,89] patients' disconcert with technology,[79,80,87] less patient autonomy,[74,85,89] time consuming,[77,87] perceived lack of usefulness,[90] and patient/caregiver resistance on using telemedicine.[77] Despite many barriers, telemedicine is still a viable option for patients with COPD because current healthcare resources are limited compared with the growing needs in the COVID-19 pandemic. Therefore, alternative strategies need to be developed to improve the clinical pathway of patients with COPD treated at home in the era of COVID-19.

Conclusion

Given the unknowns in this global pandemic, actions must be taken to ensure the resilience and well-being of patients with COPD in the era of COVID-19 and beyond. Patient education and improving access to healthcare are some of the most pressing needs in patients with COPD. Therefore, using telemedicine in this patient population is paramount, along with

the development and implementation of creative strategies to achieve success with clinical standards and established self-management practices in aerosol drug delivery to patients with COPD who are treated at home. Through the suggested treatment strategies on device selection, interface selection, delivery technique, and infection control, clinicians can provide safe and effective treatments for patients with COPD treated at home in the era of COVID-19 and beyond.

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