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Review article

Practical strategies for a safe and effective delivery of aerosolized medications to patients with COVID-19

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ABSTRACT

The COVID-19, the disease caused by a novel coronavirus and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly across the globe. It has caused outbreaks of illness due to person-to-person transmission of the virus mainly via close contacts and droplets produced by an infected person's cough or sneeze. Exhaled droplets from infected patients with COVID-19 can be inhaled into the lungs and leads to respiratory illness such as pneumonia and acute respiratory distress syndrome. Although aerosol therapy is a mainstay procedure used to treat pulmonary diseases at home and healthcare settings, it has a potential for fugitive emissions during therapy due to the generation of aerosols and droplets as a source of respiratory pathogens. Delivering aerosolized medications to patients with COVID-19 can aggravate the spread of the novel coronavirus. This has been a real concern for caregivers and healthcare professionals who are susceptible to unintended inhalation of fugitive emissions during therapy. Due to a scarcity of information in this area of clinical practice, the purpose of this paper is to explain how to deliver aerosolized medications to mild-, subintensive, and intensive-care patients with COVID-19 and how to protect staff from exposure to exhaled droplets during aerosol therapy.

1. Introduction

The COVID-19, the disease caused by a novel coronavirus and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly across the globe. It has caused outbreaks of illness due to person-to-person transmission of the virus mainly via close contacts and droplets produced by an infected person's cough or sneeze [1]. Exhaled droplets from infected patients with COVID-19 can deposit in the noses, mouths, and eyes of people nearby. They can also be inhaled into the lungs and leads to respiratory illness such as pneumonia and acute respiratory distress syndrome.

Although aerosol therapy is a mainstay procedure used to treat pulmonary diseases at home and healthcare settings, it has a potential for fugitive emissions during therapy due to the generation of aerosols and droplets as a source of respiratory pathogens. Fugitive emission is defined as aerosols that have been released from the aerosol device during patient expiration. It is also medical aerosols that are not inhaled by the patient but passes into the atmosphere. According to previous studies, the particle size of fugitive emissions ranges from 0.860 to 1.437 μm and up to 50% of the generated aerosol during therapy was fugitive aerosol remain airborne in the indoor environment for several hours [2–6]. The device, interface, patient type, and flow rate affect the quantity and characteristics of the fugitive emissions, while the dimensions and layout of the room, air turbulence, airflow rates, and temperature impact dispersion and decay [4,7,8]. In a recent in vitro study, a home attending healthcare worker was simulated with a manikin using a facemask that was placed at three different distances. The findings of this study showed that total aerosol concentration ranged from 0.002 to 0.10 mg/m^3, depending on the distance of the manikin relative to the aerosol source [9]. Although previous studies showed an increase in the quantity of aerosol concentration in the ambient air, it is important to note that they are in vitro studies that cannot differentiate medical aerosol from bioaerosol. While bioaerosols are generated by patients, medical aerosols are produced by aerosol devices. It is clear that COVID-19 is spread by droplets generated as bioaerosols. Also, it has been reported that aerosol transmission of SARS-CoV-2 is plausible because the virus can remain viable and infectious in aerosols for hours [10,11]. For instance, most of the contamination seems to be from surfaces where the droplets settle and persist for up to a week. That is why dispersion distance of aerosols is such an important point. If a patient coughs without a mask the dispersion is much wider than wearing a simple mask, and it is safer for

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the healthcare workers to be within 3 feet. The studies conducted by Hui et al. identified dispersion distances depending on the aerosol generating procedures and the intervention (like mask over cannula) [12–16]. Therefore, the "radius of risk" associated procedures can offer some guidance for healthcare professionals at the bedside.

Delivering aerosolized medications to patients with COVID-19 can aggravate the spread of the novel coronavirus. This has been a real concern for caregivers and healthcare professionals who are susceptible to unintended inhalation of fugitive emissions during therapy. Due to a scarcity of information in this area of clinical practice, the purpose of this paper is to explain how to deliver aerosolized medications to mild-, sub-intensive, and intensive-patients with COVID-19 and how to protect staff from exposure to exhaled droplets during aerosol therapy.

Aerosol Therapy in Mild-Patients with COVID-19: While aerosol therapy is a critical and integral part of the clinical management of patients with pulmonary diseases, it increases the droplet generation and risk of disease transmission. Therefore, it is crucial to avoid unnecessary aerosol drug delivery to patients with COVID-19. According to previous research, patients with asthma have a risk for other coronaviruses such as middle eastern respiratory syndrome coronavirus (MERS-CoV) infection and have a potential risk for COVID-19 [17]. However, in spontaneously breathing patients with COPD or asthma, the routine use of aerosolized medications is essential to keep the disease symptoms under control. While some reports have suggested avoiding the use of corticosteroids during the COVID-19 pandemic, it is important to note that the reports were made based on data obtained in hospitalized patients with COVID-19 who had a poor response to systemic corticosteroids after the onset of the disease. Therefore, the Global Initiative for Asthma (GINA) recommends using prescribed inhaled corticosteroids to prevent the worsening of asthma and the serious consequences of asthma attacks [18]. Also, there is a lack of information on the risk of patients taking oral or inhaled corticosteroids for asthma control or risk of poor outcomes from coronavirus.

In mild-patients with COVID-19 who are awake and can perform specific breathing techniques with inhalers, clinicians should consider using pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) for aerosol drug delivery instead of nebulizers. It is essential to use a valved-holding chamber with pMDIs during treatment. Also, priming before first use, pMDI actuation at the beginning of inspiration, hand breath coordination, inhalation with low inspiratory flows, and breath-hold is vital for the efficiency of pMDI. Since DPIs are breath-actuated inhalers, clinicians should emphasize the specific inspiratory flow needed to draw medication from the device and disperse the particles. Thus, patients can operate the DPI correctly and receive therapeutic benefit from the drug. However, patients with acute respiratory failure may not generate the adequate inspiratory flow needed for the specific DPI used for treatment. In addition, if the inhaler increases cough, other alternatives should be pursued. Using nebulizers with a mouthpiece or high flow nasal cannula should be considered in such cases.

Unlike inhalers, nebulizers can deliver a variety of drug formulations that may be needed for patients with COVID-19. Although conventional jet nebulizers are commonly used to deliver aerosolized medications, they may also spew 2/3 of the emitted aerosol into the ambient environment [19–21]. In this case, healthcare providers are exposed not only the inhaled medications but also to the droplets from the patient's airways and lungs. In addition, the driving gas up to 10 L/min can increase the dispersion of both medical and bioaerosols. If aerosols generated with nebulizers carry the virus during exhalation and transmit it to the hospital environment, health care providers and other patients are under the risk of infection. Recently, some companies manufacturing jet nebulizers provided filters to use with their device in the treatment of patients with COVID-19. While the placement of a filter to the nebulizer was 93% effective in capturing exhaled aerosol droplets [22] and will reduce second hand exposure of aerosol medication to health care professionals [23,24], the efficiency of these filters in preventing the transmission and the magnitude of the risk acquiring coronavirus through filtered nebulizers are not fully known. Also, current publications on fugitive emissions are based on in vitro studies that may not be a true representative of a real exhalation in coronavirus infected patients. Using the high-efficiency particulate air (HEPA) filters with nebulizers might be a good option during aerosol drug delivery to patients with COVID-19. Due to a greater surface of filtration, they are more effective in collecting droplets compared to other bacterial filters available on the market. However, their bulky designs and requirement to use various adapters to attach them to nebulizers make it difficult to use them compared to low volume bacteria filters.

Interface selection is as important as device selection in aerosol therapy. Using a facemask is not recommended for aerosol therapy in the treatment of coronavirus infected patients. When a jet nebulizer is combined with a facemask, the airflow of jet nebulizer will force aerosol out of the device during expiration and breath-hold. McGrath et al. showed that the face mask had the highest-time averaged fugitively emitted aerosol concentration when a jet nebulizer was combined with a facemask. They also reported that placing a filter on the exhalation port of the mouthpiece lead to the lowest concentration [6]. Therefore, the jet nebulizers need to be used with the mouthpiece, and clinicians should attach filters or one-way valves to the large bore tubing of the nebulizer to prevent fugitive emissions during aerosol therapy. Another option would be to use a mesh nebulizer combined with the mouthpiece in patients with COVID-19. In this case, clinicians should add a filter to the other end of the mouthpiece to eliminate the release of aerosols to the environment.

Many suspected patients with COVID-19 are recommended to stay at home. Telehealth would be a good option to evaluate them at home and minimize the utilization of healthcare facilities by them. Smart phones can be used to provide telehealth services to patients with COVID-19 as they are equivalent of a hand-held computer. Although healthcare providers and patients do not need to be in the same physical location, there are some challenges with the use of telehealth in this pandemic. For instance, the healthcare provider cannot measure the temperature if the patient does not have a thermometer at home. Lighting at the patient's home can make assessing cyanosis difficult. Evaluation of throat, nose or ears is also difficult if patient has upper respiratory symptoms. Using telehealth in this pandemic is a strategic initiative and achieving a careful balance of treatment effectiveness and patient safety require policy makers and stakeholders shape telehealth moving forward through a thoughtful framework for the practice, use and reimbursement of telehealth in coronavirus infected patients. Table 1 includes a list of practical strategies for aerosol drug delivery to mild-patients with COVID-19.

Table 1
Practical strategies for aerosol drug delivery to mild-patients with COVID-19.

1. Avoid unnecessary aerosol drug delivery to patients with COVID-19.
2. Use prescribed inhaled corticosteroids to prevent the worsening of asthma and the serious consequences of asthma attacks.
3. Use pMDIs or DPIs for aerosol drug delivery instead of nebulizers, if your patient is awake and can perform specific breathing patterns.
4. Consider using nebulizers with a mouthpiece or high flow nasal cannula, if the inhaler increases cough or if the patient has acute respiratory failure.
5. Attach filters to nebulizers before delivering aerosolized medications to patients. Use HEPA filters if possible.
6. Do not use a face mask with nebulizers.
7. Prefer using a mouthpiece with jet and mesh nebulizers.
8. Attach filters or one-way valves to the large bore tubing of the jet nebulizer to prevent fugitive emissions during aerosol therapy.
9. Add a filter to the other end of the mouthpiece to eliminate the release of aerosols to the environment, when a mesh nebulizer is used.
10. Administer aerosol therapy in negative pressure rooms.
11. Wear personal protective equipment, including an N95 respirator, goggles/face shield, double gloves, gown or apron if the gown is not fluid resistant.
12. Consider using telehealth to evaluate coronavirus infected patients staying at home and minimize their utilization of healthcare facilities.

Aerosol Therapy in Sub-Intensive-Patients with COVID-19: High flow nasal cannula (HFNC) is commonly used in patients with hypoxemic respiratory failure [25–27]. Due to a limited number of ventilators available at hospitals, using HFNC may be a good option to use before patients with asthma and COPD develop severe hypoxemic respiratory failure. However, secondary inhalation of emissions released from the patients with COVID-19 using HFNC is a real concern. It leads to the risk of dispersion of aerosolized virus because HFNC does not have a closed circuit, unlike ventilators. Although previous studies showed a low risk of airborne transmission with HFNC when good interface fitting is achieved [14,16,28], the safety of using HFNC in patients with coronavirus as well as the risk/benefit ratio for aerosol drug delivery through HFNC, has not been investigated. Previous research reported that increasing the flow decreased the fugitive emissions and particle size of aerosols during therapy [6]. If aerosolized medications need to be delivered through HFNC, clinicians should place surgical masks on the face of infected patients during HFNC [13,29,30] and administer aerosol therapy in negative pressure rooms. Respiratory therapists should also wear personal protective equipment, including an N95 respirator, goggles/face shield, double gloves, gown or apron if the gown is not fluid resistant. Table 2 includes a list of practical strategies for aerosol drug delivery to sub-intensive patients with COVID-19.

Aerosol Therapy in Intensive-Patients with COVID-19: Recently published studies showed that two thirds of patients with COVID-19 develop acute respiratory distress syndrome [31]. It takes 9–10 days for patients with COVID-19 deteriorate and require intensive care for respiratory support [32]. Nebulizers may be needed in critically ill patients with COVID-19 receiving ventilatory support. In this case, it is vital to keep the circuit intact and prevent the transmission of the virus. Therefore, delivering aerosolized medications via jet nebulizer or pMDIs will not be appropriate due to the breakage of the circuits for the placement of the device on the ventilator circuit before aerosol therapy. A recently published Chinese guideline suggests using the mesh nebulizer in critically ill patients with COVID-19 receiving ventilator support [30]. Mesh nebulizers can stay in-line for up to 28 days, and reservoir design allows adding medication without requiring the ventilator circuit to be broken for aerosol drug delivery. Unlike jet nebulizer, the medication reservoir of mesh nebulizers is isolated from the breathing circuit that eliminates the nebulization of contaminated fluids. Also, placing the mesh or jet nebulizer prior to the humidifier can improve the efficiency of the treatment and further reduce retrograde contamination from the patient [33–38].

Also, it is important to remember that exhaled particles from intubated patients are less than 2 μm that do not deposit via sedimentation or inertial impaction. They remain suspended in the air and can pose a serious risk to healthcare professionals as low concentration exposure is sufficient for the transmission of coronavirus. In our previous research, we quantified the amount of aerosol collected at the exhaust outlet of a ventilator operated with and without filters in the expiratory limb of the circuit [23]. We found that drug deposited at the exhaust port without expiratory filters was >160 fold higher than with expiratory filters, and placing a filter in the expiratory limb significantly reduces secondhand aerosol exposure [23]. Since aerosol drug delivery to ventilator-dependent patients can readily be transmitted to the ambient environment, it is critical to use the HEPA filters to prevent the transmission of infectious droplet nuclei through the ventilators.

Sometimes aerosol therapy is combined with pulmonary clearance techniques such as chest physical therapy and suctioning. Since coughing generates droplet nuclei capable of transmitting the coronavirus, it is not recommended to administer aerosolized medications along with chest physical therapy in the acute phase of the disease. If the patient with COVID-19 is intubated and needs endotracheal suctioning during mechanical ventilation, in-line, or closed system suction catheters should be preferred as they can be utilized up to 7 days without having to break the ventilator circuit. Although there are multiple designs of closed suction catheters, no significant difference was found on aerosol drug delivery to simulated ventilator dependent adults using different designs of closed suction catheters [39]. Table 3 consists of a list of practical strategies for aerosol drug delivery to intensive-care patients with COVID-19.

Infection Control during Aerosol Therapy: The risk of exposure to exhaled aerosols among health care professionals has been a real concern in the COVID-19 pandemic. Aerosols entering the ambient environment increase the risk of exposure to the virus and may expose respiratory therapists and other healthcare professionals to the pathogen during patient treatment, monitoring, equipment cleaning, and maintenance in the hospital setting. Previous research showed that exposure to the virus and poor compliance with infection control procedures are associated with occupationally acquired infection in healthcare settings [40–44].

Delivering aerosolized medications to patients with COVID-19 who have spontaneous breathing or receive noninvasive ventilation or high flow nasal cannula are of particularly high risk [45]. If aerosolized medications need to be used in patients with COVID-19, clinicians should isolate patients in an airborne infection isolation room (AIIR) or negative pressure rooms with a minimum of 12 air changes per hour or at least 160 liters/s/patient in facilities with natural ventilation. In addition, respiratory therapists and other health care professionals providing aerosol therapy should be trained on infection prevention and control recommendations for COVID-19. They must adhere to airborne precautions and use personal protective equipment properly. Hand hygiene and double gloving should be a standard practice in all healthcare facilities. In addition, healthcare professionals should use surgical respirators such as N95 or FFP2 standard or equivalent, goggles/face shield, gloves, gowns, and aprons (if gowns are not resistant to fluid) during aerosol therapy [46]. Cleaning hands before and after treatment with soap and water or an alcohol-based hand sanitizer is extremely

Table 2
Practical strategies for aerosol drug delivery to sub-intensive patients with COVID-19.

1. Due to a limited number of ventilators available at hospitals, consider using HFNC for aerosol drug delivery to patients with asthma and COPD before they develop severe hypoxemic respiratory failure.
2. Place surgical masks on the face of infected patients during aerosol drug delivery through HFNC.
3. Administer aerosol therapy in negative pressure rooms.
4. Wear personal protective equipment, including an N95 respirator, goggles/face shield, double gloves, gown or apron if the gown is not fluid resistant.

Table 3
Practical strategies for aerosol drug delivery to intensive-care patients with COVID-19.

1. Do not use a jet nebulizer or pMDIs for aerosol delivery to ventilator-dependent patients with COVID-19 due to the breakage of the circuits for the placement of the device before aerosol therapy.
2. Use mesh nebulizers in critically ill patients with COVID-19 receiving ventilator support as they can stay in-line for up to 28 days, and reservoir design allows adding medication without requiring the ventilator circuit to be broken for aerosol drug delivery. Unlike jet nebulizer, the medication reservoir of mesh nebulizers is isolated from the breathing circuit that eliminates the nebulization of contaminated fluids.
3. Placing the mesh nebulizer prior to the humidifier can improve the efficiency of the treatment and further reduce retrograde contamination from the patient.
4. Attach a HEPA filter to the expiratory limb of the ventilator to reduce secondhand aerosol exposure and prevent the transmission of infectious droplet nuclei through the ventilators.
5. Do not combine aerosol therapy with pulmonary clearance techniques such as chest physical therapy and suctioning.
6. Use in-line, or closed system suction catheters if the patient with COVID-19 is intubated and needs endotracheal suctioning during mechanical ventilation because they can be utilized up to 7 days without having to break the ventilator circuit.
7. Wear personal protective equipment, including an N95 respirator, goggles/face shield, double gloves, gown or apron if the gown is not fluid resistant.

important. Other infection control strategies include minimizing the number of times that healthcare workers enter the rooms of COVID-19 patients by bundling the activities/treatments and restricting others who are not involved in direct patient care from entering the patient's room. Currently, a shortage of surgical N95 respirators is expected. In this case, healthcare professionals should consider using the same mask in the treatment of multiple patients with COVID-19. However, previous studies reported that the use of the same respirator for more than 4 h might lead to discomfort [47,48].

This pandemic has taught us the importance of infection prevention and control measures as well as teamwork in health care settings. It is important for respiratory therapists to team up with other healthcare professionals in isolating coronavirus infected patients in AIIR and assigning designated staff who can provide effective and safe delivery of aerosolized medications to this patient population. Although respiratory therapists and other healthcare providers face a major and unique challenge in this pandemic, they are on the front stage and build a strong platform to ensure the health, safety and well-being of patients with coronavirus. The upside of this pandemic is that we can teach respiratory therapists and other healthcare professionals the importance of personal protection and safe practices that might carry over for a safer workplace in the future.

The treatment of patients with COVID-19 is different from the disease management of patients with pulmonary diseases who need aerosol therapy. However, it is imperative during the pandemic to assume that all patients may be infected, so good personal protection and aerosol administration practices should be applied. Clinical studies on COVID-19 are limited, and there is a lack of information and guidance on how to administer aerosolized medications to this patient population. Also, the effective delivery of aerosolized medications to patients with COVID-19 may require modifications in the dose, frequency, and delivery technique that need to be used during aerosol therapy . While our deepest fear is that we are inadequate in terms of resources and knowledge about coronavirus, the choice does not belong to pessimism and scare; it belongs to us. As Marie Curie said, "nothing in life is to be feared, it is only to be understood. Now is the time to understand more so that we may fear less." We are strong when we know our fears and limitations. Therefore, it is time to start thinking about what is necessary and doing what is possible using a proactive and comprehensive approach to aerosol drug delivery to patients with COVID-19. Respiratory therapists have enormous experience in aerosol therapy and the foundation of delivering aerosolized medications to coronavirus infected patients should be grounded in their experience and current guidelines on COVID-19.

Declaration of competing interest

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