INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the global pandemic of coronavirus disease 2019 (COVID-19), has afflicted more than 245 million people worldwide and caused more than 5 million deaths (1). COVID-19 primarily affects the respiratory tract and infected persons generate respiratory droplets and aerosols containing the virus that transmit the infection to susceptible hosts (2). Patients with COVID-19 need inhaled therapies, either for pre-existing respiratory diseases or because of new onset respiratory distress and hypoxemia in patients with no previous pulmonary problems. Aerosolized therapies increase particle concentrations in the vicinity of patients receiving such treatments (3, 4). Inhalers (pMDIs, DPIs and SMIs) have a very low risk of contamination and the risk of spreading infection with those devices is largely due to “bioaerosols” generated by the patient during breathing, speaking, coughing or sneezing (2,5,6). In contrast, nebulizers, especially those that are operated continuously, release “fugitive emissions” that could remain in the indoor environment (7, 8) (Figure 1).

Fugitive emissions generated during nebulization are composed of a mixture of aerosol generated by the nebulizer (medical aerosol) and bioaerosols exhaled by the patient (8,9). Because jet nebulizer operation requires a gas flow of 6 to 8 L/min, use of nebulizers has the potential to further disperse virus particles generated by infected individuals in the environment. Dispersion of bio-aerosols and stimulation of cough during nebulizer treatment could spread infection to susceptible hosts in the vicinity (10,11). These concerns severely limited nebulizer use since the early days of the COVID-19 pandemic.
ALTERNATIVES TO NEBULIZERS

The use of pMDIs and spacers has been suggested as an alternative to nebulizer therapy (11, 12). A significant proportion of patients without previous history of respiratory disorders are unaccustomed to using hand-held inhalers correctly and therefore may not derive the maximum benefits from this treatment method. Patients with a history of respiratory diseases with poor inhalation-actuation coordination, inadequate inspiratory effort, or other comorbid physical or mental/cognitive disabilities may also be deprived of the full treatment benefits from medication delivered by hand-held inhalers (13). Inadequate treatment can result in the loss of disease control and exacerbations that lead to disease progression, therefore increasing the likelihood those patients will require emergency care, longer hospital stays, and other invasive procedures, such as endotracheal intubation, that increase aerosol exposure risks and further add to the possibility of SARS-CoV-2 exposure by patients and hospital staff (14). In children, nebulizers are most commonly employed for inhalation therapy and use of nebulizers allows administration of higher doses of medication as well as co-administration of compatible drug mixtures (15). Moreover, several treatments for respiratory disorders, such as bronchodilators, inhaled corticosteroids, antibiotics, prostacyclin and its analogs, and mucolytics, are administered by nebulization (16). Avoiding nebulizer use altogether limits therapeutic options for patients who need such therapies. Thus, the concerns about using nebulizers in patients with COVID-19 must be balanced with the risk associated with avoiding their use which could jeopardize the health and well-being of patients as well as Health Care Providers (HCPs).

At present, there are no conclusive data showing that nebulizers increase the transmission of acute respiratory infections from a real-world perspective (8,9). Transmission of infection early on in the SARS-CoV-2 pandemic could be attributed to the lack of adequate personal protective equipment by HCPs and other procedural confounders (17). The influence of nebulizers in dispersing aerosols in the environment has been investigated with simulation experiments by several investigators (3, 4, 10, 18-20). In these studies, droplet dispersion was demonstrated in the environment after nebulization of saline or live attenuated influenza virus (3, 4, 18-20). While using smoke to simulate dispersion of aerosols, the exhaled air dispersion distance was found to be greater with nebulization than with a simple oxygen mask and noninvasive ventilation (3). As such, nebulization was considered among other aerosol generating procedures (AGPs) (21, 22, 23). Due to concerns that aerosol generated by the nebulizer might carry virus to the surrounding environment, especially with reports of SARS-CoV-2 being viable in aerosols for up to 3 hours (24), several clinical societies made recommendations against the use of nebulizers during the COVID-19 pandemic (25,26). However, guidelines from other expert groups, such as NICE in UK, NERVTAG and The Centers for Disease Control and Prevention (CDC) recommend continued use of nebulizers because the aerosol generated by nebulizers has not been shown to contain infectious particles (27-29).

DIFFERENCES IN FUGITIVE AEROSOL EMISSIONS WITH VARIOUS NEBULIZERS AND INTERFACES

Li and colleagues conducted a study in 9 healthy volunteers who were given 3 mL saline with a small volume nebulizer (SVN) or vibrating mesh nebulizer (VMN) with a mouthpiece, a mouthpiece with an exhalation filter, an aerosol mask with open ports for SVN and a valved facemask for VMN, and a facemask with a scavenger (Exhalo) in random order (30). Five of the participants received treatments using a face tent scavenger (Vapotherm) and a mask with exhalation filter with SVN and VMN in a random order. They found that SVN produced higher fugitive aerosol concentrations than VMN, while facemasks generated higher aerosol concentrations than mouthpieces. Adding an exhalation filter to the mouthpiece or a scavenger to the facemask reduced aerosol concentrations for both SVN and VMN. Vapotherm scavenger and filter facemask reduced fugitive aerosol as effectively as a mouthpiece with an exhalation filter (30). This study provides guidance for reducing fugitive aerosol emissions from nebulizers in clinical practice.

Jain and coworkers performed a pilot clinical study using scintigraphy to investigate the dispersion pattern of technetium (Tc) radiolabeled exhaled droplets during nebulization with a jet nebulizer and compressor (31). They reported that nebulizer use did not affect the dispersion of respiratory aerosols in both near-zone (within 1 foot on each side) and far-zone (1.5 feet on either side and 2 feet in front) during tidal breathing. In agreement with previous studies, they found that both coughing and sneezing cause distant dispersion of aerosol in far-zone, nearly 4-6 fold higher than tidal breathing under normal conditions. The results of Jain and colleagues suggest that nebulization per se has a clinically
insignificant role in producing fugitive emissions and dispersion of exhaled aerosols. These findings provide assurance that nebulizer therapy has a limited role in transmission of Covid-19 or other droplet borne infections unless the nebulizer solution induces coughing or sneezing when inhaled (31).

Given the absence of any conclusive data that link nebulized treatments to the transmission of SARS-CoV-2, most international societies (8,27,28) and CDC (29) have not advised against the use of nebulizers during the Covid pandemic. Recommended technique for using nebulizers during the COVID-19 pandemic in the hospital is shown in Table 1.

MITIGATING RISK OF TRANSMITTING INFECTION WITH NEBULIZERS

Independent of the nebulizer type used, a risk of bio-aerosol dispersion exists in case of contamination of the reservoir while loading the medication loading, which need to be performed using aseptic techniques. A mouthpiece should be preferred over a face mask to improve treatment efficiency and reduce fugitive emissions because a mouthpiece does not force aerosols out of the interface during therapy (8). Furthermore, placing a filter on the nebulizer’s outlet has been found to reduce fugitive emissions and exposure of HCPs to aerosol medications (4,30,32). An exhalation filter attached to the nebulizer has been shown to reduce exhaled aerosol droplets between 0.06 to 0.1 µm in size by 98% (33). In summary, jet or mesh nebulizers should be used with a mouthpiece and a filter attached to the exhalation port of the nebulizer could effectively reduce emission of exhaled aerosol droplets (Figure 2).

![Image of nebulizer setup]

Figure 2: Use of expiratory filters and use of mouthpieces with either jet or vibrating mesh nebulizers is recommended to reduce aerosol dispersion

CONCLUSION

Apprehension that nebulizers could increase transmission of SARS-CoV-2 infection has severely limited their use in clinical practice. Evidence to support increased risk of SARS-CoV-2 by nebulizer treatments is inconclusive and is based mainly on experimental and simulation studies. However, clinicians should exercise caution and protect themselves from SARS-CoV-2. Some measures to mitigate spread of infection include using a mouthpiece rather than a mask for inhalation of the nebulized medication and placement of a filter on the exhalation port of the nebulizer and instructions to the patient to seal their lips tightly around the mouthpiece during inhalation and exhalation. Other considerations include using a breath synchronized nebulizer that only generates an aerosol during inhalation to minimize the release of medical aerosols or employing vibrating mesh nebulizers in place of jet nebulizers. Health care workers are advised to limit the number of people in the room and stay two meters away from the infected patient during procedures that provoke coughing or sneezing. Bystanders and health care professionals should wear N95 or other respirators, in addition to eye protection in rooms where nebulizer treatments are being administered. Such measures could minimize spread of aerosols in the environment and avoid close and prolonged exposures to patients with COVID-19 during nebulizer treatments.
Drug Delivery to the Lungs, Volume 32, 2021 - Nebulizers and COVID-19: Aerosol Generation vs. Aerosol Dispersion

References


30. Li J, Harnois L, Alolaiwat A, Fink JB, Dhand R. Efficacy of various interfaces in reducing fugitive emissions from nebulizers: a randomized crossover trial in healthy volunteers. Respiratory Care. Accepted for publication


### Table 1: General Procedures for Nebulizer Administration during COVID-19 Pandemic

**JET NEBULIZER USE IN HOSPITAL**

**Before Entering the Room**
During the pandemic treat every patient as potentially infected because asymptomatic infected patients can shed virus

Put on PPE for aerosol and droplet protection (N-95 mask, face shield, gloves, and gown). Use additional PPE such as PAPRs, if available, for high risk procedures

Wash hands and put on fresh gloves (preferably use double gloves)

**After Entering the Room**
Use proper aseptic technique to avoid contamination of aerosol reservoirs and medication

Perform nebulization in a negative pressure room for COVID-19 patients, or rooms with high air exchange rates (6–12 air exchanges/hour)

Have tissues available and face mask to cover the patient’s mouth during coughing or sneezing; discard used tissue immediately

**Filling the Nebulizer**
Assemble apparatus

Add medication to nebulizer cup

Use a fill volume of 3 to 6 mL

Attach a compressor or a pressurized gas supply (eg, compressed air or oxygen) with a flow of 6 to 8 L/min. If using a compressor, ensure that it is compatible and recommended for use with the nebulizer brand#
Use a mouthpiece with a filter attached to the exhalation port
Maintain distance of 3 to 6 feet or more from patient
Try to stay at least 1 foot (dispersion distance with medical aerosol) away from the patient’s airway

**Administration of Nebulizer Treatment**
Have patient sitting up or partially supine in a comfortable position (there is a risk of spillage if the patient is lying flat)
Instruct patient to use a slow breathing pattern with a normal tidal volume and an occasional deep breath (there is no need to take deep breaths)
Keep the nebulizer upright during the treatment
Periodically tap nebulizer to return impacted droplets to reservoir
Continue treatment for a few minutes (~5 to 12 minutes)** and stop when the nebulizer sputters despite tapping

**Nebulizer Cleaning and Disinfection**
Discard any remaining solution from the medication cup
Rinse with soapy tap water
Allow to air dry
Store the plastic tubing and medication chamber in a plastic bag between uses
Change nebulizer daily

# Matching a nebulizer with a compressor is important for optimal performance and to ensure delivery of an adequate therapeutic dose.

** Time for the treatment may vary depending on the type of nebulizer, volume of solution and air flow rate.