INTRODUCTION

Nebulized medications are frequently administered in both acute and chronic conditions—viz., management of acute asthma and COPD exacerbations, home maintenance treatment for chronic respiratory diseases like COPD, bronchiectasis, and cystic fibrosis, etc. However, the viral pandemic of COVID-19 has raised concerns on the use of nebulization. This document is intended to provide guidance to physicians on the role and use of nebulization in the current pandemic, based on current evidence and understanding.

AEROSOL EMISSIONS: FUGITIVE EMISSIONS AND MEDICAL AND BIO-AEROSOLS

The spread of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can occur through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions or their respiratory droplets, which are ejected when an infected person talks, sneezes, coughs, or sings. Even though aerosol therapy is the principal procedure used for treating pulmonary diseases at health-care and home settings, there is a possibility for generating fugitive emissions during therapy in the form of droplets and aerosols that may serve as a source of respiratory pathogens. The spread of respiratory droplets can occur when a person is in close contact (>2 m) with an infected person who has respiratory symptoms (e.g., coughing or sneezing) or who is talking or singing. In these situations, respiratory droplets that include virus can reach the mouth, nose, or eyes of a susceptible person and can result in infection. Indirect contact spread involving contact of a vulnerable host with a contaminated object or surface (fomite transmission) is also possible. Most of the droplet spread probably occurs at close range because of inactivation and dilution of viruses over longer periods and greater distances. During exhalation, the larger droplets between 60 and 100 μm in size are anticipated to completely evaporate before traveling 2 m. These large droplets are carried farther away when they are expelled at a high velocity, such as with cough and sneeze. The time taken by the particles to fall on the floor depends on their size, for example, particles 100 μm in diameter take about 10 s, whereas 10-μm diameter particles are estimated to take 17 min to fall on the floor and 1-3-μm diameter particles could remain suspended almost indefinitely.

The proportion of exhaled droplet nuclei or respiratory droplets that evaporate to generate aerosols and the infectious dose of viable SARS-CoV-2 required to cause infection in another person are not identified. In addition, transmission of SARS-CoV-2 by aerosol route has not been demonstrated, and much more research is needed given the possible consequences of such a route of transmission. Investigational studies have generated aerosols of infectious samples using high-powered jet nebulizers under controlled laboratory conditions. These studies found SARS-CoV-2 virus RNA in air samples within aerosols for up to 3 h and 16 h, with viable virus capable of undergoing replications. However, we must note that these findings were from experimentally induced aerosols that do not reflect normal human cough conditions. A recent clinical study of health workers exposed to coronavirus disease 2019 (COVID-19) cases, in the absence of aerosol-generating procedure (AGP), found no nosocomial spread when contact and droplet safety measures were properly followed, including the donning of medical masks as an element of the personal protective equipment (PPE). These observations endorse that aerosol spread did not occur in this context. Further studies are needed to conclude whether it is likely to detect viable SARS-CoV-2 in air samples from settings where no procedures that generate aerosols are performed and what role aerosols might play in transmission.

Fugitive emission can be defined as aerosol that comes out from the aerosol device when the patient exhales. Studies have concluded that airborne transmission has been the main transmission route for the SARS-CoV-2 virus in the indoor cases. Available resources and epidemiological data have concluded that small particles containing the virus may spew in indoor environments covering distances up to 10 m from the emission sources, thus representing a kind of aerosol spread. Based on the results published in previous studies, the particle size of fugitive emissions varies from 0.860 to 1.437 μm. In addition, during aerosolization, approximately 50% of the aerosol produced is fugitive aerosol that remains suspended in the indoor environment for several hours. The device used for aerosolization, patient interface, type of patient characteristics, and flow rate influence the characteristics and quantity of the fugitive emissions, while the air turbulence, airflow rates, layout and size of the room, and temperature affect the dispersion and decay. Recently, in an in vitro study, a manikin using a facemask was simulated for health-care workers at home and was positioned at three different distances. Based on the distance of the manikin with respect to the source of aerosol, the results obtained from this study demonstrated that the concentration of total aerosol varied from 0.002 to 0.10 mg/m². Even though earlier findings demonstrated an increase in the quantity of aerosol concentration in the
ambient air, it is very important for us to make a note that they are in vitro studies that cannot distinguish between bio-aerosol and medical aerosol.

Bio-aerosols are generally defined as aerosols or particulate matter of animal, plant, or microbial, origin. Bio-aerosols can contain nonpathogenic or pathogenic dead or live viruses, bacteria, fungi, bacterial endotoxins, mycotoxins allergens, peptidoglycans, pollen, and plant fibers. Bio-aerosols are aerosols that are generated by patients, whereas medical aerosols are aerosols produced by aerosol devices. On the other hand, it is documented that the transmission of COVID-19 may occur by droplets generated as bio-aerosols.

Medical aerosols are aerosols that are not inhaled by the patient but spreads into the surrounding atmosphere. Medical aerosols are produced by aerosol-generating medical procedures (AGMPs). Any procedure including nebulization, performed on a patient that can generate aerosols of various sizes, including droplet nuclei can be termed as AGMP.

**ROLE OF FILTERS IN NEBULIZATION**

Conventional jet nebulizers are commonly used to deliver aerosolized medications; they may also discharge 2/3 of the emitted aerosol into the ambient environment. In this case, HCPs are exposed not only to the inhaled medications but also to the droplets from the patient’s airways and lungs. Moreover, the driving gas up to 10 L/min can increase the dispersion of both medical and bio-aerosols. If aerosols generated with nebulizers carry the virus during exhalation and transmit it to the hospital environment, patients and HCPs are under the risk of getting infected. Lately, few companies manufacturing jet nebulizers have provided filters to use with their device in the treatment of COVID-19 patients. Placing a filter to the nebulizer has been found to be 93% effective in sieving exhaled aerosol droplets and can decrease second-hand exposure of aerosol medication to HCPs. However, the effectiveness of these filters in preventing the spread and the magnitude of the risk obtaining coronavirus through filtered nebulizers are not fully known. Using high-efficiency particulate air (HEPA) filters with nebulizers might be a good option during aerosol drug delivery to patients with COVID-19. These filters have greater surface of filtration, hence are more effective in collecting droplets compared to other bacterial filters. Nevertheless, their bulky designs and the necessity to use various adapters to attach them to nebulizers make them problematic to use as compared to low-volume bacterial filters.

It is imperative to remember that exhaled particles from intubated patients are <2 μm that do not deposit via sedimentation or inertial impaction. These particles remain suspended in the air and can pose a serious risk to HCPs as low-concentration exposure is sufficient for the transmission of coronavirus. A recent study conducted by Ari et al. found that drug deposited at the exhaust port without expiratory filters was >160 fold higher than that with expiratory filters, and positioning of the filter in the expiratory limb significantly decreases second-hand aerosol exposure.

**ROLE OF PATIENT–DEVICE INTERFACE**

Selection of interface is as critical as selection of inhalation device in aerosol therapy. Using a facemask is not recommended for aerosol therapy in the treatment of COVID-19 patients. When a jet nebulizer is combined with a facemask, the airflow of jet nebulizer will spew the aerosol out of the device during expiration and breath-hold. It is reported that placing a filter on the exhalation port of the mouthpiece leads to the lowest concentration of fugitive aerosols. Hence, jet nebulizers are recommended to be used with the mouthpiece, and HCPs should attach filters or one-way valves to the large-bore tubing of the nebulizer to avoid fugitive emissions during aerosol therapy. Another option would be to use a mesh nebulizer combined with the mouthpiece in COVID-19 patients. In this case, HCPs should add a filter to the other end of the mouthpiece to prevent the release of aerosols to the environment.

**JET NEBULIZERS VERSUS MESH NEBULIZERS**

Jet nebulizers that are open to and positioned below the gas pathway can be contaminated by patient’s exhaled bio-aerosols or secretions when they are directly attached to the patient interface (mouthpiece or endotracheal tube). Unlike jet nebulizers, mesh nebulizers are preferred as nebulizing device because their medication reservoir is isolated from the breathing circuit that eliminates the nebulization of contaminated fluids. Nebulizers may be required in critically ill COVID-19 patients receiving ventilatory support. In that case, it is important to keep the circuit intact to avoid the spread of the virus. Hence, delivering aerosolized medications via jet nebulizer or pressurized metered dose inhalers (pMDIs) will not be suitable due to the need for breakage of the circuits for placing the device on the ventilator circuit before aerosol
therapy. A recently published guideline recommends using the mesh nebulizer in critically ill COVID-19 patients receiving ventilator support.\textsuperscript{[5]} Mesh nebulizers can stay in line for up to 28 days, and the reservoir design permits adding medication without requiring the ventilator circuit to be broken for aerosol drug delivery. Furthermore, placing the mesh or jet nebulizer prior to the humidifier can improve the effectiveness of the treatment and also decrease retrograde contamination from the patient.\textsuperscript{[9]} The time required for nebulization is equally important because the risk of viral transmission through aerosol is directly proportional to the nebulization. Therefore, mesh nebulizers are recommended in such cases as they have efficient drug delivery with the shortest nebulization time as compared to the commonly used jet nebulizers. With recent advances in technology, more innovative nebulizers, including breath-actuated and breath-enhanced nebulizers, decrease the amount of exhaled aerosol lost to the atmosphere while increasing the efficiency of drug delivery, thereby increasing the total inhaled drug mass. These will further minimize the risk of spreading the infection.\textsuperscript{[23]}

**GUIDANCE ON HOME NEBULIZATION IN THE CURRENT PANDEMIC**

Administering aerosolized medicines to patients with COVID-19 can probably spread the novel coronavirus. However, in the current pandemic of COVID-19, there are insufficient evidences, in the form of studies and reports on the perils associated in the transmission of SARS-CoV-2, due to nebulization. During the current pandemic, HCPs and caregivers are the ones who are at risk because they are exposed to the inhalation of fugitive emissions during aerosol therapy. Considering the shortage of evidence in this part of clinical practice, the purpose of this commentary is to discuss aspects on home nebulization pertaining to the current pandemic condition which we believe will provide guidance for practicing physicians. Use of nebulization at home should be considered a part of the maintenance regimen for obstructive airway diseases.

People who can benefit from using a nebulizer at home include:\textsuperscript{[26]}

- People with severe disease and those who are unable to inhale as deeply and quickly as desired to use some inhaler devices
- Old people with arthritis that makes it difficult to use an inhaler
- People who have trouble using or cannot handle an inhaler device
- People who require medicines that are only accessible as nebulizer solutions or suspensions.

**Recommendations to be followed by COVID-19 patients for nebulization at home**

Using nebulizers at home may be essential for COVID-19 patients or for patients who are suspected to have COVID-19 with asthma, chronic obstructive pulmonary device, or any another respiratory ailment. In such scenarios:

- Patients must have their full supply of medication at home. Consider having at least a 30-day supply of all medications on hand to reduce the need for leaving the home, or select delivery options at your pharmacy, or have trusted individuals pick up your medication\textsuperscript{[27]}
- It is advised to use alcohol-based hand rub with >60% ethanol or 70% isopropanol. Unless hands are visibly soiled, an alcohol-based hand rub is preferred over soap and water in most clinical situations due to evidence of better compliance compared to soap and water. Hand rubs are generally less irritating to hands and are effective in the absence of a sink\textsuperscript{[28]}
- Ensure that the nebulizer accessories (accept the tubing) are clean and dry before nebulization. Cleaning and disinfecting your equipment is very important\textsuperscript{[6]}
- It is very important that if the patient is COVID-19 positive or suspected with COVID-19 using a nebulizer at home, perform nebulization in a separate, well-ventilated room such as open area, balcony, or terrace\textsuperscript{[29,30]}
- Opening windows and doors maximizes natural ventilation so that the risk of airborne contagion is much lower\textsuperscript{[31]}
- Avoid central air conditioning in the room altogether during nebulization\textsuperscript{[32]}
- Do not let the caretaker get too close while nebulization is being conducted. Maintain a distance of >2 m (>6 feet) from other household members\textsuperscript{[32,33]}
- The caregiver, when possible, should not be someone who is at higher risk for severe illness from COVID-19. If caretaker/family member is required to share space, make sure that the room has good air flow. Open the window and turn on a fan (if possible) to increase air circulation. Improving ventilation helps remove respiratory droplets from the air\textsuperscript{[34]}
- Close the door while nebulization is being undertaken\textsuperscript{[35]}
- Do not share nebulizers between family members\textsuperscript{[36]}
- The room should be left vacant, with the door closed for 30 min after the patient has vacated the room post nebulization\textsuperscript{[37]}
- Clean and disinfect the nebulizer accessories using liquid/hospital-grade disinfectants such as isopropanol (70%) or hydrogen peroxide (3%)\textsuperscript{[38]}
- Cleaning and disinfection of common areas and surfaces (doorknobs, bedrails, table-tops, light switches, and patient handsets) should also be taken care of\textsuperscript{[37,39]}
- Hospital-grade cleaning and disinfecting agents are recommended for all horizontal and frequently touched surfaces
- Many disinfectants are active against enveloped viruses, such as the COVID-19 virus, including commonly used hospital disinfectants. Currently, 70% ethyl alcohol is preferred to disinfect small areas between uses, such as reusable dedicated equipment. Sodium hypochlorite at 0.5% (equivalent to 5000 ppm) can be used for disinfecting surfaces.
Recommendations to be followed by non-COVID-19 patients for nebulization at home
If the patient is not infected with COVID-19, there are no known infection-associated perils that prevent the use of a nebulizer. In addition, asthmatic patients devoid of symptoms or a confirmed diagnosis of COVID-19 should continue essential nebulized drugs for their treatment, as recommended by the physician.

In-hospital nebulization strategies for COVID-19 patients
The world has experienced two outbreaks with coronaviruses in the past, and studies suggested that there was no definite evidence of transmission as a result of nebulization treatment. Of note, a study performed in 2004 with air sampling around a patient with SARS, did not find evidence of virus using RT-PCR method. A review article published in 2012 concluded that there was no significant evidence of transmission risk related to nebulizers, utilizing evidence from the SARS outbreak.

The CDC reported that only 3 out of 121 exposed health-care persons developed COVID-19 infection while taking care of an unsuspected patient with infection. This patient underwent multiple AGPs including nebulization. Thus, it is difficult to determine the role of nebulization as a source of SARS-CoV-2 transmission in hospital. For those patients requiring high-flow nasal cannula (HFNC) for respiratory failure, aerosolized medicines may need to be delivered through HFNC. Because HFNC does not have a close circuit, a good interface fitting should be achieved. The aerosolized therapy in such a situation should preferably be administered in negative-pressure rooms, else clinicians should place a surgical mask on the face of infected patients. Based on these data, nebulization administration likely represents a lower infection risk, but close-range aerosol generation remains a possibility, as suggested by the stability of SARS-CoV-2 in laboratory settings.

Recommendations
1. Health-care workers should observe complete precautions, namely, facemask, eye protection, gloves, and gown
2. Maintain a safe distance (6 feet or greater), possibly outside the door, upon the setup of nebulizer. Limit the time the HCP is in the room without compromising patient care
3. In case filters are used, ensure that filters are removed well in time after nebulization and replace it with a fresh one in case there is surge in expiratory resistance
4. Close patient’s door while providing nebulizer treatment
5. Proper disposal of used equipment, which preferably should be disposable. A fresh mask, mouthpiece, and tubing should be preferred for each nebulization treatment
6. Patients need not to be transferred to higher level facilities just for the need of nebulization treatment

Nebulization strategies in COVID-19 intensive care unit
In the ICU delivering noninvasive ventilation, high-flow nasal oxygenation and nebulization to patients with COVID-19 can aggravate the spread of novel coronavirus. If nebulized therapy or aerosolized procedures are used, patients should be in an airborne infection isolation room (AIIR) or negative-pressure rooms with a minimum of 12 air changes per hour or at least 160 L/s/patient in facilities with natural ventilation. Health-care workers should use contact and airborne precautions with PPE; this includes a N95 mask with goggles and face shield, gloves, and gown, and providing aerosol therapy should be trained on infection prevention and control recommendations for COVID-19. Hand hygiene and double gloving should be a standard practice in all health-care facilities. Cleaning hands before and after treatment with soap and water or an alcohol-based hand sanitizer is extremely important. All nonessential personnel should leave the room during nebulization and not re-enter the room for 2–3 h following nebulizer administration. Other infection control strategies include minimizing the number of times that health-care workers enter the rooms of COVID-19 patients and restricting others who are not involved in direct patient care from entering the patient’s room. In case of shortage of surgical N95 respirators, HCPs may use the same mask in the treatment of multiple patients with COVID-19.

Aerosol therapy in intensive care patients with COVID-19
In critically ill patients with COVID-19 receiving ventilatory support, nebulization should be given in a close circuit to prevent the transmission of the virus. Therefore, mesh nebulizer is preferred over jet nebulizer or pMDI in delivering aerosolized medications. 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. Use of HEPA filters prevents the transmission of infectious droplet nuclei through the ventilators as aerosol drug delivery to ventilator-dependent patients can readily be transmitted to the ambient environment.

Recommendations
1. Place surgical masks on the face of the infected patients during aerosol drug delivery through HFNC
2. Use mesh nebulizers, if available, in critically ill patients with COVID-19 receiving ventilator support
3. Avoid the use of 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
4. Place a mesh nebulizer prior to the humidifier to improve the efficiency of the treatment and to reduce retrograde contamination from the patient
5. Attach a HEPA filter to the expiratory limb of the ventilator to reduce second-hand aerosol exposure and to prevent the transmission of infectious droplet nuclei through the ventilators
6. Do not combine aerosol therapy with pulmonary clearance techniques such as chest physiotherapy and suctioning
7. Use in-line, or closed system suction catheters in intubated patients
8. Health-care workers should wear PPE. Cleaning hands before and after treatment with soap and water or an alcohol-based hand sanitizer is extremely important
9. All nonessential personnel should leave the room during nebulization and not re-entering the room for 2–3 h following nebulizer administration
10. Disinfect the equipment with isopropanol (70%) or hydrogen peroxide (3%).

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Key messages
- The current evidence on nebulization being an AGP is limited. Based on the available data, nebulization administration represents a low infection risk
- Mouthpiece is the preferred patient interface over facemask during nebulization
- Placing a filter on the exhalation port of the mouthpiece leads to the lowest concentration of fugitive aerosols and can decrease second-hand exposure of aerosol medication to HCPs
- Mesh nebulizers are preferred over jet nebulizers because the medication reservoir is isolated from the breathing circuit that eliminates the nebulization of contaminated fluids
- Use of nebulization at home should be considered as a part of the maintenance regimen for obstructive airway diseases for patients who were already on home nebulization or unable to use handheld inhalers
- Performing nebulization at home should be done with safety precautions which include using a clean nebulizer in a room having good air ventilation, disinfecting the nebulizer after every use, and not sharing the nebulizer with other family members
- Nebulization in hospital setting can be performed by HCPs by following complete precautions, namely, face mask, eye protection, gloves, and gown and maintaining a safe distance (6 feet or greater)
- Nebulization in the ICU setting should be performed with additional safety precautions such as using AIIR or negative-pressure rooms with a minimum of 12 air changes per hour or at least 160 L/s patient in facilities with natural ventilation.