CHEST

Guidance on Mitigating the Risk of Transmitting Respiratory Infections During Nebulization by the COPD Foundation Nebulizer Consortium

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BACKGROUND: Nebulizers are used commonly for inhaled drug delivery. Because they deliver medication through aerosol generation, clarification is needed on what constitutes safe aerosol delivery in infectious respiratory disease settings. The COVID-19 pandemic highlighted the importance of understanding the safety and potential risks of aerosol-generating procedures. However, evidence supporting the increased risk of disease transmission with nebulized treatments is inconclusive, and inconsistent guidelines and differing opinions have left uncertainty regarding their use. Many clinicians opt for alternative devices, but this practice could impact outcomes negatively, especially for patients who may not derive full treatment benefit from handheld inhalers. Therefore, it is prudent to develop strategies that can be used during nebulized treatment to minimize the emission of fugitive aerosols, these comprising bioaerosols exhaled by infected individuals and medical aerosols generated by the device that also may be contaminated. This is particularly relevant for patient care in the context of a highly transmissible virus.

RESEARCH QUESTION: How can potential risks of infections during nebulization be mitigated?

STUDY DESIGN AND METHODS: The COPD Foundation Nebulizer Consortium (CNC) was formed in 2020 to address uncertainties surrounding administration of nebulized medication. The CNC is an international, multidisciplinary collaboration of patient advocates, pulmonary physicians, critical care physicians, respiratory therapists, clinical scientists, and pharmacists from research centers, medical centers, professional societies, industry, and government agencies. The CNC developed this expert guidance to inform the safe use of nebulized therapies for patients and providers and to answer key questions surrounding medication delivery with nebulizers during pandemics or when exposure to common respiratory pathogens is anticipated.

RESULTS: CNC members reviewed literature and guidelines regarding nebulization and developed two sets of guidance statements: one for the health care setting and one for the home environment.

INTERPRETATION: Future studies need to explore the risk of disease transmission with fugitive aerosols associated with different nebulizer types in real patient care situations and to evaluate the effectiveness of mitigation strategies. CHEST 2024; 165(3):653-668

KEY WORDS: aerosol; aerosol dispersion; aerosol-generating procedure; bioaerosols; COVID-19; fugitive aerosols; nebulizer; occupational exposure

The mainstay of pharmacotherapy for chronic respiratory conditions including COPD and asthma is the administration of inhaled medications using an aerosol delivery device, commonly one of several types of pressurized metered dose inhalers, soft mist inhalers, dry powder inhalers, or nebulizers.[1,2] Nebulizers and inhalers deliver medication through aerosol generation. As such, clarification is needed on what constitutes safe aerosol delivery for patients with an infectious respiratory disease such as TB or COVID-19, which is caused by SARS-CoV-2 and has claimed > 6.8 million lives worldwide.[3]

Generation of bioaerosols that contain virus from infected individuals is a well-established means of transmitting SARS-CoV-2.[4-6] SARS-CoV-2 can be aerosolized by routine activities such as breathing, talking, and singing.[7] The COVID-19 pandemic raised concerns for the overall safety of aerosol-generating procedures (AGPs).[8] According to the Centers for Disease Control and Prevention, procedures classified as AGPs include open suctioning of airways, sputum induction, CPR, endotracheal intubation and extubation, noninvasive ventilation, bronchoscopy, and manual ventilation.[8] Consensus among professional bodies is lacking regarding whether drug administration via a nebulizer is an AGP.[9]

Major clinical organizations, public health agencies, professional societies, and other stakeholder groups from the United States, other countries, and globally have expressed different opinions regarding the safety of nebulized treatments during and after the COVID-19 pandemic.[4,8,10-17] As a result, many clinicians opted for other alternatives, including pressurized metered dose inhalers and dry powder inhalers.[18,19] The resulting significant increase in their use caused severe shortages of inhalers during the early stages of the pandemic.[20] Moreover, in addition to bronchodilator therapy used in treating obstructive lung diseases, multiple other treatments, including antibiotics, pulmonary vasodilators, airway hydration, and mucolytics (eg, hypertonic saline, nebulized surfactant), are administered by nebulization to treat various conditions, and it may not always be possible to find inhaled alternatives for patients receiving such therapies.[21]

The COPD Foundation Nebulizer Consortium (CNC) is an international collaboration formed in 2020 to improve the understanding of any infection risks that may be associated with the administration of nebulized therapies and to develop solutions that ensure the safety of patients, caregivers, and health care providers. The CNC comprises patient advocates, pulmonary physicians, critical care physicians, respiratory therapists, clinical scientists, and pharmacists from research centers, medical centers, professional societies, industry, and government agencies. Full details for the CNC and its members can be viewed at: https://www.copdfoundation.org/Research/Research-Projects-and-Consortia/COPDF-Nebulizer-Consortium.aspx.

This report was developed by the guidance committee of the CNC and aims to inform the safe use of nebulized therapies for patients and providers and to address key

ABBREVIATIONS: AGP = aerosol-generating procedure; CNC = COPD Foundation Nebulizer Consortium; HCW = health care worker; HFNC = high-flow nasal cannula; JN = jet nebulizer; PPE = personal protective equipment; VMN = vibrating mesh nebulizer

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TABLE 1] Aerosol Types and Definitions

Aerosol Type	Definition
Bioaerosol	Exhaled aerosols comprised of small droplets of airway-lining fluid. Provides an important vector for the spread of infectious diseases.
Medicinal or medical aerosol	Aerosol particles created by a nebulizer and derived from medication.
Fugitive aerosol	Aerosols released from the nebulizer during patient expiration; includes medicinal aerosols not inhaled by the patient but that pass into the atmosphere.

TABLE 2] Current Published Recommendations for Nebulizer Use During the COVID-19 Pandemic

Organization	Recommendation (and Setting Where Appropriate)
American Association for Respiratory Care, 2020	States that if a nebulizer must be used during mechanical ventilation, a closed system that does not break the circuit is desirable. The use of pressurized metered-dose inhalers to deliver bronchodilators may be more prudent.[13]
European Centre for Disease Prevention and Control, 2020	Guidance on infection prevention and control preparedness for COVID-19 in health care settings states that infection risk linked to nebulized treatment is unclear; no specific recommendations regarding nebulizer use.[11]
Global Initiative for Asthma, 2022	Where COVID-19 is confirmed or suspected, or local risk is moderate or high, recommends avoiding the use of nebulizers where possible and switching to inhalers. If the use of a nebulizer is required in a setting where COVID-19 infection is possible, infection control procedures should be followed.[14]
Global Initiative for Chronic Obstructive Lung Disease, 2022	Where possible, recommends using inhalers instead of nebulizers because of the potentially increased risk of infection with nebulizers. Nebulizers may be needed in patients who are critically ill with COVID-19 receiving ventilatory support. In this case, it is vital to keep the circuit intact and prevent the transmission of the virus. Using a vibrating mesh nebulizer in patients who are ventilated allows for the addition of medication without requiring the circuit to be broken for aerosol drug delivery.[15]
Health Protection Surveillance Centre, Antimicrobial Resistance and Infection Control Team, Ireland, 2020	Guidance on COVID-19 states that delivery of nebulized medications via a simple mask is unlikely to pose an increased risk of transmission of respiratory infections because of low levels of droplet dispersion and the health care worker not being close to the airway.[10]
International Society of Aerosols in Medicine, 2020	Medical aerosols from nebulization derive from a nonpatient source (the fluid in the nebulizer chamber) and have not been shown to carry patient-derived viral particles. Concerns of medical aerosol becoming contaminated in the lungs before exhalation are not supported by evidence. Recommends avoiding so-called breaking open of the ventilator circuit to add medication or change nebulizers—this generates aerosol from condensate that may be infectious; recommends use of a vibrating mesh nebulizer that maintains pressure in the ventilator circuit, or, if a jet nebulizer is used, a valved T adapter should be used in line with the ventilator circuit.[4]
Spanish Multidisciplinary Group, 2020	Classifies nebulized treatments as a high-risk procedure for viral transmission and recommends using pressurized metered-dose inhalers with a valved holding chamber whenever possible.[17]
Surviving Sepsis Campaign, international, 2020	Guidelines on the management of critically ill adults with COVID-19 recognize nebulized treatment as an aerosol-generating procedure, but do not discourage its use. Recommends appropriate personal protective equipment, including a fitted respirator, during nebulizer administration.[16]
Centers for Disease Control and Prevention, United States, 2022	COVID-19 guidance recommends continuing any required nebulizer treatments as recommended by national professional organizations; uncertainty exists regarding whether aerosols generated by nebulizer administration pose an increased risk of infection.[8]
World Health Organization, 2020	States that evidence is insufficient to classify nebulizer therapy as an aerosol-generating procedure that is associated with transmission of COVID-19. More research is needed.[12]

questions surrounding safe medication delivery with nebulizers during infectious respiratory disease outbreaks in situations where they are deemed medically necessary.

Study Design and Methods

In this narrative review, the lead and senior authors (I. N. B. and R. D., respectively) conducted a comprehensive PubMed search of the global literature and existing guidelines regarding nebulization (published from 2000 through 2022). They used a variety of search terms including *nebulization*, *guidelines*, *coronavirus transmission*, *infection transmission*, *inhaler technique*, and *mitigation strategies*, and other terms as appropriate for each section of the review. Abstracts were reviewed to identify articles appropriate for inclusion. In addition, the references of the articles were scanned to identify relevant articles that may have been missed in the initial search. The information from the selected articles was synthesized into key topics and questions as presented below, and statements were developed to guide the safe use of nebulization for both patients and providers.

A modified Delphi method was used with the entire CNC team in which these statements were proposed initially by consensus over several rounds, with discussion in between, and were categorized for relevance to the health care and home environments. The draft statements were presented to the full author group for a single round of anonymous voting using a five-point Likert scale (from strongly agree to strongly disagree) to ascertain the level of agreement on each statement, with revisions made where necessary. Seventy-five percent agreement (strongly agree or agree) was needed for endorsement of the statement. The key questions and relevant evidence are discussed by topic below, with the finalized expert statements for the health care setting and the home environment tabulated separately and the strength of agreement indicated for each statement.

Results

The initial literature search and review of references identified > 300 articles. After reviewing the abstracts and their citations, we selected 86 relevant articles that ultimately were included for this review.

How Does Nebulizer Design and Delivery Interface Impact Fugitive Aerosol Emissions?

Fugitive aerosols are released during nebulized treatment and consist of bioaerosols, which are exhaled by infected individuals during normal tidal breathing or while talking, coughing, or sneezing, and medical aerosols, which are generated by an aerosol device and escape into the environment before inhalation by the patient (Table 1).[22,23] Medical aerosols also could contain bioaerosols if the aerosol device is contaminated during use (eg, because of improper cleaning of the nebulizer cup or by coughing or drooling into the nebulizer cup).[24] An additional type of particle in aerosols might be mixed particles containing patient-derived material mixed with treatment-derived material via mechanisms such as particle agglomeration or contamination of the aerosol-generating device with oral or respiratory secretions.

The risk of contamination and dispersion of fugitive aerosols is influenced by nebulizer design, delivery circuit, and patient interface.[25] Various nebulizers (Table 2) have been reviewed previously[26,27]; examples of common types of nebulizers are shown in Figure 1. The design of some jet nebulizers (JNs) potentially allows the gravitational flow of a patient's secretions into the medication reservoir, causing contamination, and the continuous airflow contributes to aerosol dispersion to the environment (Table 3).[28,29] In contrast, active vibrating mesh nebulizers (VMNs) do not require a driving gas and the medication chamber is physically separated from the patient's secretions. Ultrasonic nebulizers have an open connection between the patient and the solution chamber (like JNs); they are unable to nebulize suspensions and also may denature some medications.[30]

Nebulized medications can be delivered using a face mask or mouthpiece or, if needed, a T-piece connecting a nebulizer to a tracheostomy tube in spontaneously breathing patients.[31] For patients requiring respiratory support, the aerosolized drug can be delivered with a high-flow nasal cannula (HFNC), noninvasive ventilation, or mechanical ventilation by connecting the nebulizer in line with the breathing circuit.[32]

Harnois et al[33] compared fugitive aerosol concentrations at baseline, during, and after treatment in nine healthy volunteers in an ICU room who received nebulized treatment with one type of JN or a VMN, with both mouthpiece and mask applications. They found higher aerosol concentrations in the room with the JN vs the VMN and with a face mask vs a mouthpiece. In a study to evaluate fugitive aerosol emissions into the environment during nebulization, McGrath et al[34] connected a standard JN or VMN to a breathing simulator using either a mouthpiece or a face mask. Lower fugitive aerosol concentrations were recorded with the VMN compared with the JN across all interfaces used, but only valved face masks were used with the VMN, whereas open face masks were used with the JN. For both nebulizer types, using an unfiltered mouthpiece generated less fugitive aerosol than a face mask.

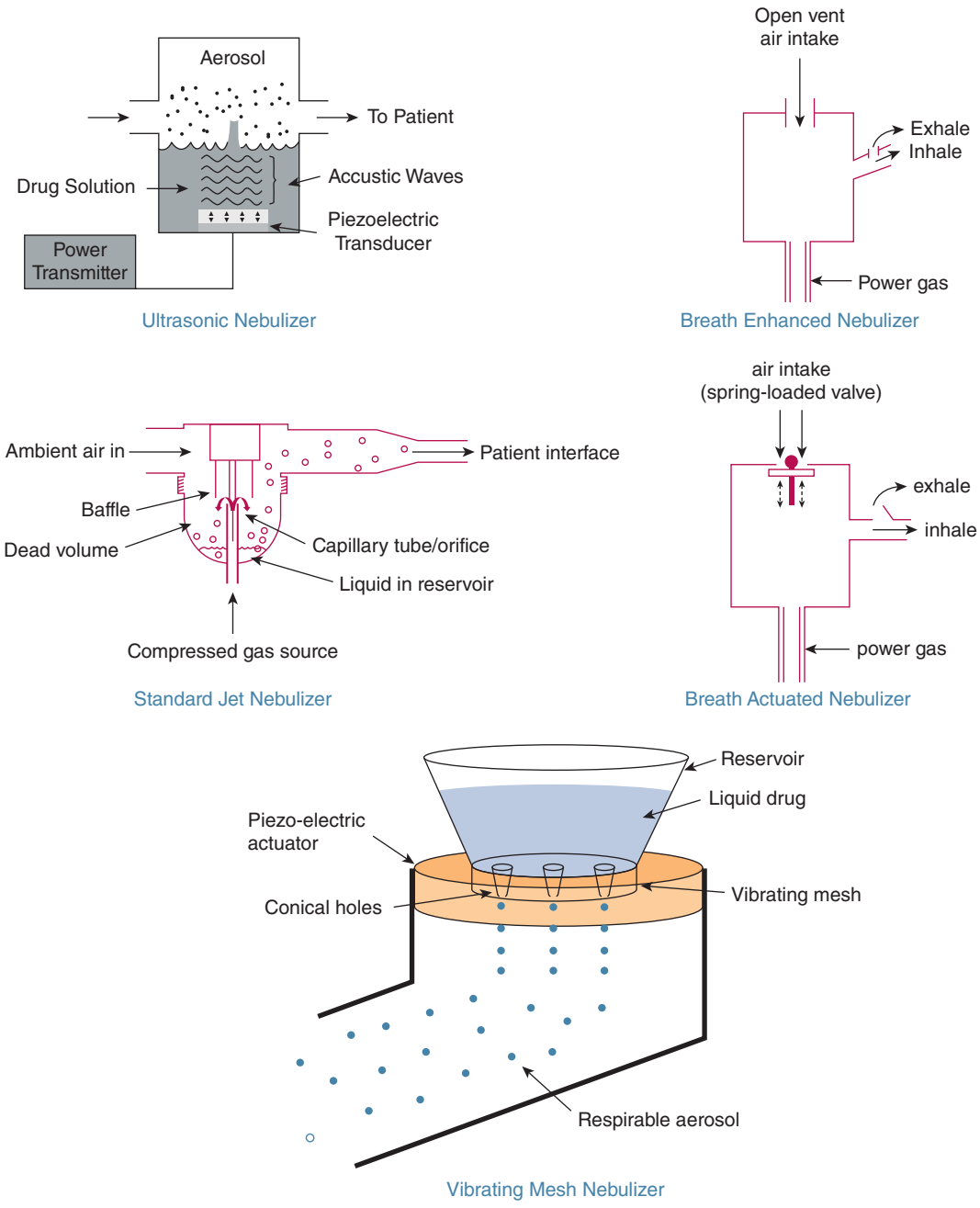

Figure 1 – *Illustrations of different types of nebulizers.*

In delivering nebulized medication with an HFNC in a simulated adult breathing profile, fugitive aerosol emission decreased as the flow rate was increased when delivered by either nasal cannula or tracheostomy.[22] It is believed that increasing turbulent flows with higher flow rates cause impactive aerosol losses within the tubing.[35] Fugitive aerosol concentration was higher for the tracheostomy interface compared with the HFNC. In a separate study, the amount of aerosol collected at the exhaust outlet of a mechanical ventilator was quantified when aerosol was delivered using a continuous JN with and without filters in the expiratory limb.[36] Without filters, bystanders were at risk of being exposed to 45% of the nominal dose of the aerosol compared with 0.25% when proprietary filters (PB 840; Covidien-Nellcor and Puritan Bennett) were used. A recent randomized controlled trial compared fugitive aerosols from nebulization in line via two different HFNC systems (Airvo 2 [Fisher and Paykel Healthcare] and Vapotherm [Vapotherm, Inc]).[37] Nine healthy

volunteers received a HFNC alone and with VMN nebulization (Aerogen Solo [Aerogen, Inc]) with both systems. In addition, the investigators compared the mitigation effect of a scavenger mask and a surgical mask placed over the cannula. They demonstrated higher inhaled doses and fugitive aerosols with the Airvo 2 during nebulization compared with the Vapotherm, which can be explained by the low inhaled dose with the Vapotherm in the in vitro studies. Placing a surgical mask over the cannula effectively reduced fugitive aerosol concentration in the room during HFNC application.[37]

Overall, few studies have explored exposure to fugitive aerosols associated with different nebulizer designs, delivery circuits, and patient interfaces. Future studies to understand the effect of these variables on aerosol dispersion are crucial to developing mitigation strategies and policies that ensure safe nebulized medication delivery in both health care and home environments.

Is Drug Delivery by Nebulization an Aerosol-Generating Procedure?

The World Health Organization considers the current evidence insufficient to classify nebulizer therapy as an AGP that is associated with COVID-19 transmission.[12] Although increased dispersion distance of aerosols during nebulizer therapy has been reported in several studies, no conclusive evidence exists that these dispersed particles are generated by the patients receiving nebulization or that they contain infectious particles (Table 4).[33,38-43] Tang et al[44] used live-attenuated influenza vaccine as a surrogate virus tracer and a Collison nebulizer (CH Technologies) to generate expiratory flow from a heated manikin wearing a portable JN and detected the virus in air samples from three different locations around the manikin's bed using an influenza-specific digital polymerase chain reaction assay. They concluded that nebulization should be considered a potential AGP; however, dispersion without using the JN was not evaluated, and therefore the authors' conclusion may not be valid.

In the CNC's opinion, evidence from the published literature is insufficient to classify nebulized therapy as an AGP. Available studies have demonstrated an increase in aerosol concentrations with nebulized therapy, but either have not been able to distinguish between medical and bioaerosols in the aerosols generated or have not been able demonstrate increased viral dispersion in comparison with other respiratory activities such as coughing and shouting.

Is the Risk of Infection Transmission Increased With Nebulized Therapy?

Studies conducted before the COVID-19 pandemic that mostly involved coronaviruses (severe acute respiratory syndrome coronavirus 1 and Middle Eastern respiratory syndrome coronavirus) suggested an increased risk of infection associated with nebulized therapy.[45-50] Two meta-analyses showed increased odds of transmission of coronaviruses resulting from nebulized treatment.[18,45] However, most of the included studies involved a small number of health care workers (HCWs) with variable use of personal protective equipment (PPE). In a large cohort study including 420 front-line HCWs (116 doctors, 304 nurses) who were equipped with appropriate PPE, 197 performed at least one aerosol inhalation procedure, and no SARS-CoV-2 transmission was reported.[48] More recently, a post hoc subanalysis of the Respiratory Protection Effectiveness Clinical Trial, including 137 outpatient sites at seven United States health systems (2011-2016), yielded a univariate OR of 1.81 (95% CI, 1.34-2.42) for laboratory-confirmed endemic coronavirus infection (strains HKU1, OC43, NL63, or 229E) vs no coronavirus infection among HCWs performing nebulizer treatments (devices not stated).[46] This finding should be interpreted with caution because the trial was not designed or powered specifically to assess coronavirus infection as an isolated outcome and was not adjusted for severity of infection, and the laboratory-confirmed endemic coronavirus infections for each AGP were analyzed and reported as univariate, not multivariate, ORs.[46]

Concerns were raised that nebulizer use may have played a role in a large cluster of SARS-CoV-2 infections, despite rigorous infection control policies, in an acute care hospital in the United States in 2020.[51] However, the infected staff members were more likely to report interacting with other staff members with positive SARS-CoV-2 results and reported lapses in their use of PPE. The index patient in this cluster resided in a positive pressure room and was probably infecting staff and patients for about 1 week before detection. The largest investigation of SARS-CoV-2 in hospital and patient room air involved a total of 310 air samples, of which nine samples were obtained while nebulizer treatment (device types not specified) was being administered; none of these nine samples showed positive results for SARS-CoV-2 (by reverse transcription-quantitative polymerase chain reaction targeting the SARS-CoV-2 N gene).[52] One limitation of this study is that the lower particle size limit of the air

TABLE 3] Comparison of Characteristics of Jet, Vibrating Mesh, and Ultrasonic Nebulizers[a]

Features	Jet Nebulizer	Vibrating Mesh Nebulizer	Ultrasonic Nebulizer
Power source	Compressed gas or electrical mains	Batteries or electrical mains	Electrical mains
Portability	Limited	Portable	Limited
Process of aerosolization	Pressurized gas flows through a narrow jet at 2-10 L/min and drug is aerosolized by the Venturi effect	Micropump technology generates aerosol by forcing the drug solution through multiple apertures without the need for a driving gas	Ultrasonic waves are focused on the surface of the drug solution to generate aerosols that are delivered by a fan or inspiratory flow to the patient
Treatment time	Long (depends on jet nebulizer type)	Short	Intermediate
Output rate	Low (depends on jet nebulizer type)	Highest	Higher
Residual volume	0.5-2.0 mL	Variable, but low	Variable, but low
Risk of environmental contamination			
Continuous use	High	High	High
Breath actuated	Low	Not applicable	Not applicable
Breath enhanced	Medium (low with filtered mouthpiece)	Not applicable	Not applicable
Performance variability	Low-high (depends on jet nebulizer type)	Low	Intermediate
Formulation characteristics			
Concentration	Increases	No change	Variable
Temperature	Decreases	Minimal change	Increases
Suspensions	Low efficiency	Variable	Poor efficiency
Denaturation[a]	Possible	Possible	Probable
Cleaning	Required; single-patient use	Required; single-patient use	Required; multiple-patient use
Cost	Very low	High	High

(Adapted from Dolovich and Dhand[26]).
[a]Denaturation of DNA occurs with all the nebulizers.

TABLE 4] Studies Evaluating Nebulization as an Aerosol-Generating Procedure

Study and Country	Population Characteristics and Setting	Intervention and Exposure	Outcomes	Comments
Harnois et al (2022),[33] United States	Healthy adult volunteers in an ICU room (n = 9)	Saline delivered by a SVN or VMN with various interfaces	Fugitive aerosol (0.3-5.0 μm) concentrations were higher than baseline for both the SVN and VMN, whether using a mouthpiece or mask. SVN produced higher fugitive aerosol concentrations than VMN.	The study evaluated fugitive aerosols as a whole and did not distinguish between medical aerosols and bioaerosols.
Hui et al (2009),[38] China	A human patient simulator. Lung compliance and oxygen consumption programmed to mimic three different lung conditions: normal, mild lung injury, and severe lung injury in an isolation room.	A continuous flow JN using a face mask	The maximum dispersion distance was > 0.8 m, with the distance increasing when worsening lung injury was mimicked.	Prior studies by the same group[39,40] in manikins receiving oxygen by a simple mask delivered at 6 L/min or NIV showed maximum exhaled air dispersion distances of 0.22 m and 0.45 m, respectively.
Simonds et al (2010),[42] United Kingdom	Three different adult groups: healthy participants (n = 12), patients with coryzal symptoms (n = 11), and patients with chronic lung disease admitted with an infective exacerbation (n = 21). Experiments were conducted in a standard patient room.	Spontaneous coughs with and without a surgical mask, oxygen via a ventimask, NIV with a nonvented full-face mask, NIV with a vented mask, and nebulized saline using a standard JN with a mouthpiece	Increases in all groups of droplet sizes ranging from 0.3 to 3.5 μm at positions adjacent to the patient's mouth and a distance of 1.0 m were observed with the use of JN.	It was impossible to separate droplets generated by the nebulizer from those generated by the patient because the nebulizer generated droplets with a mass mean diameter of 3.3 μm and 72% of droplets were < 5 μm in diameter. Droplets used as a proxy for viral dissemination, and therefore unclear if droplet count confers increased infection risk.
Wan et al (2004),[43] Taiwan	A single patient with confirmed SARS infection in a negative pressure room	Treatment with a large-volume nebulizer	None of the environmental samples revealed any positive SARS-CoV-1 findings using filter sampling and SARS-CoV-1-specific reverse transcriptase-polymerase chain reaction.	This was a study of only one patient.
O'Neil et al (2017),[41] United States	Inpatients on contact precautions for DROs and patients undergoing bronchoscopy	Patient care activities including nebulized medication administration, bronchoscopy, NIV, bathing, changing bed linens, pouring, and flushing liquid waste	Nebulized medication administration significantly increased aerosol particle concentrations in air sampled from patient rooms compared with prenebulization baseline, but DROs were not recovered from any of the samples.	Details of the nebulizer type, delivery interface, or whether the DROs were respiratory pathogens were not given.

DRO = drug-resistant organism; JN = jet nebulizer; NIV = noninvasive ventilation; SARS = severe acute respiratory syndrome; SARS-CoV-1 = severe acute respiratory syndrome coronavirus 1; SVN = small-volume nebulizer; VMN = vibrating mesh nebulizer.

TABLE 5] CNC Guidance Statements and Strength of Agreement for Nebulizer Drug Delivery in Patients With Respiratory Infections in the Health Care Setting With Respect to the Generation of Fugitive Aerosols[a]

Guidance Statements: Health Care Setting	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Mean Rank[b]
1. **While administering nebulizer therapy to patients with respiratory infections, health care workers should wear a mask, preferably an N95 respirator.**[c]	79.2	20.8	0.0	0.0	0.0	1.79
2. **A mouthpiece with an attached filter should be the preferred interface if the patient can use it effectively.**	70.8	25.0	4.2	0.0	0.0	1.67
3. **Aseptic techniques should be adhered to during the medication loading process.**	79.2	8.3	12.5	0.0	0.0	1.67
4. **Patients should be instructed to exhale through the mouthpiece and not to remove the interface while the nebulizer is still running.**	66.7	25.0	8.3	0.0	0.0	1.58
5. ***A proprietary filter[d] should be attached to the expiratory limb of the ventilator circuit to capture exhaled aerosol.***	58.3	37.5	4.2	0.0	0.0	1.54
6. **Face masks with exhalation filters or scavenger systems are an alternative if a mouthpiece is not appropriate.**	50.0	33.3	16.7	0.0	0.0	1.33
7. ***In a patient receiving mechanical ventilation, a valved T adapter should be used to connect a jet nebulizer in the circuit so as to avoid depressurizing the circuit during the medication loading process.***	41.7	37.5	20.8	0.0	0.0	1.21
8. ***For patients receiving noninvasive ventilation, a mask with a good seal and an expiratory filter placed on the expiratory port of the circuit should be used. Vented masks should be avoided.***	37.5	45.8	16.7	0.0	0.0	1.21
9. **Disposable[e] jet nebulizers are preferred over reusable jet nebulizers.**	33.3	54.2	12.5	0.0	0.0	1.21
10. **For a patient undergoing nebulized therapy, the use of negative-pressure rooms, disposing of used equipment after use, and maintaining an appropriate distance from the patient are important considerations.**[c]	33.3	50.0	16.7	0.0	0.0	1.17
11. **A T piece with an expiratory filter is preferred for spontaneously breathing patients who have undergone tracheostomy.**[f]	45.8	37.5	8.3	0.0	8.3	1.13
12. **Patients receiving nebulized medication by high-flow nasal cannula should wear a surgical face mask over the mouth and nose.**	33.3	45.8	16.7	4.2	0.0	1.08
13. Jet nebulizers with breath-actuation mode are preferred over those with continuous mode.	29.2	41.7	20.8	8.3	0.0	0.92
14. Where indicated, vibrating mesh nebulizers are preferred over jet nebulizers in patients with respiratory infections to reduce fugitive aerosol emissions.[g] This applies to patients with or without respiratory support.[f]	33.3	20.8	25.0	8.3	12.5	0.54

Data are presented as percentages except for mean rank. Boldface statements reached the 75% agreement threshold. Italicized statements are specific to ventilators. CNC = COPD Foundation Nebulizer Consortium.

[a]The 24 CNC members who authored this article all voted on each of the 14 guidance statements.

[b]Calculated using a numerical rank assignment according to a Likert scale, as follows: strongly agree = 2, agree = 1, neutral = 0, disagree = −1, and strongly disagree = −2. Guidance statements are ordered by mean rank score.

[c]Centers for Disease Control and Prevention guidance includes considerations about the pathogen(s) involved, device instructions for use, availability of negative pressure rooms, and other available space,[73,74] using a layered approach to reduce exposures.[70]

[d]Defined as any filter that is required for use with a specific ventilator and that cannot be substituted easily with any other filter.[36]

[e]Refers to one-time use or use in a single patient for up to 24 h. Some fragile patients may need more intense interventions.

[f]Percentages do not total to 100% because of rounding.

[g]Some specific medication or device combinations must be used as prescribed.

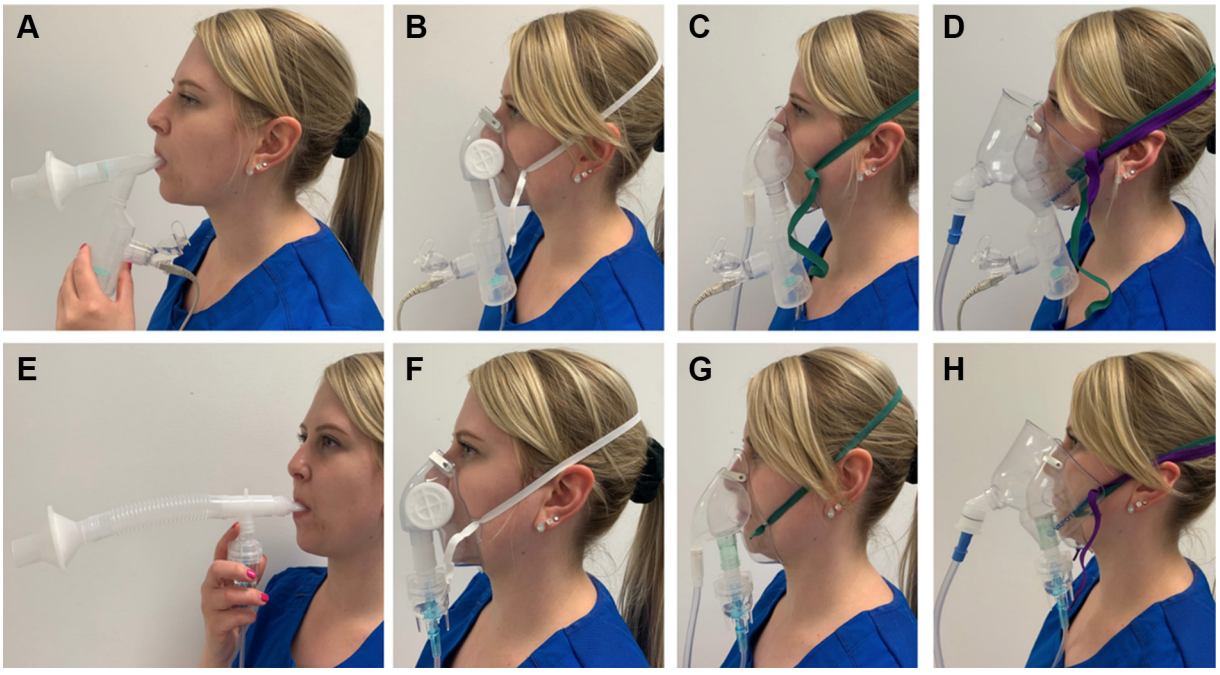

Figure 2 – *A-H, Photographs showing different devices to reduce fugitive aerosol concentrations: a mouthpiece with an expiratory filter, vibrating mesh nebulizer (VMN) (A) and small-volume nebulizer (SVN) (E); face mask with exhalation filters, VMN (B) and SVN (F); exhalo scavenger with an aerosol face mask, VMN (C) and SVN (G); Vapotherm scavenger with an aerosol face mask, VMN (D) and SVN (H). Reproduced with permission from Harnois et al.*[33]

TABLE 6] CNC Guidance Statements and Strength of Agreement for Nebulizer Drug Delivery in Patients With Respiratory Infections in the Home Environment With Respect to the Generation of Fugitive Aerosols[a]

Guidance Statements: Home Environment	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Mean Rank[b]
1. **Strictly adhere to the manufacturer's guidelines for cleaning and disinfecting the device.**	79.2	20.8	0.0	0.0	0.0	1.79
2. **Adhere to aseptic principles during the medication loading process.**	62.5	25.0	8.3	4.2	0.0	1.46
3. **Treatments should be administered either in an area where the air is not recirculated into the house or near an open window.**[c]	29.2	54.2	16.7	0.0	0.0	1.13
4. **In general, continuous jet nebulizers should be used and in a separate room with no other people present, if possible.**[d]	37.5	37.5	20.8	4.2	0.0	1.08
5. **A mouthpiece is preferred over a face mask. Face masks with exhalation filters may be used.**	20.8	66.7	12.5	0.0	0.0	1.08
6. **Air purifiers may be used and should be placed in a favorable location.**[c]	29.2	50.0	16.7	4.2	0.0	1.04
7. For optimal safety, those physically close to the individual receiving nebulized therapy should wear a mask, preferably an N95 respirator.[c]	29.2	37.5	29.2	4.2	0.0	0.92
8. Disposable[e] jet nebulizers are preferred over reusable jet nebulizers.	12.5	50.0	25.0	8.3	4.2	0.58

Data are presented as percentages except for mean rank. Boldface statements reached the 75% agreement threshold. CNC = COPD Foundation Nebulizer Consortium.

[a]The 24 CNC members who authored this article all voted on each of the eight guidance statements.

[b]Calculated using a numerical rank assignment according to a Likert scale, as follows: strongly agree = 2, agree = 1, neutral = 0, disagree = −1, and strongly disagree = −2. Guidance statements are ordered by mean rank.

[c]Percentages do not total to 100% because of rounding.

[d]Some specific medication or device combinations must be used as prescribed.

[e]Refers to one-time use or use in a single patient for up to 24 h.

sampling collection method (approximately 0.5 μm) excluded the presence of viruses in smaller aerosol particles.

Few investigators have evaluated the risk of transmission of infections, other than coronaviruses, among patients, HCWs, or both with nebulized treatment. Kuster et al[53] found that HCWs with symptomatic influenza more likely were present during AGPs (adjusted OR, 2.0; 95% CI, 1.1-3.5) during the 2009 influenza A (H1N1) pandemic. Administration of nebulized therapy was identified as an AGP in this study; however, the risk associated with individual types of AGPs was not evaluated, and the specific nebulizer devices were not reported. Among patients with HIV with multidrug-resistant TB, administration of pentamidine via nebulization was implicated in higher numbers of cases of subsequent multidrug-resistant TB in exposed patients.[54] Risk factors for the transmission of multidrug-resistant TB include an inadequately ventilated environment.[55]

In summary, most published literature either is inconclusive or did not substantiate a direct relationship between nebulized therapy and the transmission of infections, and no studies actually have verified virus viability in dispersed aerosols because detection was by polymerase chain reaction, which indicates only the presence of genetic material.[44] Importantly, no reports indicate increased transmission risk when guidelines for appropriate PPE are followed adequately. Understanding the importance of access to nebulized therapies in inpatient settings, the CNC concludes that adherence to recommended safety measures[33,37] should be emphasized, and at the same time, nebulizer use should not be discouraged when clinically indicated. Large, well-designed prospective observational studies with microbiologic analysis of generated aerosols are needed to clarify whether nebulizers present an additional risk for transmission of SARS-CoV-2 or other infections to HCWs.

What Are the Risks of Secondary Exposure to Aerosolized Medication During Nebulizer Treatment?

Unintended health consequences have been reported in HCWs administering nebulized medications, including pentamidine, ribavirin, antibiotics, and albuterol, to patients.[32,56-60] Although the CNC is aware of the importance of this topic, further discussion is beyond the scope of this report.

What Mitigation Strategies Are Effective for Enhancing the Safety of Aerosol Drug Delivery?

Several mitigation strategies have been proposed to ensure the safe use of nebulizers in health care and home environments (Fig 2). First, nebulizer use should be limited to patient populations who clearly benefit and in whom meter dose inhaler delivery is either impossible or ineffective. With respect to nebulizer type and patient interface use, two in vitro studies using a breathing simulator and a small study in healthy human patients reported that, regardless of the patient interface used, VMNs generated fewer fugitive aerosols than continuous JNs.[33,34,61] The combination of a VMN with a filtered mouthpiece generated the least amount of fugitive aerosol.[33,34] Furthermore, measurements with an aerodynamic particle sizer showed that a VMN (combined with a valved spacer) produced the lowest fugitive emissions compared with a JN used in continuous mode or breath-actuated mode.[61] Use of a filter with a mouthpiece or scavenger with a mask reduces fugitive aerosols for both devices. Using a face mask generated higher fugitive aerosols than a mouthpiece, and using an exhalation filter or scavenger system with the face mask was as effective as a filtered mouthpiece in reducing fugitive aerosols.[33] With the caveat that these studies evaluated a single VMN relative to a single JN, if emissions are of concern in a particular administration setting, use of a filter system may be warranted. In cases where using a mouthpiece is not feasible because of mental or physical disabilities, a fitted face mask with expiratory filters or one of the commercially available scavenger systems can be used. If a JN must be used, these mitigation strategies also are effective in reducing fugitive aerosol emissions.[33,34] A breath-actuated nebulizer further reduces fugitive emissions compared with a constant-output nebulizer.[32,61-63] During simulated adult breathing, dosimetric nebulizers (that produce an aerosol only when the patient presses a button) showed the lowest drug lost to the ambient air compared with constant-output nebulizers or breath-enhanced nebulizers.[64] Breath-actuated JNs also have shown a $< 20\%$ change in respirable delivered dose across different inhalation to exhalation ratios (1:1 to 1:4).[65] Similarly, during simulated methacholine bronchoprovocation testing, particle generation was reduced significantly with breath-enhanced and breath-actuated delivery compared with continuous nebulization.[66] Extractor tents act as a type of local exhaust ventilation and consist of a tent surrounding the patient with an exhaust air passage via a

high-efficiency particulate air filter that captures and removes fugitive aerosol emissions at source.[67] To reduce fugitive aerosols, patients should not remove the mouthpiece or face mask while the nebulizer is still running[68]; use of a breath-actuated delivery device could mitigate this concern.

In-Hospital Use: Disposable nebulizers are suggested for use in the hospital setting to address the potential risk of contaminating the medication reservoir of a JN during treatment. After each use, the residual medication should be rinsed out with sterile water, the mouthpiece or face mask should be wiped with an alcohol pad, and the nebulizer should be discarded after 24 h.[69] Reusable nebulizers should be cleaned, disinfected, and rinsed with sterile water or reprocessed after each use. JNs with drool guards prevent the flow of patient secretions into the open medication reservoir and potentially can reduce the risk of contamination of the reservoir and subsequent aerosolization. Regardless of the nebulizer type, bioaerosol generation can occur if the reservoir is contaminated during the medication loading process, and therefore this procedure needs to be performed using aseptic techniques.[4]

The hierarchy of controls espoused by the National Institute for Occupational Safety and Health in the United States can be used to reduce the risk of exposures to workplace hazards.[70] Wearing of PPE is one component of this hierarchy. Although wearing a face mask can reduce exposure to particulates, a National Institute for Occupational Safety and Health-approved N95 respirator is designed to reduce exposure to aerosols more efficiently than a surgical mask,[71,72] a characteristic that depends, in part, on facial fit and properly wearing it during the period of exposure. Practice guidelines that include standard and transmission-based precautions can be used to inform specific scenarios.[73,74]

Spontaneously Breathing Patients With a Tracheostomy and Patients Receiving Assisted Ventilation: A T-piece with an expiratory filter should be used to deliver nebulized treatments to spontaneously breathing patients with a tracheostomy, and masks placed over the tracheostomy tube do not prevent aerosol escape into the environment adequately and should be avoided.[31] A prospective, randomized, crossover trial with 12 spontaneously breathing patients who received a tracheostomy reported no differences in ambient aerosol particle concentrations among five different humidification devices and interfaces, including at baseline with a heat-moisture exchanger.[75] In contrast, significant aerosol generation higher than baseline was reported during simulated tracheostomy surgical and clinical conditions; the use of different tracheostomy coverings significantly reduced aerosolization, with the greatest reductions seen with simultaneous use of a surgical mask and heat-moisture exchanger.[76] A simple surgical face mask placed over the mouth and nose effectively reduces droplet dispersion during the use of an HFNC.[77,78] Therefore, it is likely to reduce fugitive aerosol emissions when nebulized treatment is delivered with an HFNC. When nebulized therapy is used in patients receiving noninvasive ventilation, a well-fitted mask with a good seal and an expiratory filter placed distal to the exhalation valve reduces the escape of aerosols into the environment.[25] Vented masks should be avoided in this setting, if possible. During mechanical ventilation, explosive depressurization that occurs by breaking the closed circuit could release bioaerosols into the environment. A JN should be used with a valved T adapter, which allows the nebulizer to be removed without breaking the circuit.[4] Using a VMN allows the medication to be reloaded without breaking the circuit, and it can stay in line for up to 28 days.[79] The JN, with its open reservoir below the ventilator circuit, allows for a potential flow of circuit rainout and patient secretions into the medication cup and subsequent aerosolization.[4] The VMN does not have an open reservoir, and the device's design separates the aerosol-producing mechanism from contact with the patient interface.[4] The ventilator should be operated with a filter on the expiratory limb. Filters designed for use with specific ventilators (ie, proprietary filters) typically are larger, more complex, high-efficiency particulate air filters that can remove aerosols efficiently for a longer time before increasing resistance to gas flow compared with nonproprietary filters, and therefore the former are suggested during mechanical ventilation.[36]

Home Use: Suggestions for device and interface selection in the hospital setting, such as the use of VMNs, may not be feasible for nebulizer use in the home environment. Nebulizer access at home may be governed by insurance coverage, affordability, or drug label indications. From a practical perspective, JNs are used most widely and are the standard of care for the delivery of nebulized medications at home. A filtered mouthpiece attached to a breath-enhanced JN significantly reduced fugitive emissions to $< 1\%$ of the total amount of aerosolized drug in an in vitro study.[80]

Aerosol treatment should be administered in a location where the air is not recirculated into the house.[81,82] Operating the nebulizer near open windows and in areas with increased air circulation,[83] using one or more air purifiers,[84,85] minimizing the number of household members, or a combination thereof could reduce the risk of household exposures to fugitive aerosols further.

What Is the Importance of Access to Medications Administered by Aerosol Delivery Devices: Handheld Device, Nebulization, or Both?

No single aerosol delivery device is suitable for all patients. It is critically important to develop a personalized approach to device selection, one that considers patient satisfaction with the aerosol device because this may impact adherence to treatment and clinical outcomes. Further discussion around selection of the right device for the right patient is provided in e-Appendix 1.

CNC Guidance for Nebulizer Drug Delivery

The culmination of this guidance from the CNC is the provision of guidance statements to help patients, caregivers, and providers in the safe use of nebulized therapies at a time when the COVID-19 pandemic has heightened the need for updated guidance. Understanding that nebulizer use varies by setting, two sets of guidance statements are provided: one specific to nebulizer use in the health care setting (Table 5)[36,70,73,74] and the other specific to nebulizer use in the home environment (Table 6). The extent to which the CNC members who authored this guidance agreed with each statement is indicated. Additional discussion of the guidance statements is provided in e-Appendix 2.

Conclusions and Future Directions

The overall safety of administering aerosol treatments by nebulization during a pandemic has been questioned; the lack of objective evidence and differing opinions precludes making a conclusive statement. Current evidence supporting the increased risk of disease transmission with nebulized treatments is inconclusive. Nevertheless, it is prudent to develop strategies to minimize fugitive aerosol emissions and to minimize exposure with appropriate PPE during nebulized treatments, particularly for patient care in the context of a highly transmissible virus such as SARS-CoV-2. Understanding that nebulizer design, delivery circuit, and patient interface impact the dispersion of fugitive aerosols is key to developing such strategies. We propose strategies for nebulizer use in both the health care and home environments, based on the best and limited available evidence. Future studies need to explore the risk of transmission with fugitive aerosols that is associated with different nebulizer types and delivery circuits in real patient care situations, and the effectiveness of various mitigation strategies in reducing this risk.

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Additional information: The e-Appendixes are available online under "Supplementary Data."

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