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## Short review

## Guidance on nebulization during the current COVID-19 pandemic

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## ABSTRACT

Awareness of the risk of airborne transmission of SARS-CoV-2 makes patients hesitant about using inhaled medications that are considered as a potential source of viral transmission and immunosuppression. However, patients with asthma or COPD should continue all prescribed inhaled medications. Apparently, inhalers, including pMDIs, DPIs, or SMIs, have a low risk of contamination although characteristics of drug formulation can precipitate cough, whereas some researchers do not rule out the probability that nebulizer treatments may increase the risk of infection transmission via droplet nuclei and aerosols. Considering that aerosol therapy generates fugitive emissions that are not inhaled by the patient and are released from the device during expiration, several international professional bodies have provided recommendations for drug delivery via inhalers and in particular, nebulizers. Unfortunately, these recommendations are often in conflict with each other and do not clarify whether it is appropriate to use nebulizers during this COVID-19 pandemic. Considering what is available in literature, there are no known infection-related hazards to an uninfected patient and also a patient with COVID-19 that preclude the use of a nebulizer at home, but it is fundamental that all patients, regardless of whether or not suffering from COVID-19, always follow some practical advices.

## 1. The problem

An increasing body of evidence is documenting that most transmission of SARS-CoV-2 is via the respiratory route, with the virus that is included in droplets or, less commonly, in aerosols [1]. Transmission dynamics are extremely heterogeneous, and some super-spreading events have a major role in supporting the epidemic [1]. In particular, these events affect mainly people who remain in close contact in indoor environments with poor ventilation for extended periods. It has not yet been established whether SARS-CoV-2 might spread through aerosols from respiratory droplets; so far, air sampling has found virus RNA in some studies but not in others [2]; however, apparently airborne transmission occurs when a susceptible individual inhales virus-laden fine respiratory droplets that remain viable in the environment [3]. The virus can be transmitted either directly by inhalation of fine droplets expelled from an infected person or during aerosol-generating procedures on an infected individual. Therefore, bioaerosols generated by infected patients are a major potential source of transmission for SARS-CoV-2 and other infectious agents [4].

Awareness of the risk of airborne transmission of the virus makes

patients hesitant about using inhaled medications because they are considered as a potential source of viral transmission and immunosuppression [5]. This hesitation on the part of patients frequently does not find a strong encouragement for such use by doctors, often due to lack of solid information. In particular, although there are a lot of discussions on COVID-19, little attention has been paid to patients with pulmonary diseases treated at home [5]. Anyway, many doctors and patients believe that it is important to avoid unnecessary aerosol therapy in patients with COVID-19 and pulmonary diseases treated at home [6].

However, against this point of view there are the guideline and strategy recommendation. In particular, in the 2020 version the Global Initiative for Asthma (GINA) strategy states that it is recommended that also during the COVID-19 pandemic all asthma patients continue all inhaled medications including inhaled corticosteroids, as prescribed by their doctor [7]. The presence of asthma in a well-controlled patient does not seem to increase the risk of infection from SARS-CoV-2 or developing complications due to COVID-19 [8]. Furthermore, the possibility that an infection with the coronavirus may cause an asthma exacerbation is currently not supported by any solid evidence [9]. Therefore, patients should continue their controller medications, ensure

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optimal control of asthma, and follow the other advice for the general public during this period (e.g. ensuring good personal hygiene, staying at home as much as possible, wearing masks in public areas, practising social distancing) [9]. Daily experience suggests that these advices are not a real problem for older people, who usually suffer more from COPD than asthma, but are not well accepted by young people who are the ones most likely to suffer from asthma, and this can be a problem when dealing with them. Also the GOLD strategy advises that patients with COPD must continue their regular therapy [10].

However, established treatments for both asthma and COPD are generally administered by inhalation. The GINA strategy recommends the use of inhaled corticosteroids and inhaled bronchodilators [11]. The GOLD strategy also recommends the use of bronchodilators always by inhalation and, in some circumstances, the addition of an inhaled corticosteroid [12]. However, the risk of airborne transmission of SARS-CoV-2 can make doctors and patients reluctant to follow these recommendations. In fact, aerosol and fomite transmission of SARS-CoV-2 is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces up to some days. Indeed, it has been shown that SARS-CoV-2 remains viable in the air with a half-life on the order of 1 h [13].

It is therefore easy to understand why national and international guidelines recommend droplet/airborne and contact precautions for those caring for COVID-19 patients in ambulatory and acute care settings [4]. Increased risk of transmission has been associated with aerosol generating procedures that include endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, noninvasive positive-pressure ventilation, tracheostomy, cardiopulmonary resuscitation [4]. Some of these procedures, such as intubation, open suctioning, tracheotomy, manual ventilation, and bronchoscopy can significantly increase the risk of production of bioaerosols possibly containing pathogens by the patient [4]. Others procedures, such as oxygen administration, high-flow nasal oxygen, and use of medical aerosols potentially act to disperse bioaerosols from the patient to the surrounding area but there is not evidence that they generate additional contaminated aerosols [4].

Nonetheless, it has been repeatedly suggested that aerosols produced by medical aerosol generators do not contain pathogens unless the aerosol device is contaminated [3]. Consequently, inhalers, including pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), or soft mist inhalers (SMIs), have a low risk of contamination [14].

However, some researchers do not rule out the probability that nebulizer treatments may increase the risk of infection transmission via droplet nuclei and aerosols. In fact, there is the potential to generate a high volume of respiratory aerosols that may be propelled over a longer distance than is involved in a natural dispersion pattern [15]. Furthermore, there is a real risk that larger particles may stimulate both patients' and bystanders' cough and thus increase the probability of spreading the disease [16]. These risks suggest that there is a possibility that nebulizer therapy in patients with COVID-19 infection can transmit potentially viable coronavirus to susceptible bystander hosts [15].

In any case, it has been pointed out that exhaled bioaerosols whether from cough or normal exhalation are neither avoided nor limited with use of pMDIs, DPIs or SMIs [4]. In effect, characteristics of drug formulation can precipitate cough with these inhalers [17]. There is no substantial difference in the mechanism of bioaerosol generation during cough associated with inhalers and common cough, which is independent of the inhaled drug and probably generates a large amount of bioaerosol [4]. Therefore, inhalers offer no innate advantage in reducing production or dispersion of patient-generated bioaerosols [4].

On the contrary, it should be noted that a 2012 assessment of three cohort studies investigating the transmission of coronavirus to healthcare personnel during the 2002–2003 SARS-CoV outbreaks found no significantly elevated risk of SARS-CoV transmission to healthcare

workers caring for patients undergoing nebulizer treatment [18]. It has also been demonstrated that the stability of SARS-CoV-2 in aerosols and on different surfaces was similar to that of SARS-CoV-1 under the experimental conditions tested [13]. Furthermore, a study performing polymerase chain reaction air sampling around a patient with SARS undergoing nebulizer treatment found no evidence of virus [19]. According to Minnesota Department of Health, nebulizer administration likely represents a lower infection risk than other aerosol-generating procedures, although it must always be considered that close-range viral aerosol generation remains a possibility [20].

Nebulizers are often used to deliver pharmaceutical aerosols in patient populations that cannot effectively use a pMDI (even with a spacer) or a DPI, in many patients that require ventilatory support via invasive mechanical ventilation or noninvasive ventilation, and also in those who suffer from a severe exacerbation, mainly if they present alterations of consciousness [21].

The burden and severity of COVID-19 has prompted several international professional bodies to provide recommendations on the management of chronic respiratory diseases in the current context of the COVID-19 pandemic regardless of whether the patient to be managed is infected with SARS-CoV-2 or not [9]. Unfortunately, due to lack of solid evidence in producing such recommendations or even guidelines, it was not possible to follow the consolidated rigid approach that is now applied for guidance development and it was necessary to rely on the conflicting currently available evidence and on the opinion of experts. This approach explains why recommendations often conflict with each other.

## 2. Recommendations for or against the use of nebulizers during the COVID-19 pandemic

According to the updated version of GINA strategy, where possible, use of nebulizers must be avoided because of the risk of transmitting infection to other patients and to healthcare workers [11]. In fact nebulizers can transmit respiratory viral particles for approximately 1 m. Instead, the recommendation is to use a pMDI and spacer, with a mouthpiece or tightly fitting facemask, if required, when short-acting  $\beta_2$ -agonist must be delivered to treat an acute asthma episode in adults and children.

The Australian National Asthma Council recommends against the use of nebulizers to administer inhaled medicines, unless unavoidable [22]. They stress that the use of nebulisers carries a high risk of transmitting viral infections because they generate aerosols that can spread infectious droplets for several metres and remain airborne for more than 30 min. If a patient with suspected or confirmed COVID-19 must unavoidably use a nebulizer, infection control procedures must be followed. These procedures include patient isolation, use of a negative-pressure area, if accessible, but if this is not available and there is no alternative, a single room with the door closed must be used. Staff administering nebulizers should wear full protection against airborne exposures, including impermeable gown and gloves, KN95 or FFP2 mask, and protective eyewear. These precautions must be continued for at least 30 min after the nebuliser treatment.

The American College of Allergy, Asthma and Immunology recommends to always consider that SARS-COV-2 may persist in droplets in the air for 1–2 h when a patient with suspected or confirmed COVID-19 uses a nebulizer at home [23]. Therefore, the nebulizer should be used in a location that reduces exposure to non-infected members of the household. The College recommends locations such as outside the house on a porch or patio or in a garage, where air is not recirculated into the home and dependent surfaces can be easier to clean (or may not need cleaning).

FADOI, an Italian Association of Internal Medicine, recommends the use of MDI or pMDI with spacer for spontaneously breathing patients in need of aerosol therapy [24]. The vibrating mesh nebulizer should be preferred when treating ventilated patients, but in this case it is

necessary to place an additional filter on the expiratory limb of the ventilator circuit during nebulization. It is essential to avoid opening the ventilator circuit to add medication or change nebulizers, because this generates aerosol from condensate that may be infectious.

On the contrary, the British National Institute for Health and Care Excellence (NICE) advises that patients with suspected or confirmed COVID-19 may continue to use their nebulizer because the aerosols produced by them are generated from fluid within the nebulizer chamber that does not carry patient-derived viral particles [25]. Indeed, if a particle in the aerosol comes into contact with contaminated mucous membrane, it ceases to be airborne and therefore will not be aerosolized. In any case, healthcare workers should use appropriate hand hygiene (wash hands and put on fresh gloves) when helping patients remove nebulizers and oxygen masks.

Also the British Thoracic Society supports use of nebulizers because they do not consider nebulization a ‘viral’ aerosol generating procedure in accordance with the advice from Public Health England and Health Protection Scotland [26]. In fact, nebulization is not a viral droplet generating procedure since the droplets are from the machine (liquid drug particles), not the patient.

In the view of the International Society of Aerosols in Medicine (ISAM), nebulized aerosols do not carry patient derived viral particles as they are generated from the fluid in nebulizer chamber, which is a nonpatient source [4]. Medical aerosols produced by nebulizers contain pathogens only when the patient or healthcare worker contaminates the nebulizers. In fact, there is no evidence to show that aerosols get contaminated in the lungs before exhalation also because when an aerosol droplet combines with contaminated mucous membrane, it can no longer be airborne and be a part of an aerosol [27].

In any case, the ISAM, based on the recommendations by the Centers for Disease Control and Prevention, advises that jet nebulizers should be replaced, rinsed, air dried, washed, disinfected, and/or sterilized after each treatment and points out that risk of bioaerosol dispersion exists in case of contamination of the reservoir during the medication loading process independent of the type of nebulizer used [4]. In fact, care providers may contaminate nebulizers when they handle medication and the device, but the possibility that also patients will contaminate nebulizers and the role of the nebulizer design should not be overlooked [3]. In effect, the patient’s secretions or exhaled bioaerosols can contaminate small-volume jet or ultrasonic nebulizers that are open to and positioned below the gas pathway and are directly connected to the patient interface (mouthpiece or endotracheal tube) [14]. This is not a problem with vibrating mesh nebulizers generating aerosols via mesh plates that separate the sealed medication reservoir from the patient interface [3]. Actually, during nebulization, the aerosol derives from the fluid in the nebulizer chamber and does not carry patient-derived viral particles. Furthermore, vibrating mesh nebulizers are less likely to disperse patient generated bioaerosol, as they do not use external gas flow source [28]. In any case, breath-synchronized jet nebulizers, which produce aerosol only during inspiration, reduce fugitive emissions compared with nebulizers that operate continuously during the breathing cycle [29].

The ISAM stresses that during this COVID-19 pandemic every patient must be treated as potentially infected because asymptomatic infected patients can shed virus [4]. Proper aseptic technique to avoid contamination of aerosol reservoirs and medication must always be used. Therefore, personal protective equipment for aerosol and droplet protection (mask, face shield, gloves, and gown) must be used, hands must be washed and fresh gloves must be put on before filling the nebulizer reservoir and administering treatments. Furthermore, patients must wear simple mask when possible (i.e., over simple nasal cannula and high flow nasal cannula) and between treatments and cover cough or sneeze with tissues that must be discarded immediately when used. However, dispersion of aerosols must be reduced. Also GOLD strategy recommends nebulizers for those who need them, whereas MDIs must be used by patients who are suitable for them [10].

Interestingly, the American Thoracic Society in its suggestion for patients affirms that if a patient routinely uses a nebulizer to take inhaled medicine, he/she can continue to use it as directed [30]. However, if he/she is sick with COVID-19 or other respiratory infection, using a nebulizer could increase the risk of infecting others through the mist that he/she exhales. Therefore, nebulizer must be used in a location that is separate from others in household to avoid this problem. The healthcare provider could switch to an inhaler temporarily, or suggest a special nebulizer filter that reduces the amount of exhaled mist. In any case, nebulizer must be kept clean to prevent infection.

### 3. Other practical strategies for drug delivery via nebulizers

There are other practical strategies for drug delivery via nebulizers to mild-patients with COVID-19 that should be considered [6]. Nebulizers should be used with a mouthpiece or high flow nasal cannula, if the inhaler increases cough or the patient has acute respiratory failure. High efficiency particulate air filters should be attached to nebulizers before delivering aerosolized medications to patients and, in any case, face-masks should not be used with nebulizers, whereas a mouthpiece should be preferred with jet and mesh nebulizers. Filters or one-way valves should be attached to the large bore tubing of the jet nebulizer to prevent fugitive emissions during aerosol therapy and a filter should be added to the other end of the mouthpiece to eliminate the release of aerosols to the environment, when a mesh nebulizer is used.

It is important that appropriate care is taken to clean all the surfaces in the room or area where nebulization is performed [9]. Furthermore it is fundamental that patients do not share their inhalers and devices with anyone. They must wash their hands before and after using their equipment, and clean the equipment after each use regularly using a detergent, or following the manufacturer’s cleaning instructions.

### 4. Conclusion

This intense debate with diametrically opposed opinions, does not clarify whether it is appropriate to use nebulizers during this COVID-19 pandemic. However, it has been rightly pointed out that there are no known infection-related hazards to an uninfected patient and even to a patient with COVID-19 that preclude the use of a nebulizer at home [31]. In any case, if the patient follows social distancing guidelines, undertakes extra precautions such as increased nebulizer hygiene, avoidance of nebulizer use in the presence of other people, and ensures that the nebulizer treatment is done near open windows or in areas of increased air circulation, the risks toward other people can be minimized as well. Things are different when the patient is treated in hospital. Health care personnel must be protected from SARS-CoV-2 infection. Therefore, hospitals and health care facilities should continue to adhere to strict measures, including adherence to stringent sanitization protocols and use of personal protective equipment in the presence of COVID-19 patients. Furthermore, the use of negative-pressure rooms, disposing of used equipment after each use, and maintaining at least 6

**Table 1**  
Practical advices.

<ul style="list-style-type: none"> <li>• Pre-nebulization               <ul style="list-style-type: none"> <li>– Washing hands</li> <li>– Ensure the device is clean</li> <li>– Ensure adequate protection for health care workers and bystander hosts</li> </ul> </li> <li>• During nebulization               <ul style="list-style-type: none"> <li>– Separate room or negative pressure room (hospital/clinic); when possible, outside the house on a porch or patio or in a garage and in any case, near open windows or in areas of increased air circulation (home)</li> <li>– Mouthpiece preferred over facemask</li> </ul> </li> <li>• Post-nebulization               <ul style="list-style-type: none"> <li>– Cleaning and disinfection of nebulizer.</li> <li>– Cleaning of the surface and areas of nebulization.</li> </ul> </li> </ul>
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feet (1.8 m) or greater distance from the patient should be considered when a patient is undergoing nebulized treatment.

We fully share these comments and, in any case, we consider it fundamental that all patients, regardless of whether or not suffering from COVID-19, always follow the practical advice reported in Table 1.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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