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Review article / *Articolo di revisione*

Aerosol therapies during the SARS-CoV-2 pandemic

Aerosolterapia durante la pandemia da SARS-CoV-2

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Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COronaVirus Disease 2019 (COVID-19), has resulted in a worldwide pandemic and currently represents a major public health issue. It has caused outbreaks of illness due to person-to-person transmission of the virus mainly via close contacts and droplets produced by an infected person's cough or sneeze. Although aerosol therapy is a mainstay procedure for treating obstructive airway diseases at home and healthcare settings, there is concern about the hypothesized enhanced risk for transmission of SARS-CoV-2 in the form of aerosolised respiratory droplets during the nebulised treatment of patients with COVID-19. Consequently, the use of hand-held inhalers, particularly pressurised metered dose inhalers, has risen considerably as an alternative to nebulisers, which has led to inadequate supplies in some countries. However, switching to hand-held inhalers may result in unintended consequences for some patients, who may be unable to adequately use their new device or benefit fully from treatment via hand-held inhalers. Furthermore, there is no evidence supporting an increased risk of viral transmission during nebulisation in COVID-19 patients. Thus, there is no compelling reason to alter aerosol modality for patients with established nebuliser-based regimens. The purpose of this paper is to discuss the current evidence and understanding of the use of aerosol therapies during the SARS-CoV-2 pandemic and to provide some guidance on the measures to be taken to minimise the hypothetical enhanced risk of infection, if any, during aerosol therapies.

Key words: aerosol, nebuliser, SARS-CoV-2, droplets, airborne

Riassunto

La pandemia mondiale da coronavirus 2 (SARS-CoV-2) rappresenta un importante problema di salute pubblica con focolai di malattia dovuti alla trasmissione del virus da persona a persona principalmente tramite contatti stretti e goccioline ("droplets") prodotte dalla tosse o dallo starnuto di una persona infetta. L'aerosolterapia rappresenta una procedura fondamentale per il trattamento delle malattie ostruttive delle vie aeree a domicilio e in ospedale. Tuttavia, vi è preoccupazione per l'ipotetico aumentato rischio di trasmissione di SARS-CoV-2 sotto forma di goccioline aerosolizzate durante il trattamento aerosolico di pazienti affetti da COVID-19. Di conseguenza, l'uso di inalatori portatili, in particolare inalatori pressurizzati e predosati, è notevolmente aumentato come alternativa ai nebulizzatori, determinando forniture inadeguate di questo tipo di dispositivi inalatori in alcuni Paesi. È importante ricordare che la sostituzione dei nebulizzatori con inalatori portatili può associarsi a conseguenze indesiderate nei pazienti non in grado di utilizzare adeguatamente il nuovo dispositivo o trarre pieno vantaggio dal trattamento somministrato da inalatori portatili. Inoltre, non ci sono prove a sostegno di un aumento del rischio di trasmissione virale durante la nebulizzazione nei pazienti COVID-19. Pertanto, non vi è alcun motivo valido per modificare la modalità di produzione dell'aerosol per i pazienti che da tempo assumono terapia inalatoria per mezzo di nebulizzatori. Lo scopo di questo articolo è quello di discutere le attuali conoscenze sull'uso dell'aerosolterapia durante la pandemia da SARS-CoV-2 e fornire indicazioni sulle misure da adottare per ridurre al minimo il supposto rischio di infezione, se presente, durante la terapia aerosolica.

***Parole chiave**: aerosol, nebulizzatore, SARS-CoV-2, goccioline, trasmissione aerea*

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Conflict of interest

Federico Lavorini has served as a consultant and speaker for AstraZeneca, Boehringer Ingelheim, Chiesi Farmceutici, GlaxoSmithKline, HIKMA, Menarini International, Novartis, Orion, TEVA, Trudell International. He received research grants from AstraZeneca and GlaxoSmithKline. Fabrizio Pregliasco has served as consultant and speaker for Baush & Lomb, Chiesi Farmaceutici, GlaxoSmithKLine, Proxima, Sanofi and Sofar.

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Background

The Coronavirus disease 2019 (COVID-19) is a worldwide pandemic caused by the highly contagious novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The latter belongs to the same class of coronaviruses as those that resulted in SARS and Middle East respiratory syndrome, both of which infected many health care professionals (HCPs) in the course of providing patient care [1]. The SARS-CoV-2 virus, an acute respiratory infectious agent, is primarily transmitted between people through respiratory droplets and contact routes [2,3] (Fig. 1). A recognized key to transmission of COVID-19, and droplet infections generally, is the dispersion of bio-aerosols from the patient. Bio-aerosol, defined as aerosols or particulate and matter of animal, plant or microbial origin with a range from 0.1 to >100 µm in diameter [4], can contain viruses, bacteria, fungi and are generated by infected persons when they cough, sneeze, talk, sing, or breathe [5-7]. They can land in the mouth, nose, or eyes of those in proximity, and they have the potential to be inhaled into the lungs (Fig. 1). However, larger droplets in the cloud produced by coughing and sneezing settle quickly on surfaces around the infected subject, where they could be infectious by contact for several days [8]. It is not clear that contact with surfaces is a major way for transmission for SARS-Cov-2 [9]. The respiratory droplets evaporate to form smaller droplet nuclei that carry infectious agents, remain suspended in air, and transported over longer distance by airflow are highly respirable [9]. Although airborne transmission of COVID-19 between individuals over long distances has been shown, this does not appear to be the major route of transmission of infection [7].

Guidelines recommend droplet/airborne and contact precautions for those caring for COVID-19 patients in ambulatory and acute care settings [1,10-13]. Increased risk of transmission has been associated with aerosol generating procedures (AGPs), an acronym arised during the 2003 SARS (*severe acute respiratory syndrome*) epidemic, where small retrospective studies showed a higher infection rate among healthcare workers who had performed certain medical procedures [14]. Analyses of the international literature revealed that there are several, sometimes conflicting, definitions of AGPs, mostly based on theoretical concerns rather than on documented transmission of infections [15,16]. A recent definition states that an AGP is a medical procedure that can result in the release of airborne particles (aerosols) from the respiratory tract when treating someone who is suspected or known to be suffering from an infectious agent transmitted wholly or partly by the airborne or droplet route [17]. If there is limited consensus on the definition, there is even less on which procedures are to be included in the list of AGPs. In particular, the doubts concern nebulisation as an AGP. Certain procedures may generate an aerosol from material other than patient's secretions and therefore are not considered to represent a significant infectious risk for COVID-19 as medication via nebulisation [16]. Other opinions consider nebulised treatment potentially act to disperse bio-aerosols from the patient to the surrounding area without evidence that they generate additional contaminated aerosols [10]. Despite the lack of evidence, there is currently a concern regarding the hypothetical enhanced risk of transmission of SARS-CoV-2 in the form of aerosolised respiratory droplets from patients with COVID-19 undergoing nebulised treatment, in

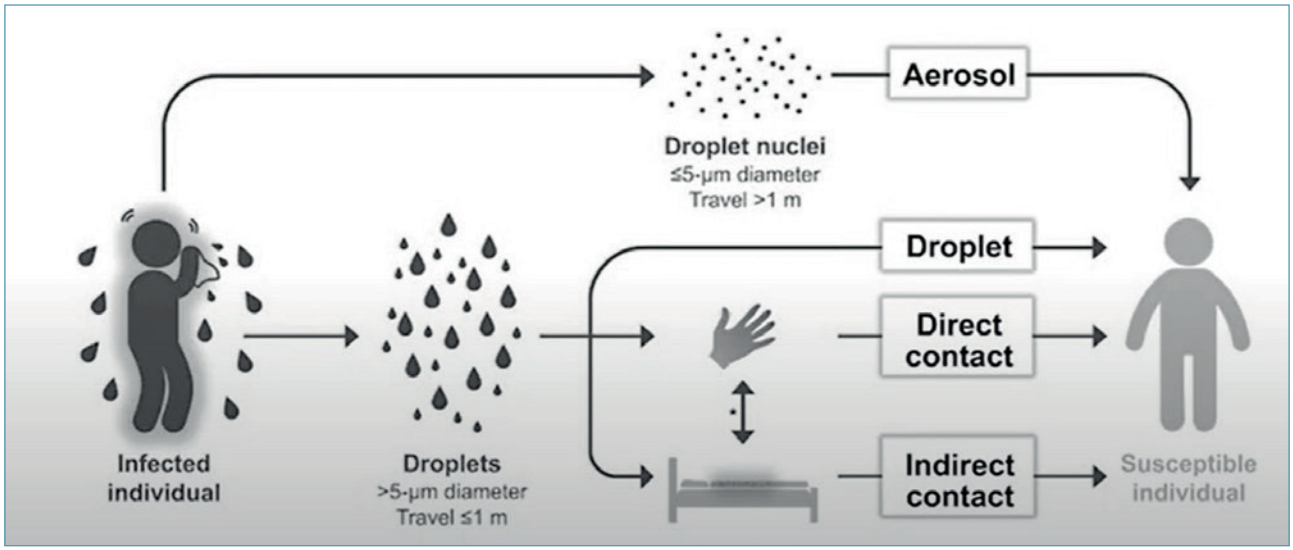

Figure 1. Overview of SARS-CoV-2 transmission.

comparison to established risk of transmission of SARS-CoV-2 in the form of aerosolised respiratory droplets from patients with COVID-19 not undergoing nebulised treatment [18,19]. Furthermore, while some authorities [20-22] have advised against the use of nebuliser treatment unless absolutely necessary, others [10,12,23] have recommended the continued use of nebulised treatment when applicable. This intense debate with diametrically opposed opinions may have induced confusion and mis-interpretation among doctors thus encouraging them to avoid unnecessary aerosol therapy in patients with COVID-19 and obstructive airway diseases treated at home, or to switch patients from nebulised therapies to portable inhalers. It seems worth noting to recall that a sudden switching to handheld inhalers, particularly to pressurised metered-dose inhalers (pMDIs), may result in unintended consequences for some patients who may be unable to adequately use their new devices or benefit fully from treatment delivered by handheld inhalers [24,25]. The present paper aims at providing guidance to physicians on aerosol therapies in hospital or home settings during the SARS-CoV-2 pandemic, and, based on all current available information, illustrating measures to be taken in any case to minimise the hypothetical enhanced risk of infection.

Aerosol delivery systems and the risk of infection transmission

Pressurized metered-dose inhalers, dry powder inhalers (DPIs), and nebulisers are main aerosol delivery systems commonly used in the treatment of airway obstructive diseases [26]. Each of these delivery systems has advantages, limitations, and risks for device contamination [26]. Although there is no ranking system that assesses the risk of transmission with various aerosol delivery devices, the rationale behind such an evaluation system could be the treatment time, the amount of emitted dose and aerosol mass generated by the device during aerosol therapy, as well as the design of the device that impacts the risk of contamination during device preparation, cleaning and maintenance [7]. For instance, portable inhalers (i.e. pMDIs, and DPIs) have shorter treatment times, deliver a lower emitted dose and generate less aerosol mass than nebulisers [26]. Since the drug is enclosed in the inhaler, they are hard to contaminate compared to nebulizers with an open medication reservoir [26]. On the other hand, one of the factor that may explain risk of infection transmission during medical procedures, such as cardiopulmonary resuscitation, non-invasive positive pressure ventilation, spirometry, is forced air. Any time air is forced over moist respiratory mucosa, it will generate more virus-laden respiratory particles [27]. Conceivably, inhalation manoeuvres associated with the use of portable inhalers could also be considered aerosol generating because this activity also increases the velocity and volume of air being forced over respiratory mucosa. Because of these rationales, it is difficult to reasonably conclude that there is a difference in risk between the various devices for aerosol therapies. However, pMDIs offer multi-dose convenience with consistent and accurate dosing and can be used in conjunction with spacers or valved-holding chambers (VHCs) to improve aerosol delivery and overcome device-related issues, such as high oropharyngeal deposition and poor hand-breath coordination [26,28]. Dry-powder inhalers are breath-actuated and overcome issues with hand-breath coordination [26]. However, errors in using DPIs exist due to inadequate inspiratory effort needed to deliver the drug to the patient [26]. While forceful inspirations draw the medication from the inhaler and disperse drug particles within the respirable range, they may cause cough thus increasing the distance of exhaled air dispersion and the risk of viral transmission in the era of COVID-19. Therefore, some authors [29] recommend caution with the use of DPIs in patients with coughing and airway irritations. In summary, at present there does not appear to be a concern with SARS-CoV-2 transmission and portable inhalers provided that the patient can use the device correctly.

Nebulisers are the oldest delivery systems developed to produce aerosols and delivery inhaled medications [26]. They are frequently used in hospital setting for treating acute asthma or COPD exacebations and at home in elderly patients unable to handle portable inhalers correctly [26,30]. Jet nebulisers are by far the most common type of nebulisers used worldwide. A jet nebuliser is powered by a compressed gas (usually air or oxygen) that draws medication through a capillary tube in the nebuliser' chamber, shearing the liquid formulation and directing to a baffle-generating aerosol. Coarse droplets impact on baffles while smaller droplets may be inhaled or may land on internal walls returning to the reservoir for re-nebulisation [26]. A 6-8 L/min flow and a fill volume of 4-5 ml are generally needed to generate medical aerosols, unless some nebulisers are specifically designed for different flow and a smaller fill volume [26]. Jet nebulisers have well known limitations, including reduced portability, lengthy administration time, low efficiency in drug delivery and significant waste of medication [26]. Indeed, close to two-third of the aerosol droplets are emitted into the environment [22], thus increasing the risk of exposure of HCPs to aerosolised medications. However, in recent year nebuliser technology has significantly evolved with the development of adaptive (i.e. breath-enhanced and breath-actuated

nebulisers) and vibrating mesh nebulisers. These "next generation" nebulisers are more portable, lighter and efficient than "traditional" jet nebulisers; they also provide a precise and reproducible dose delivery with deeper aerosol deposition in the lungs and reduced loss of medication to the environmental [26].

At present, the evidence about the risk of viral transmission through aerosols generated by nebulizer is largely limited [31]. Aerosols generated by a nebuliser is derived from a medication solution and is not a bio-aerosol – potentially infectious – as that generated during cough or sneeze [7]. However, nebulisers generate fugitive emissions from the properly sterilised device which is added to patient expiration potentially infectious [32,33]. It has been shown that the particle size of fugitive emissions varies from 0.86 to 1.43 μm and approximately 50% of the generated aerosol is fugitive aerosol that remains suspended in the indoor environment for several hours [32,33], as is the case of for potentially infecting bio-aerosols produced by patients.

At present, there is no data to support contamination of nebuliser by the SARS-CoV-2. Theoretically, aerosol delivery devices, including nebulisers, could be considered as fomites, and, therefore, required strict hygiene rules before, during and after use. To investigate the hypothesis of virus spread during nebulisation, Tang and co-workers [34] simulated a spontaneously breathing adult patient with a heated manikin receiving nebulised therapy with a Collison jet nebulizer and a face mask. Using a live-attenuated influenza vaccine as a surrogate virus tracer, the authors found that air samples obtained from three separate locations indicated 612 viruses per litre near the head, 174 viruses per litre near the abdomen, and 118 viruses per litre near the feet. These findings indicate aerosols spreading at decreasing concentration with increasing distance from the head of the patient [34]. However, the lack of control data as as well as the fact that these findings were obtained under strict laboratory conditions (fixed tidal volume, respiratory rate and exhalation flow, use of distilled water), that may not reflect what happen in a real-life setting, do not allow us to draw firm conclusions except that that nebulisation is not able to block virus release from the Collison nebuliser. A retrospective pooled analysis on the risk of SARS-CoV transmission to HCPs with various aerosol generating procedures showed that the risk of infection to HCPs increased by 6.6 times with intubation, as opposed to 0.9 times with the use of nebulisers [14]. Unlike other aerosol-generating procedures that carry contaminated particles derived from patients, the medication in the nebuliser is considered a non-patient source that might not generate bioaerosols carrying pathogens, unless the nebuliser is contaminated [35].

Jet nebulisers that are open to and positioned below the gas pathway could be contaminated by patient's secretions when they are directly connected to the patient interface trough a mouthpiece [7]. In contrast, by design vibrating mesh nebulisers generate aerosols via mesh plates that separate the medication from the patient interface [7]. In addition, mesh nebulisers have less residual volume (< 0.5 mL) at the end of nebulisation than jet nebulisers (about 2 ml) – which may create a hospitable environment for microorganisms. Therefore, vibrating mesh nebulisers could be preferred over jet nebulisers for aerosol therapies. However, it should be noted that mesh nebulisers need careful hygiene techniques as those of jet nebulisers.

Independent of the nebuliser type used, a mouthpiece could be preferred over a face mask to improve treatment efficiency and reduce fugitive emissions because a mouthpiece does not force aerosols out of the interface during therapy [35]. Although the risk of enhanced emission of virus during nebulisation is limited, placing a filter on the nebuliser's outlet has been found to reduce fugitive emissions and exposure of HCPs to aerosol medications [32,36]. In summary, jet or mesh nebulisers should be used with a mouthpiece and a filter attached to the exhalation port of the nebuliser (Fig. 2). Care should be taken to ensure that the reservoir cap of the mesh nebuliser is closed after each use and the exhalation valve of the mouthpiece is not blocked with the attachment of the filter to the mouthpiece. To avoid this problem, a silicon adaptor can be used between the filter and the mouthpiece of the mesh nebuliser.

Strategies to increase the safety use of portable inhalers and nebulisers during SARS-CoV-2 pandemic

Evidences on the perils associated with the transmission of SARS-CoV-2 during aerosol therapy are largely insufficient. However, undertaking extra precautions to improve the safety and effectiveness of the aerosol delivery systems are essential in this global pandemic (Tab. I). Ensuring device safety and effectiveness depends on selecting the most appropriate device for each patient after careful evaluation of device features, the hypothetical risk for device contamination and supposed viral transmission. The pMDI should be used in conjunction with a dedicated spacer or a VHC and not transferred from patient to patient. The mouthpiece should be preferred over the face mask when using spacers/VHCs; the latter should be cleaned and disinfected according to the manufacturer's guidelines. Although not recommended,

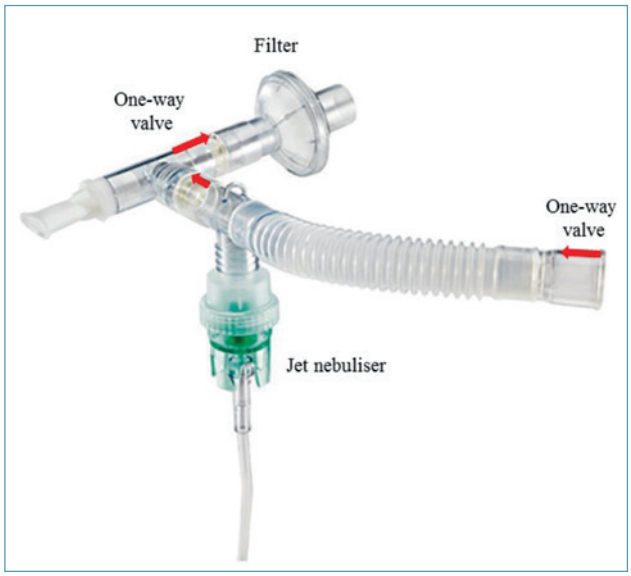

Figure 2. Example of a filtered nebuliser set-up with one-way valves.

there are institutions that employ the common canister protocol, which is a cost-saving strategy used in hospitals and clinics to deliver pMDI medications or to teach pMDI technique using a placebo MDI. In both scenarios, the MDI is reused between patients, along with an individual spacer/VHC. In these cases, hand hygiene and wiping the MDI with 70% alcohol before and after use between patients are recommended [37]. Similarly, wiping the DPI mouthpiece off with a dry clean cloth such as a paper towel, and proper storage are necessary [37]. Nebulisers should be disposed of, rinsed air dried washed and sterilised between treatments by using liquid/hospital-grade disinfectants. Nebuliser accessories can be cleaned and disinfected following manufacturer's instructions or by using an isopropanol 79% or hydrogen peroxide 3% solution [37]. The use of one-way valves and filters, particularly high-efficiency air filters, is recommended with the nebulisers to reduce fugitive emissions and exposure of HCPs (in hospital) and family members (at home) to aerosol medications; although with limited evidence, mouthpiece could be preferred while face masks avoided as the delivery interface.

Conclusions

Guidance for the treatment of patients with obstructive airway diseases during the SARS-CoV-2 pandemic is rapidly evolving as new details of viral transmission are being elucidated. At present, there is scarse information whether nebulised treatment represent an enhanced risk for infection transmission. Furthermore, there is no precedent to guide the treatment of patients with respiratory disease in the current situation. Given the absence of any conclusive data that link nebulised treatments to the transmission of SARS-Cov-2, most international societies [12,13,23] and the Center for Disease Control [10] have recommended the continued use of nebuliser treatment and do not advise against the use of nebulisers. Notably, new drugs and/or repurposed out-of-patent medicines are candidate to manage COVID-19 by nebulisation [38].

Moving forward, we believe that the more sensible ap-

Table I. Suggestions to increase the safety use of portable inhalers and nebulisers during COVID-19 pandemic.

	Suggestions
Portable inhalers	• Prefer the use of pMDIs in conjunction with a spacer or a VHC instead of the pMDI only • Use a spacer or a VHC with a mouthpiece instead of a face mask • Train the patient to exhale into the spacer or the VHC to minimise exhaled aerosol dispersion to the environmental • Clean and disinfect the spacer or the VHC according to the manufacturer's guidelines • Do not share pMDIs, spacers or VHCs with multiple patients • Clean and disinfect pMDI canister and DPI mouthpiece with a 70% alcohol pad
Nebulisers	• Wash hand before filling the nebuliser reservoir and administering treatments • Avoid nebulisation in the presence of other people • Carry out nebulisation near open windows or areas of increased air circulation • Close the door while nebulisation is being undertaken • Prefer a mouthpiece instead of a facemask • Prefer vibrating mesh over jet nebulisers • Attach a filter to the expiratory port of the nebuliser • Rinse the nebuliser cup with distilled or sterile water • Keep the reservoir cap of mesh nebuliser close after use • Clean and disinfect the nebuliser according to the manufacturer's guidelines or use isopropanol 79% or hydrogen peroxide 3% solution • Clean the surface and areas of nebulisation

Portable inhalers include pressurised metered-dose inhaler (pMDI), dry powder inhaler (DPI) and soft mist inhalers. VHC, valved-holding chamber

proach for administration of aerosol therapies would be to recommend an appropriate device tailored specifically to patients' abilities and clinical conditions, rather than follow a "one size fits all" approach. Proper use of pMDIs and DPIs requires coordination between inspiration and inhaler actuation, and a fast and deep inhalation, respectively [26]. If the patient can perform these manoeuvres correctly, it is recommended to use pMDIs or DPIs for delivery of aerosolised medications. However, in patients with inadequate hand-breath coordination, poor inspiratory strength, and/or cognitive impairments, nebulisers still represent the device of choice for delivery of aerosolised medications [30]. A sudden switching of these patients from nebulised treatment to portable inhalers may present certain challenges that should be considered [24,25]. If not accompanied by adequate training for the patient, switching from one device to another can be linked with poor adherence and technique [24,25]. Suboptimal inhalation delivery could lead to exacerbations and increased healthcare utilization [24,25], potentially increasing the risk of nosocomial SARS-CoV-2 exposure. Although there is a lack of clear evidence to suggest that nebulisation can transmit viral particles, clinicians should continue to adhere to strict measures, including stringent sanitization protocol and wear personal protective equipment during aerosol delivery to patients with known or suspected SARS-CoV-2 infection. Therefore, it is vital to train patients and clinicians on the risk of contamination and viral transmission in general while providing suggestions on how to use each device safely in patients with SARS-CoV-2 and likely with any other viral infection. If a patient takes precautions, such as nebuliser hygiene, avoidance of nebuliser use in the presence of other people, ensure that nebuliser use is done near open window or in areas of increased air circulation, the possible risks, even if today still not proven, towards other people can be minimised.

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