The following information resources have been selected by the National Health Library and Knowledge Service Evidence Virtual Team in response to your question. The resources are listed in our estimated order of relevance to practicing healthcare professionals confronted with this scenario in an Irish context. In respect of the evolving global situation and rapidly changing evidence base, it is advised to use hyperlinked sources in this document to ensure that the information you are disseminating to the public or applying in clinical practice is the most current, valid and accurate. For further information on the methodology used in the compilation of this document—including a complete list of sources consulted—please see our National Health Library and Knowledge Service Summary of Evidence Protocol.

QUESTION 15

Is there an increased risk of transmission of COVID-19 associated with the use of nebulizers? Do nebulizers aerosolize SARS-CoV-2 particles?

Is there an increased risk of transmission of COVID-19 associated with the use of nebulizers? Do nebulizers aerosolize SARS-CoV-2 particles?

Main Points

1. AGP-related pathogen transmission in the delivery of nebulized medications is not supported by evidence or plausible hypothesis.
2. During nebulization, the aerosol derives from a non-patient source and does not carry patient-derived viral particles. If a particle in the aerosol coalesces with a contaminated mucous membrane, it will cease to be airborne and will not be part of an aerosol.
3. One potential complication is that nebulization significantly increases fugitive aerosols in within 1 meter of the patient, and can provoke coughing or sneezing, raising the possibility that infectious bio-aerosols might be dispersed.
4. There are no known infection-related hazards to an uninfected patient or to a patient with COVID-19 that preclude the use of a nebulizer at home. Patients should adhere to standard precautions: social distancing; increased nebulizer hygiene; nebulizer treatment in areas of increased air circulation.
5. Hospitals and healthcare facilities should continue to adhere to stringent sanitization protocols and use of PPE in the presence of COVID-19 patients.

Summary of Evidence

The Health Protection Surveillance Centre states that AGP-related increased risk of pathogen transmission in the delivery of nebulized medications via simple face mask is not supported by evidence or plausible hypothesis and not recognized by most national organizations[1].

Public Health England states that the administration of medication via nebulisation is not considered a significant infectious risk for COVID-19[3]. The New and Emerging Respiratory Viral Threat Assessment Group advised that during nebulisation, the aerosol derives from a non-patient source [fluid in the nebuliser chamber] and does not carry patient-derived viral particles. If a particle in the aerosol coalesces with a contaminated mucous membrane, it will cease to be airborne and therefore will not be part of an aerosol[3, 14].

UpToDate notes that one potential complication is that nebulization significantly increases aerosol concentration in the patient's vicinity (fugitive aerosols), particularly within 1 meter of the patient, and can provoke coughing or sneezing, raising the possibility that use of aerosolized therapies might disperse infectious bio-aerosols and cross-infect healthcare workers[4].

In a recent review of the literature, Cazzola et al[5] point to intense debate with opposing opinions on whether or not it is appropriate to use nebulizers during this COVID-19 pandemic. However, the authors conclude 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. 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. In acute hospital scenarios, healthcare personnel must be protected from SARS-CoV-2 infection. Therefore, hospitals and healthcare 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 1.8 m or greater distance from the patient should be considered when a patient is undergoing nebulized treatment[5].

Sethi et al state that on the basis of current guidance and limited evidence[9, 13] of increased infection risk with nebulized therapy, the use of nebulized treatment at home by a patient with COVID-19 has no known hazards for the patient using the nebulizer. In order to reduce the risk of affecting other people, patients should follow social distancing guidance and avoid nebulizer use in the presence of others. Stringent nebulizer hygiene should be implemented, and nebulization should be carried out near open windows or in areas of increased air circulation.

The authors go on to reiterate that hospitals and healthcare facilities should continue to abide by the strict measures that protect healthcare workers from COVID-19, including adherence to stringent sanitization protocols and the use of PPE in the presence of patients with COVID-19. In the case of a patient undergoing nebulized treatment, the use of negative-pressure rooms, disposing or disinfecting PPE after each use, and maintaining at least 2 m or greater distance from the patient should be considered. In order to minimize viral transmission, it is recommended that nebulizers are used with a mouthpiece and a filter[9].

Irish and/or International Guidance

What does the Health Protection Surveillance Centre (Ireland) say?

Health Protection Surveillance Centre (2020) Use of PPE to support infection prevention and control practice when performing aerosol generating procedures on confirmed or clinically suspected COVID-19 cases in a pandemic situation[1]

We identified 5 case-control and 5 retrospective cohort studies which evaluated transmission of SARS to HCWs. Procedures reported to present an increased risk of transmission included [n; pooled OR(95%CI)] tracheal intubation [n=4 cohort; 6.6 (2.3, 18.9), and n=4 case-control; 6.6 (4.1, 10.6)], non-invasive ventilation [n=2 cohort; OR 3.1(1.4, 6.8)], tracheotomy [n=1 case-control; 4.2 (1.5, 11.5)] and manual ventilation before intubation [n=1 cohort; OR 2.8 (1.3, 6.4)]. Other intubation associated procedures, endotracheal aspiration, suction of body fluids, bronchoscopy, nebulizer treatment, administration of O2, high flow O2, manipulation of O2 mask or BiPAP mask, defibrillation, chest compressions, insertion of nasogastric tube, and collection of sputum were not significant. Our findings suggest that some procedures potentially capable of generating aerosols have been associated with increased risk of SARS transmission to HCWs or were a risk factor for transmission, with the most consistent association across multiple studies identified with tracheal intubation.

AGP-related increased risk of pathogen transmission in the delivery of nebulized medications via simple face mask is not supported by evidence or plausible hypothesis and not recognized by most national organizations.

[1] Health Protection Surveillance Centre (2020) Use of PPE to support infection prevention and control practice when performing aerosol generating procedures on confirmed or clinically suspected COVID-19 cases in a pandemic situation https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/guidance/infectionpreventionandcontrolguidance/aerosolgeneratingprocedures/ Accessed 28 January 2021

What does the World Health Organization say?

Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations[2]

In the context of COVID-19, airborne transmission may be possible in specific circumstances and settings in which procedures or support treatments that generate aerosols are performed: 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, non-invasive positive-pressure ventilation, tracheostomy, and cardiopulmonary resuscitation.

What does Public Health England say?

Public Health England (2020) COVID-19 infection prevention and control guidance: aerosol-generating procedures[3]

Certain other procedures or equipment may generate an aerosol from material other than patient secretions but are not considered to represent a significant infectious risk for COVID-19. Procedures in this category include administration of humidified oxygen, administration of Entonox or medication via nebulisation.

The New and Emerging Respiratory Viral Threat Assessment Group advised that during nebulisation, the aerosol derives from a non-patient source [fluid in the nebuliser chamber] and does not carry patient-derived viral particles. If a particle in the aerosol coalesces with a contaminated mucous membrane, it will cease to be airborne and therefore will not be part of an aerosol.

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[2] World Health Organization (29 March 2020) Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-COVID-19-implications-for-ipc-precaution-recommendations Accessed 28 January 2021

[3] Public Health England (2020) COVID-19 infection prevention and control guidance: aerosol-generating procedures https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control/COVID-19-infection-prevention-and-control-guidance-aerosol-generating-procedures Accessed 28 January 2021

Point-of-Care Tools

What does UpToDate say?

UpToDate (2020) Delivery of Inhaled Medication in Adults[4]
Delivery of aerosolized medication to treat bronchoconstriction is common in patients with respiratory viral infections, including COVID-19. A potential problem is that nebulization significantly increases aerosol concentration in the patient's vicinity (fugitive aerosols), particularly within 1 meter of the patient, and can provoke coughing or sneezing, raising the possibility that use of aerosolized therapies might disperse infectious bio-aerosols and cross-infect healthcare workers.
During a nebulizer treatment, the exhaled air from the patient passes over the reservoir in standard jet nebulizers potentially contaminating the reservoir with respiratory secretions. In modeling studies, jet nebulization led to 0.8 meter dispersion of the exhaled aerosol with more extensive dispersion in models with stiffer lungs mimicking severe lung injury. Coughs provoked during nebulizer or inhaler therapy can disperse large respiratory droplets over approximately 2 meters, while smaller droplet nuclei can travel further. It is unclear whether nebulizer treatments can spread respiratory viruses by cough provoked by the treatment. According to the Centers for Disease Control and Prevention and World Health Organization, it is uncertain whether aerosols generated from nebulizer administration are infectious.
Interventions that may decrease the risk of virus spread during administration of inhaled medications include the following:

— Use a dry powder inhaler (DPI), soft mist inhaler (SMI), or pressurized metered dose inhaler (pMDI) to deliver respiratory medications instead of a nebulizer (when possible).

[4] UpToDate (2020) Delivery of Inhaled Medication in Adults https://www.uptodate.com/contents/delivery-of-inhaled-medication-in-adults/ Accessed 28 January 2021

— Use a mouthpiece rather than a mask for inhalation of the nebulized medication and place a filter on the exhalation port of the nebulizer and instruct the patient to seal their lips tightly around the mouthpiece during inhalation and exhalation.
— Consider use of a breath synchronized nebulizer that only generates an aerosol during inhalation to minimize the release of medical aerosols.
— Advise healthcare workers to stay 2 meters away from the infected patient during procedures that provoke cough or sneeze or generate an aerosol and to wear N95 or other respirators in addition to eye protection, gloves, and a gown.

International Literature

What does the international literature say?

Cazzola et al (2020) Guidance on nebulization during the current COVID-19 pandemic[5]

Awareness of the risk of airborne transmission of SARS-CoV-2 makes patients hesitant about using inhaled medications that are considered a potential source of viral transmission and immunosuppression. However, patients with asthma or COPD should continue all prescribed inhaled medications. 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 best available evidence, 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 practical precautions.

A 2012 assessment of 3 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

[5] Cazzola M, Ora J, Bianco A, Rogliani P, Matera MG. Guidance on nebulization during the current COVID-19 pandemic. Respir Med. 2020 Nov 19;176:106236. doi: 10.1016/j.rmed.2020.106236. Epub ahead of print. PMID: 33248363; PMCID: PMC7676318.

transmission to healthcare workers caring for patients undergoing nebulizer treatment. Furthermore, a study performing polymerase chain reaction air sampling around a patient with SARS undergoing nebulizer treatment found no evidence of the virus. According to the 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.

Recommendations for and 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. Instead, the recommendation is to use a pMDI and spacer, with a mouthpiece or tightly fitting facemask, if required, when short-acting β_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. 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, or use of a single room with the door closed. Staff administering nebulizers should wear full protection against airborne exposures. 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.

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. 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. 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 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. 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 the nebulizer chamber, which is a non-patient source. Medical aerosols produced by nebulizers contain pathogens only when the patient or healthcare worker contaminates the nebulizers. 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.
Based on the recommendations by the Centers for Disease Control and Prevention, the ISAM 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. Vibrating mesh nebulizers are less likely to disperse patient generated bioaerosol, as

they do not use external gas flow source. 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.
The ISAM stresses that during this COVID-19 pandemic every patient must be treated as potentially infected because asymptomatic infected patients can shed virus.
The American Thoracic Society affirms that if a patient routinely uses a nebulizer to take inhaled medicine, he/she can continue to use it as directed. However, if the patient is sick with COVID-19 or another respiratory infection, using a nebulizer could increase the risk of infecting others through the mist that the patient exhales. Therefore, the nebulizer must be used in a location that is separate from others in the household. 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.

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. 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. In acute hospital scenarios, healthcare personnel must be protected from SARS-CoV-2 infection. Therefore, hospitals and healthcare 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 1.8 m or greater distance from the patient should be considered when a patient is undergoing nebulized treatment.

Elnadoury et al (2020) Uninterrupted Continuous and Intermittent Nebulizer Therapy in a COVID-19 Patient Using Sequential Vibratory Mesh Nebulizers: A Case Report[6]

Interruptions in continuous nebulized pulmonary vasodilators, such as epoprostenol, can potentially result in clinical deterioration in respiratory status. Coadministration of other intermittent nebulized therapies may require opening the ventilator circuit to facilitate administration. However, in patients with SARS-CoV2 infection, it is preferred to avoid opening the circuit whenever feasible to prevent aerosolization of the virus and exposure of healthcare workers. In this study, we describe a unique method of administering continuous epoprostenol nebulization and intermittent nebulized antibiotics, mucolytics, and bronchodilators, using Aerogen vibrating mesh nebulizers without interruptions in epoprostenol or opening the ventilator circuit. This approach was successful in allowing concomitant delivery of intermittent and continuous nebulized therapy without interruptions.

Fink et al (2020) Reducing Aerosol-Related Risk of Transmission in the Era of COVID-19: An Interim Guidance Endorsed by the International Society of Aerosols in Medicine[7]

National and international guidelines recommend droplet/airborne transmission and contact precautions for those caring for coronavirus disease 2019 (COVID-19) patients in ambulatory and acute care settings. The SARS-CoV-2 virus, an acute respiratory infectious agent, is primarily transmitted between people through respiratory droplets and contact routes. A recognized key to transmission of COVID-19 and droplet infections generally is the dispersion of bioaerosols from the patient. Increased risk of transmission has been associated with aerosol generating procedures that include endotracheal intubation,

[6] Elnadoury O, Beattie J, Lubinsky AS. Uninterrupted Continuous and Intermittent Nebulizer Therapy in a COVID-19 Patient Using Sequential Vibratory Mesh Nebulizers: A Case Report. J Aerosol Med Pulm Drug Deliv. 2020 Dec;33(6):357-360. doi: 10.1089/jamp.2020.1636. Epub 2020 Aug 25. PMID: 32852238.
[7] Fink JB, Ehrmann S, Li J, Dailey P, McKiernan P, Darquenne C, Martin AR, Rothen-Rutishauser B, Kuehl PJ, Häussermann S, MacLoughlin R, Smaldone GC, Muellinger B, Corcoran TE, Dhand R. Reducing Aerosol-Related Risk of Transmission in the Era of COVID-19: An Interim Guidance Endorsed by the International Society of Aerosols in Medicine. J Aerosol Med Pulm Drug Deliv. 2020 Dec;33(6):300-304. doi: 10.1089/jamp.2020.1615. Epub 2020 Aug 12. PMID: 32783675; PMCID: PMC7757542.

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, and cardiopulmonary resuscitation. The knowledge that COVID-19 subjects can be asymptomatic and still shed virus, producing infectious droplets during breathing, suggests that healthcare workers should assume every patient is potentially infectious during this pandemic. Taking actions to reduce risk of transmission to HCWs is, therefore, a vital consideration for safe delivery of all medical aerosols. Bioaerosols generated by infected patients are a major source of transmission for SARS CoV-2, and other infectious agents. In contrast, therapeutic aerosols do not add to the risk of disease transmission unless contaminated by patients or HCWs.

Pandian et al (2020) Critical Care Guidance for Tracheostomy Care During the COVID-19 Pandemic: A Global, Multidisciplinary Approach[8]

PURPOSE: Critical care nurses caring for patients with a tracheostomy are at high risk because of the predilection of SARS-CoV-2 for respiratory and mucosal surfaces. This review identifies patient-centered practices that ensure safety and reduce risk of infection transmission to healthcare workers during the coronavirus disease 2019 (COVID-19) pandemic. METHOD(S): Consensus statements, guidelines, institutional recommendations, and scientific literature on COVID-19 and previous outbreaks were reviewed. A global interdisciplinary team analyzed and prioritized findings via electronic communications and video conferences to develop consensus recommendations. RESULT(S): Aerosol-generating procedures are commonly performed by nurses and other healthcare workers, most notably during suctioning, tracheostomy tube changes, and stoma care. Patient repositioning, readjusting circuits, administering nebulized medications, and patient transport also present risks.

[8] Pandian V, Morris LL, Brodsky MB, Lynch J, Walsh B, Rushton C, Phillips J, Rahman A, DeRose T, Lambe L, Lami L, Wu SPM, Garza FP, Maiani S, Zavalis A, Okusanya KA, Palmieri PA, McGrath BA, Pelosi P, Sole ML, Davidson P, Brenner MJ. Critical Care Guidance for Tracheostomy Care During the COVID-19 Pandemic: A Global, Multidisciplinary Approach. Am J Crit Care. 2020 Nov 1;29(6):e116-e127. doi: 10.4037/ajcc2020561. PMID: 32929453.

Standard personal protective equipment includes an N95/FFP3 mask with or without surgical masks, gloves, goggles, and gown when performing aerosol-generating procedures for patients with known or suspected COVID-19. Viral testing of bronchial aspirate via tracheostomy may inform care providers when determining the protective equipment required. The need for protocols to reduce risk of transmission of infection to nurses and other healthcare workers is evident.

Sethi et al (2020) The use of nebulized pharmacotherapies during the COVID-19 pandemic[9]

The COVID-19 pandemic has highlighted the need for clear and accurate guidance on the use of aerosol-generating procedures such as nebulization for the treatment of patients with respiratory diseases with or without COVID-19. Despite the lack of evidence, there is heightened concern about the potential risk of transmission of SARS-CoV-2 in the form of aerosolized respiratory droplets during the nebulized treatment of patients with COVID-19. Consequently, the use of metered-dose inhalers (MDIs) has risen considerably as an alternative to nebulized therapy, which has led to inadequate supplies of MDIs in some parts of the United States. The following two important questions are addressed: 1. should nebulized therapy be used in hospital or home settings by patients infected with SARS-CoV-2; and 2. should nebulized therapy be continued in patients already using it for chronic respiratory disease management in hospital or home settings?

Based on the current guidance and limited evidence of increased infection risk with nebulized therapy, the following should be considered. The use of nebulized treatment at home by a patient with COVID-19 has no known hazards for the patient using the nebulizer; to reduce the risk of affecting other people, patients should follow social distancing guidance and avoid nebulizer use in the presence of others. Furthermore, precautions such as stringent nebulizer hygiene

[9] Sethi S, Barjaktarevic IZ, Tashkin DP. The use of nebulized pharmacotherapies during the COVID-19 pandemic. Ther Adv Respir Dis. 2020 Jan-Dec;14:1753466620954366. doi: 10.1177/1753466620954366. PMID: 33167796; PMCID: PMC7675890.

should be implemented, and nebulization should be carried out near open windows or in areas of increased air circulation. Nebulized treatment with long-acting agents, which allows for less frequent dosing, could be considered when applicable to further minimize exposure.

From the perspective of public health, hospitals and healthcare facilities should continue to abide by the strict measures that protect healthcare workers from COVID-19, including adherence to stringent sanitization protocols and the use of PPE in the presence of patients with COVID-19. In terms of PPE, the CDC currently recommends that HCP wear an N95 respirator or equivalent, eye protection, gown, and gloves when performing an aerosol-generating procedure or providing care in the intensive care unit to patients with known or suspected COVID-19. In the case of a patient undergoing nebulized treatment, the use of negative-pressure rooms, disposing or disinfecting PPE after each use, and maintaining at least 6 ft or greater distance from the patient should be considered. In order to minimize viral transmission, it is recommended that nebulizers are used with a mouthpiece and a filter.

Jackson et al (2020) Classification of aerosol-generating procedures: A rapid systematic review[10]

In the context of COVID-19, aerosol generating procedures have been highlighted as requiring a higher grade of personal protective equipment. We investigated how official guidance documents and academic publications have classified procedures in terms of whether or not they are aerosol-generating. We determined the level of agreement across different guidelines for each procedure group, in terms of its classification as aerosol generating, possibly aerosol-generating, or nonaerosol-generating. 128 documents met our inclusion criteria; they contained 1248 mentions of procedures that we categorised into 39 procedure groups.

[10] Jackson T, Deibert D, Wyatt G, Durand-Moreau Q, Adisesh A, Khunti K, Khunti S, Smith S, Chan XHS, Ross L, Roberts N, Toomey E, Greenhalgh T, Arora I, Black SM, Drake J, Syam N, Temple R, Straube S. Classification of aerosol-generating procedures: a rapid systematic review. BMJ Open Respir Res. 2020 Oct;7(1):e000730. doi: 10.1136/bmjresp-2020-000730. PMID: 33040021; PMCID: PMC7549490.

Procedures classified as aerosol-generating or possibly aerosol-generating by >=90% of documents included autopsy, surgery/postmortem procedures with high-speed devices, intubation and extubation procedures, bronchoscopy, sputum induction, manual ventilation, airway suctioning, cardiopulmonary resuscitation, tracheostomy and tracheostomy procedures, non-invasive ventilation, high-flow oxygen therapy, breaking closed ventilation systems, nebulised or aerosol therapy, and high frequency oscillatory ventilation. Disagreements existed between sources on some procedure groups.

Swarnakar et al (2020) ICS [Indian Chest Society] guidance for nebulization during the COVID-19 pandemic[11]

Recommendations

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

Nebulization Strategies in the COVID-19 Intensive Care Unit
In the ICU, delivering noninvasive ventilation, high-flow nasal oxygenation and nebulization to patients with COVID-19 can

[11] Swarnakar R, Gupta NM, Halder I, Khilnani GC. ICS guidance for nebulization during the COVID-19 pandemic. Lung India 0;0:0 Available https://www.aerogen.com/wp-content/uploads/2020/12/ICS-guidance-for-nebulization-during-the-COVID%E2%80%9119.pdf Accessed 29 January 2021

aggravate the spread of novel coronavirus. If nebulized therapy or aerosolized procedures are used, patients should be in an airborne infection isolation room (AIIR) or negative-pressure rooms with a minimum of 12 air changes per hour or at least 160 L/s/patient in facilities with natural ventilation. Healthcare workers should use contact and airborne precautions with PPE including a N95 mask with goggles and face shield, gloves and gown; and those providing aerosol therapy should be trained on infection prevention and control recommendations for COVID-19. Hand hygiene and double gloving should be a standard practice in all healthcare facilities. Cleaning hands before and after treatment with soap and water or an alcohol-based hand sanitizer is extremely important. All non-essential personnel should leave the room during nebulization and not re-enter the room for 2–3 h following nebulizer administration. Other infection control strategies include minimizing the number of times that healthcare workers enter the rooms of COVID-19 patients and restricting others who are not involved in direct patient care from entering the patient's room.
In critically ill patients with COVID-19 receiving ventilatory support, nebulization should be given in a close circuit to prevent the transmission of the virus. Therefore, a mesh nebulizer is preferred over a jet nebulizer or pMDI in delivering aerosolized medications. Placing the mesh or jet nebulizer prior to the humidifier can improve the efficiency of the treatment and further reduce retrograde contamination from the patient. Use of HEPA filters prevents the transmission of infectious droplet nuclei through the ventilators as aerosol drug delivery to ventilator-dependent patients can readily be transmitted to the ambient environment.

Recommendations

1. Place surgical masks on the face of the infected patients during aerosol drug delivery through HFNC.
2. Use mesh nebulizers, if available, in critically ill patients with COVID-19 receiving ventilator support.
3. Avoid the use of a jet nebulizer or pMDIs for aerosol delivery to ventilator-dependent patients with COVID-19 due to the

breakage of the circuits for the placement of the device before aerosol therapy.
4. Place a mesh nebulizer prior to the humidifier to improve the efficiency of the treatment and to reduce retrograde contamination from the patient.
5. Attach a HEPA filter to the expiratory limb of the ventilator to reduce second-hand aerosol exposure and to prevent the transmission of infectious droplet nuclei through the ventilators.
6. Do not combine aerosol therapy with pulmonary clearance techniques such as chest physiotherapy and suctioning.
7. Use in-line, or closed system suction catheters in intubated patients.
8. Healthcare workers should wear PPE. Cleaning hands before and after treatment with soap and water or an alcohol-based hand sanitizer is extremely important.
9. All nonessential personnel should leave the room during nebulization and not re-entering the room for 2–3 h following nebulizer administration.
10. Disinfect equipment with isopropanol (70%) or hydrogen peroxide (3%).

Reychler et al (2020) Nebulization: a potential source of SARS-CoV-2 transmission[12]

The Aerosol therapy workgroup (GAT) of the Sociétéde Pneumologie de Langue Francaise decided at SARS-CoV-2 pandemic preparedness to suggest avoiding a drug delivery via nebulization to reduce the risk of spreading the virus. Indeed, some arguments suggested that the aerosol generated from the patient during nebulization or from the nebulizer can directly exposes mucosae and eyes of the healthcare workers and contaminate surfaces with potentially infective droplets.

[12] Reychler G, Vecellio L, Dubus JC; 'group Aerosoltherapy GAT' of the French Language Respiratory Society-Société de Pneumologie de Langue Française SPLF. Nebulization: A potential source of SARS-CoV-2 transmission. Respir Med Res. 2020 Nov;78:100778. doi: 10.1016/j.resmer.2020.100778. Epub 2020 Aug 4. PMID: 32763845; PMCID: PMC7399661.

Woods (2020) Evidence-based treatment during the SARS-CoV-2 pandemic: Identifying the knowns and unknowns of nebulization[13]

Despite the lack of evidence, there is heightened concern about the potential risk for transmission of SARS-CoV-2 in the form of aerosolized respiratory droplets during the nebulized treatment of patients with COVID-19. A review of the literature suggested that there is a lack of clear evidence to suggest that nebulized treatment transmits SARS-CoV-2 particles. Based on the lack of evidence, healthcare providers should critically evaluate the available data and exercise clinical judgment when considering treatment for patients.

Hess (2020) [Letter] Nebulized therapy in the COVID-19 era: The right tool for the right patient[14]

Nebulizers should remain the preferred option for patients who require that treatment, especially in light of the severe shortage of MDIs. This approach does not conflict with recent COVID-19 guidance and can serve as an example encouraging best practices even after the pandemic.

The National Institute for Health and Care Excellence (NICE) and the UK Government guidance from the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) recommend the continued use of nebulizers because the aerosols produced are generated from fluid within the nebulizer chamber that does not carry patient-derived viral particles. If a particle in the aerosol coalesces with contaminated mucous membrane, it ceases to be airborne and therefore will not be aerosolized. The Global Initiative for Chronic Obstructive Lung Disease advises that patients with chronic obstructive pulmonary disease maintain their regular therapy and recommends nebulizers for those who need them and MDIs for patients who are suitable for them.

At present, only a few studies have investigated the risk of aerosol-generating treatments spreading any type of coronavirus. A 2012

[13] Woods JA. Evidence-based treatment during the SARS-CoV-2 pandemic: Identifying the knowns and unknowns of nebulization. J Am Pharm Assoc (2003). 2020 Sep 30:S1544-3191(20)30475-1. doi: 10.1016/j.japh.2020.09.014. Epub ahead of print. PMID: 33160867; PMCID: PMC7524663.

[14] Hess MW. Nebulized Therapy in the COVID-19 Era: The Right Tool for the Right Patient [Letter]. Int J Chron Obstruct Pulmon Dis. 2020 Sep 7;15:2101-2102. doi: 10.2147/COPD.S272382. PMID: 32982202; PMCID: PMC7489944.

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. A recent article by Dr Arzu Ari indicates that, while unnecessary aerosol therapy should continue to be avoided, the risk of viral transmission can be minimized with basic precautions. Although limited, these studies suggest that there is no compelling reason to alter aerosol modality for patients with established nebulizer-based regimens.

Rodriguez-Martinez et al (2020) Nebulization procedures for children with unknown viral status during the COVID-19 pandemic[15]
During the COVID19 pandemic there has been much discussion about in-hospital procedures that may generate aerosols. One such procedure that has led to confusion and concern is nebulisation of children. We discuss the evidence around whether nebulisation procedures generate aerosols, and offer strategies around nebulisation of children with asthma.

Sinha et al (2020) Aerosol-Containment Device for Prevention of Aerosol Dispersion During Nebulization in COVID-19 Patients[16]
Aerosol-generating procedures and nebulization have the potential for fugitive emissions and carry a higher risk of transmission of the virus to the surrounding environment and should be performed only when absolutely necessary in negative-pressure environments with frequent air exchanges under the care of highly trained personnel. It is advised to consider pressurized metered-dose inhalers and dry powder inhalers for aerosol drug delivery instead of nebulizers whenever feasible in COVID-19 patients. However, the nebulizer is irreplaceable in uncooperative patients, patients with life-threatening respiratory disease, and poor response to metered-dose inhaler with

[15] Rodríguez-Martínez CE, Sinha IP, Whittaker E, Nagakumar P, Fernandes RM. Nebulization procedures for children with unknown viral status during the COVID-19 pandemic. J Asthma. 2020 Oct 1:1-2. doi: 10.1080/02770903.2020.1827418. Epub ahead of print. PMID: 32962456.
[16] Kumar A, Kumar A, Sinha C, Kumar N, Kumar A. Aerosol-Containment Device for Prevention of Aerosol Dispersion During Nebulization in COVID-19 Patients. J Cardiothorac Vasc Anesth. 2020 Jun 23:S1053-0770(20)30608-X. doi: 10.1053/j.jvca.2020.06.066. Epub ahead of print. PMID: 32682737; PMCID: PMC7309844.

spacer. The nebulization of drugs with a jet nebulizer causes sideways leakage of exhaled air, and the distance increases with increasing lung injury, ranging from 45 cm to 80 cm.
Some high-flow/high-velocity systems and closed positive-pressure systems have capabilities to add nebulized medications without an increased risk of particle dispersal. Placement of a viral filter in-line with a nebulizer likely decreases the risk for nosocomial or healthcare worker infection, but the efficiency of these filters in preventing the transmission and the magnitude of the risk of acquiring COVID-19 through filtered nebulizers are not fully known.

Levin et al (2020) Acute asthma management during SARS-CoV2-pandemic 2020[17]

We propose a risk stratification plan that aims to avoid nebulised therapy, when possible, by providing an algorithm to help better delineate those who require nebulised therapy. Protocols that include strategies to allow flexibility in using MDIs rather than nebulisers in all but the most severe patients should help mitigate this risk of aerosolised infection transmission to patients and healthcare providers. Furthermore, expedient treatment of patients with high dose MDI therapy augmented with more rapid initiation of systemic therapy may help ensure patients are less likely to deteriorate to the stage where nebulisers are required.

Simonds et al (2010) Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections[18]

Influenza viruses are thought to be spread by droplets, but the role of aerosol dissemination is unclear and has not been assessed by previous studies. Oxygen therapy, nebulised medication and

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[17] Levin M, Ansotegui IJ, Bernstein J, Chang YS, Chikhladze M, Ebisawa M, Fiocchi A, Heffler E, Martin B, Morais-Almeida M, Papadopoulos NG, Peden D, Wong GWK. Acute asthma management during SARS-CoV2-pandemic 2020. World Allergy Organ J. 2020 May 14;13(5):100125. doi: 10.1016/j.waojou.2020.100125. PMID: 32411315; PMCID: PMC7221365.
[18] Simonds AK, Hanak A, Chatwin M, Morrell M, Hall A, Parker KH, Siggers JH, Dickinson RJ. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Health Technol Assess. 2010 Oct;14(46):131-172. doi: 10.3310/hta14460-02. PMID: 20923611.

ventilatory support are treatments used in clinical practice to treat influenzal infection and thought to generate droplets or aerosols. Evaluation of the characteristics of droplet/aerosol dispersion around delivery systems during non-invasive ventilation (NIV), oxygen therapy, nebuliser treatment and chest physiotherapy by measuring droplet size, geographical distribution of droplets, decay in droplets over time after the interventions were discontinued. Three groups were studied: 1. normal controls; 2. subjects with coryzal symptoms; and 3. adult patients with chronic lung disease who were admitted to hospital with an infective exacerbation. Each group received oxygen therapy, NIV using a vented mask system and a modified circuit with non-vented mask and exhalation filter, and nebulised saline. The patient group had a period of standardised chest physiotherapy treatment. Droplet counts in mean diameter size ranges from 0.3 to > 10 mum were measured with a counter placed adjacent to the face and at a 1-m distance from the subject/patient, at the height of the nose/mouth of an average healthcare worker. Nebulised saline delivered droplets in the small- and medium-size aerosol/droplet range, but did not increase large-size droplet count. NIV and chest physiotherapy are droplet (not aerosol)-generating procedures, producing droplets of > 10 mum in size. Due to their large mass, most fall out on to local surfaces within 1 m. The only device producing an aerosol was the nebuliser and the output profile is consistent with nebuliser characteristics rather than dissemination of large droplets from patients. These findings suggest that healthcare workers providing NIV and chest physiotherapy working within 1 m of an infected patient should have a higher level of respiratory protection, but that infection control measures designed to limit aerosol spread may have less relevance for these procedures. These results may have infection control implications for other airborne infections, such as severe acute respiratory syndrome and tuberculosis, as well as for pandemic influenza infection.

Sandrock and Stollenwerk (2008) Acute febrile respiratory illness in the ICU: Reducing disease transmission[19]

Early recognition of a viral cause of acute febrile respiratory illness (FRI) leading to ARDS becomes important for protection of healthcare workers (HCWs), lessening spread to other patients, and notification of public health officials. These patients often have longer courses of viral shedding and undergo higher-risk procedures that may potentially generate aerosols, such as intubation, bronchoscopy, bag-valve mask ventilation, noninvasive positive pressure ventilation, and medication nebulization.

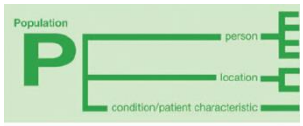
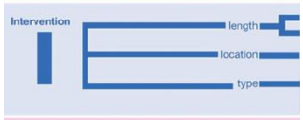
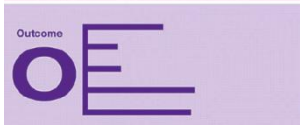
Miller and Englund (2020) Transmission and risk factors of COVID-19[20]

Aerosolization of SARS-CoV-2 can occur during procedures including bronchoscopy, endotracheal intubation, and administration of nebulized treatments.

[19] Sandrock C, Stollenwerk N. Acute febrile respiratory illness in the ICU: reducing disease transmission. Chest. 2008 May;133(5):1221-31. doi: 10.1378/chest.07-0778. PMID: 18460521; PMCID: PMC7094748.
[20] Miller R, Englund K. Transmission and risk factors of OF COVID-19. Cleve Clin J Med. 2020 May 14. doi: 10.3949/ccjm.87a.ccc029. Epub ahead of print. PMID: 32409430.

Produced by the members of the National Health Library and Knowledge Service Evidence Team†. Current as at 29 January 2021. This evidence summary collates the best available evidence at the time of writing and does not replace clinical judgement or guidance. Emerging literature or subsequent developments in respect of COVID-19 may require amendment to the information or sources listed in the document. Although all reasonable care has been taken in the compilation of content, the National Health Library and Knowledge Service Evidence Team makes no representations or warranties expressed or implied as to the accuracy or suitability of the information or sources listed in the document. This evidence summary is the property of the National Health Library and Knowledge Service and subsequent re-use or distribution in whole or in part should include acknowledgement of the service.

The following PICO(T) was used as a basis for the evidence summary:

	Patients and/or healthcare workers
	Nebulization
	
	Aerosol generation and transmission of SARS-CoV-2

The following search strategy was used:

1 exp Coronavirinae/ (22917) 2 COVID-19.ab,ti. (78267) 3 coronavirus.ab,ti. (43640) 4 "corona virus".ab,ti. (1542) 5 (Wuhan adj3 virus).ab,ti. (98) 6 ("2019-nCoV" or "2019 ncov").ab,ti. (1116) 7 "severe acute respiratory syndrome coronavirus 2".ab,ti. (8415) 8 ("2019" and (new or novel) and coronavirus).ab,ti. (7382) 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (102906) 10 exp nebulizer/ (10679) 11 (nebuliz* or nebulis* or "Aero Comfort" or "Aero Mist" or atomize* or atomise* or eRapid or nembuliz* or nembulis*).ab,ti. (17952) 12 10 or 11 (22813) 13 exp aerosol/ (56260) 14 "aerosol*".ab,ti. (64156) 15 13 or 14 (82764) 16 11 and 15 (5235) 17 9 and 16 (55)

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