Reducing Aerosol-Related Risk of Transmission in the Era of COVID-19
A Guidance Endorsed by the International Society of Aerosols in Medicine

James B Fink, PhD[1,3]; Stephan Ehrmann, MD, PhD[2]; Jie Li, PhD[3]; Patricia Dailey, MSc[4]; Paul McKiernan, PhD[4], Chantal Darquenne, PhD[5]; Andrew R. Martin, PhD[6]; Barbara Rothen-Rutishauser, PhD[7]; Philip J. Kuehl, PhD[8]; Sabine Haeussermann, PhD[9]; Ronan MacLoughlin, PhD[4,10,11,]; Gerald C. Smaldone,MD, PhD[12]; Bernhard Mullinger, BsC[13]; Timothy E. Corcoran, PhD[14]; Rajiv Dhand, MD[15].

Affiliations:

[1] Aerogen Pharma Corp., San Mateo, CA, United States
[2] CHRU Tours, Médecine Intensive Réanimation, CIC INSERM 1415, CRICS-TriggerSep research network, Tours, France ; and INSERM, Centre d'étude des pathologies respiratoires, U1100, Université de Tours, Tours, France
[3] Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University Medical Center, Chicago, IL, United States
[4]Aerogen Limited, Galway, Ireland.
[5]Department of Medicine, University of California, San Diego, La Jolla, California, United States
[6] Mechanical Engineering, University of Alberta, Edmonton, Canada
[7]Adolphe Merkle Institute, University of Fribourg, Fribourg, Switzerland
[8]Lovelace Biomedical, Albuquerque, NM, United States
[9] VisionHealth GmbH, Gate Garching, Garching Forschungszentrum, Germany
[10]School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons, Dublin, Ireland
[11]School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin, Ireland.
[12]Pulmonary, Critical Care & Sleep Medicine, Department of Medicine, State University of New York at Stony Brook, NY, United States
[13]Vectura GmbH, Gauting, Germany
[14]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PN. United States
[15]Department of Medicine, Graduate School of Medicine, University of Tennessee Health Science Center, Knoxville, TN United States

Corresponding author: James B. Fink, PhD, RRT, FCCP, FAARC
1525 Seneca Ln,
San Mateo, CA, USA 94402
Tel: +1 (650) 703-7083
Email: fink.jim@gmail.com

Abstract:

National and international guidelines recommend droplet/aerosol and contact precautions for those caring for COVID-19 patients in ambulatory and acute care settings.1,8 The new SARS-CoV-2 virus, an acute respiratory infectious agent, is primarily transmitted between people through respiratory droplets and contact routes.2,3 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 (AGPs) 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, non-invasive 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 HCWs should assume every patient is potentially infectious during this pandemic.31 Taking actions to reduce risk of transmission to HCWs is therefore a vital consideration for safe delivery of all medical

Guidance:

COVID-19 is an emerging viral pandemic affecting 213 countries. SARS-CoV-2 is the virus that causes COVID-19 and it belongs to the same class of coronaviruses as those which resulted in Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), both of which infected many health care workers (HCWs) in the course of providing patient care.[1] The new SARS-CoV-2 virus, an acute respiratory infectious agent, is primarily transmitted between people through respiratory droplets and contact routes.[2,3] A recognized key to transmission of COVID-19, and droplet infections generally, is the dispersion of bioaerosols from the patient. Droplets generated by infected persons when they cough, sneeze, talk, sing, or breathe range from 0.1 to >100 μm in diameter.[4] They can land in the mouth, nose, or eyes of those in close proximity, or may possibly be inhaled into the lungs. However, most of these droplets settle on surfaces around the infected subject, where they may remain infectious by contact for days.[5] The contribution of respirable particles < 5 μm leading to airborne transmission between individuals over long distances is less certain.[6]

Droplet transmission is by no means unique to COVID-19. Acute respiratory infections, particularly of the lower respiratory tract, are the leading cause of morbidity and mortality from infectious disease globally, accounting for greater than 4 million deaths annually.[7] Although bacteria are a common cause of lower respiratory tract infections, the majority are caused by viruses or a mix of viral/bacterial infections, all of which can be exhaled by infected patients as bioaerosols.

National and international guidelines recommend droplet/aerosol and contact precautions for those caring for COVID-19 patients in ambulatory and acute care settings.[1,8] Increased risk of transmission has been associated with Aerosol Generating Procedures (AGPs) 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, non-invasive positive-pressure ventilation, tracheostomy and cardiopulmonary resuscitation. Some of these AGPs increase the production of bioaerosols possibly containing pathogens from the patient (i.e. intubation, open suctioning tracheotomy, manual ventilation, bronchoscopy), whereas others potentially act to disperse bioaerosols from the patient to the surrounding area without evidence that they generate additional contaminated aerosols (e.g. oxygen administration, high flow nasal oxygen, and use of medical nebulizers). Medical aerosols produced by inhalers and nebulizers (such as those containing bronchodilators, anti-inflammatory agents, mucokinetics, antivirals, antibiotics and prostanoids) do not contain pathogens unless the nebulizers are contaminated by the patient or HCW. Medical aerosol from nebulization derives from a non-patient source (the fluid in the nebulizer chamber) and does not carry patient-derived viral particles. Concerns of medical aerosol becoming contaminated in the lungs prior to exhalation are not supported by evidence. Consequently, when a droplet in the aerosol coalesces with a contaminated mucous membrane, it will cease to be airborne and therefore will no longer be part of an aerosol.[9] In fact, aerosol administration could reduce

generation of bioaerosols. Edwards and colleagues reported that inhalation of an isotonic saline aerosol reduced generation of bioaerosols by as much as 72% for up to 6 hours post nebulization.[10]

Many AGPs were identified during previous outbreaks of SARS, MERS and other viral infections such as influenza A.[11,12] Early response of the SARS outbreak in Hong Kong was to ban all medical aerosols, and subsequently included them as AGPs.[11] Retrospective analysis of SARS reports and research identified pooled analysis of risk for a variety of AGPs, with intubation and non-invasive manual ventilation creating a 6.6 fold and 3.3 fold increased risk of infection of HCWs, respectively.[13] In contrast, the pooled risk from medical nebulizer treatment from 3 cohort reports was considered non-significant (0.9).[13] Nevertheless, HCWs should learn how to reduce risks associated with all aerosol delivery devices.[14,15]

Inhalers, such as pMDIs, have been suggested to reduce risk, often without supporting evidence.[16] The rationale for reduced risk may be because drug is enclosed and less open to contamination than open cup nebulizers, and the low emitted dose (100 µl/actuation) produces less aerosol mass. As with electronic nebulizer/inhalers which only emit aerosol during inspiration, exhaled bioaerosols are neither avoided nor contained with use of pMDIs or DPIs whether from cough (common with inhalers) or normal exhalation. Cough associated with inhalers or medical aerosols from nebulizers is similar to cough that is independent of inhaled medication and likely generates as much bioaerosol. Consequently, inhalers offer no innate advantage in reducing production or dispersion of patient generated bioaerosols. Even with use of valved holding chambers patient exhalation exhausts directly to the atmosphere unless there is a mechanism to filter patient exhalation.

Medical nebulizer treatments may increase the mass and dispersion of aerosol;[17,18] however, they do not increase the infective load of bioaerosols unless the nebulizer is contaminated.[19] Nebulizers with open reservoirs positioned below the ventilator circuit or mouthpiece present a risk of contamination by secretions, condensate and even bioaerosols.[20] Once medication in the nebulizer is contaminated the resulting aerosol emitted may increase the viral load with adverse consequences for both the patient and the environment. This is the basis of Centers for Disease Control and Prevention (CDC) recommendations that jet nebulizers be replaced, rinsed, air dried, washed, disinfected and/or sterilized after each treatment.[21] In addition, continuous jet nebulizers driven with flows up to 10 L/min may increase the dispersion of aerosol.[22] Breath actuated jet nebulizers, which produce aerosol only during inspiration, reduce fugitive emissions compared to nebulizers that operate continuously during the breathing cycle.[23]

By design, vibrating mesh nebulizers (VMNs) separate the medication from the patient interface, including breathing circuits by the barrier of the mesh. This mesh maintains pressure in the ventilator circuit when the medication reservoir is opened to add medication, without a measurable leak of gas through the nebulizer to atmosphere, allowing medication to be added without "breaking" the ventilator circuit. In addition, the medication reservoir of the VMN is positioned above the circuit, reducing the potential for gravity-dependent contamination from condensate in the circuit and patient generated secretions.[24] As VMNs do not use external gas flow to generate aerosol, they are less likely to contribute to dispersion of patient generated bioaerosol beyond patient exhalation. Consequently, one VMN is labeled as a single patient, multiple dose device that can remain in the ventilator circuit up to 28 days. Government recommendations defer to the manufacturer's product label for VMN.[25]

Independent of nebulizer selection, placing filters on nebulizers and ventilator circuits reduces fugitive emissions of infected bioaerosols generated by the patient and they reduce secondhand exposure of HCWs to aerosol medication.[26] Similarly, placing a filter on the expiratory limb of a ventilator circuit reduces escape of bioaerosols and medical aerosols, thereby reducing the risk of transmitting infection.[27]
Due to the required gas flow, dispersion of bioaerosols with oxygen administration, including venturi, simple and non-rebreather masks all have the potential to disperse bioaerosols from the patient farther than a medical jet nebuizer.[22] Placing a filter on the outlet of a nebulizer greatly reduces dispersion of all aerosols.[26,27] Placing a surgical mask over a nasal cannula, whether low or high flow, reduces dispersion of patient generated bioaerosols as well as medical aerosols.[28,29] Having patients wear surgical masks can reduce the risk of transmission to HCWs.[30]

The knowledge that COVID-19 subjects can be asymptomatic and still shed virus, producing infectious droplets during breathing, suggests that HCWs should assume every patient is potentially infected during this pandemic.[31] Taking actions

to reduce risk of transmission to HCWs is therefore a vital consideration for safe delivery of all medical aerosols. Guidelines for use of personal protective equipment (gloves, gowns, masks, shield and/or Powered Air Purifying Respirators (PAPRs) during high risk procedures are essential, and should also be considered for use with lower risk procedures such as administration of uncontaminated medical aerosols.

Recommendations:

Bioaerosols generated by infected patients are a major source of transmission for SARS CoV-2, and other infectious agents.[32] In contrast, therapeutic aerosols do not add to the risk of disease transmission unless contaminated by patients or health care workers.

- during the pandemic treat every patient as potentially infected because asymptomatic infected patients can shed virus[31];
- use Personal Protective Equipment (PPE) for aerosol and droplet protection (mask, face shield, gloves, gown);
- wash hands and put on fresh gloves prior to filling the nebulizer reservoir and administering treatments. Use proper aseptic technique to avoid contamination of aerosol reservoirs and medication;
- perform AGPs in a negative pressure room, if available, for COVID-19 patients, or rooms with high air exchange rates, and use additional PPE such as PAPRs;
- have patients wear simple mask when possible (i.e. over simple nasal cannula and HFNC) and between treatments;
- have tissues available and encourage covering cough or sneeze with tissues; discard used tissue immediately;
- reduce dispersion of aerosols:
    - use mouthpiece with handheld applications when possible, since both open and valved aerosol masks release more aerosol to atmosphere and are harder to filter[26];
    - social distancing: While 6 feet (2 meters) is the rule on the street, when treating patients try to stay more than 45 cm (maximum dispersion distance with oxygen and medical aerosol) away from the patient's airway[28]
    - Minimize release of medical aerosols, to minimize second-hand exposure of medication and dispersion of bioaerosols into the environment: use a VMN with valved chamber in which medical aerosol collects and is available on demand, or a breath synchronized nebulizer that does not generate aerosol after inhalation[23];
    - place filter on exhalation port of nebulizers, NIPPV circuits and ventilators [26,27];
    - avoid breaking open the ventilator circuit to add medication or change nebulizers, as this generates aerosol from condensate that may be infectious[21];
    - aerosol can be administered via HFNC; higher flows can reduce dispersion[32]
    - A surgical mask placed over oxygen cannulas, nose and mouth acts as a barrier to contain bioaerosols generated and reduce dispersion distance [28,29]
    - Medical nebulizers should be disposed of, rinsed, air dried, washed or sterilized between treatments or if VMN based on manufacturer label[21, 25]

Note: HCWs should comply with the requirements and guidelines of their region and institution.

References:

1. WHO. Coronavirus disease (COVID-19) technical guidance: infection prevention and control / [website]. Geneva: World Health Organization; 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/infection-prevention-and-control, accessed 16 March 2020).
2. Ong SWX, Tan YK, Chia PY, Lee TH, Ng OT, Su M, Wong Y, Marimuthu K. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (sars-cov-2) from a symptomatic patient. *JAMA.* 2020;e203227.
3. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EH, Wong JY, Xing X, Xiang N, Wu Y, LiC. Chen Q, Le D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yan R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Fing Z. Early transmission dynamics in wuhan, china, of novel coronavirus-infected pneumonia. *N Engl J Med.* 2020;382(13):1199-1207.
4. Yan J, Grantham M, Pantelic J, Bueno de Meqauita PJ, Albert B, Liu F, Ehrman S, Milton DK, EMIT Consortiuml. Infectious virus in exhaled breath if symptomatic seasonal influenza cases from a college community. PNAS 2018.1125(5); 1081-1086
5. van Doremalen N, Bushmaker T, Morris DH, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith, de Wit E, Munster VJ. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *The New England journal of medicine.* 2020.ce.
6. Seto WH. Airborne transmission and precautions: facts and myths. Journal of Hospital Infection 2015. 89:225-228.
7. GBD 2016 Lower Respiratory infection Collaborators. Estimates of the global, regional and national morbidity , mortality and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the global burden of disease study 2016. Lancet Infect Dis. 2018 Nov; 18(11): 1191-1210.
8. CDC, Coronavirus Disease, 2019. Interim US Guidance for risk assessment and public health management of healthcare personnel with potential exposure in a healthcare setting to patients with coronavirus disease
9. https://www.rdash.nhs.uk/wp-content/uploads/2017/08/Appendix-46-Aerosol-Generating-Procedures.pdf
10. Edwards DA, Man JC, Brand P, Katwsta JP, Sommerer K, Stone HA, Nardell E, Scheuch G. Inhaling to mitigate exhaled bioaerosols. *Proc Natl Acad Sci U S A*. 2004;101(50):17383-17388.
11. Ofner M, Lem M, Sarwal S,Vearncombe M, Simor A. Cluster of severe acute respiratory syndromecases among protected health-care workers – Toronto, Canada, April 2003.JAMA 2003; 289:2788–2789; Reprinted from MMWR, vol 52, pg 433-436,2003
12. Centers for Disease Control and Prevention (CDC). Cluster of severe acute respiratory syndrome cases among protected health-care workers--Toronto, Canada, April 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52(19):433–436.
13. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: A systematic review. PLoS One 2012; 7: e35797
14. Bing-Yuan, Zhang YH, Leung NHL, Cowling BJ, Yang ZF Role of viral bioaerosols in nosocomial infections and measures for prevention and control. J Aerosol Sci. 2018 Mar;117:200-211. doi: 10.1016/j.jaerosci.2017.11.011. Epub 2017 Dec
15. Siegel, J. D., Rhinehart, E., Jackson, M., & Chiarello, L. (2007). Health care infection control practices advisory committee. 2007 guideline for isolation precautions:preventing transmission of infectious agents in health care settings. American Journal of Infection Control, 35(10 Suppl 2), S65–S164 [PubMed:18068815].
16. Branson RD, Hess DR, Kallet R, Robinson L. *AARC SARS CoV-2 Guidance Document. https://www.aarc.org/wp-content/uploads/2020/03/guidance-document-SARS-COVID19.pdf (accessed 4 April 2020).*
17. O'Neil CA, Li J, Leavey A, Wang Y, Hink M, Wallace M, Biswas P, Burnham CD, Babcock HN+M; Centers for Disease Control and Prevention Epicenters Preogram. Characterization of Aerosols Generated During Patient Care Activities. *Clin Infect Dis*. 2017;65(8):1335–1341. doi:10.1093/cid/cix535

18 Simonds A, Hanak A, Chatwin M, Morrell M, Hall A, Parker K, et al. 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 [Internet]. 2010 Oct [cited 2020 Apr 1];14(46). Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta14460-02/

19 Liu, Y. Ning Z, Chen Y, Guo M, Liu Y, Gali NK, Sun L, Duan Y, Cai J, Westerdahl D, Liu X, Xu K, Ho K_F, Kan Hl.Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals.Nature https://doi.org/10.1038/s41586-020-2271-3 (2020).

20 Craven DE, Lichtenberg DA, Goularte TA, Make BJ, McCabe WR. Contaminated medication nebulizers in mechanical ventilator circuits. Source of bacterial aerosols. *Am J Med*. 1984;77(5):834–838. doi:10.1016/0002-9343(84)90520-5

21 Guidelines for Preventing Health-Care--Associated Pneumonia, 2003 Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee

22 Hui DS, Chan MT, Chow B. Aerosol dispersion during various respiratory therapies: a risk assessment model of nosocomial infection to health care workers. *Hong Kong medical journal = Xianggang yi xue za zhi.* 2014;20 Suppl 4:9-13.

23 O'Toole C, McGrath J, Bennett G, Joyce M, MacLoughlin RJ, Byrne M, editors. Fugitive Emissions from a Breath Actuated Jet Nebuliser and a Vibrating Mesh Nebuliser for a Paediatric Patient. ISES-ISIAQ 2019; 2019; Kaunas, Lithuania

24 O'Malley CA. Device Cleaning and Infection Control in Aerosol Therapy. *Respir Care*. 2015;60(6):917–930.

25 Nebulizer Cleaning—Final State Survey Worksheets Released; **Updated**: April 20, 2017 https://www.aarc.org/nebulizer-cleaning/

26 McGrath JA, O'Sullivan A, Bennett G, O'Toole C, Joyce M, Byrne MA, et al. Investigation of the Quantity of Exhaled Aerosols Released into the Environment during Nebulisation. Pharmaceutics. 2019;11(2):75.

27 Ari A. Secondhand aerosol exposure during mechanical ventilation with and without expiratory filters: an in-vitro study. Indian J Respir Care. 2016;5:1-6.

28 Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.00892-2020).

29 Leonard S, Atwood CW Jr, Walsh BK, DeBellis RJ, Dungan GC, Strasser W, Whittle JS. Preliminary findings of control of dispersion of aerosols and droplets during high velocity nasal insufflation therapy using a simple surgical mask: Implications for high flow nasal cannula. Chest. 2020 Apr 2. pii: S0012-3692(20)30579-1. doi: 10.1016/j.chest.2020.03.043. [Epub ahead of print]

30 Milton DK, Fabian MP, Cowling BJ, Grantham ML, McDevitt JJ. Influenza virus aerosols in human exhaled breath: particle size, culturability, and effect of surgical masks. *PLoS Pathog*. 2013;9(3):e1003205. doi:10.1371/journal.ppat.100320527

31 Bowdle A, Munoz-Price LS. Preventing Infection of Patients and Healthcare Workers Should Be the New Normal in the Era of Novel Coronavirus Epidemics [published online ahead of print, 2020 Mar 25]. *Anesthesiology*. 2020;10.1097

32 McGrath JA, O'Toole C, Bennett G, Joyce M, Byrne MA, MacLoughlin R. Investigation of Fugitive Aerosols Released into the Environment during High-Flow Therapy. Pharmaceutics. 2019;11(6):254.

33 Shiu EYC, Leung NHL, Cowling BJ. Controversy around airborne versus droplet transmission of respiratory viruses: implication for infection prevention. *Curr Opin Infect Dis*. 2019;32(4):372–379.