

## Author Response

### Reviewer #1

#### Comments to the Author

It is an important paper with a clear message and fine style.

#### Response:

- **We thank the reviewer for their encouraging comment. We note that there were no specific comments to address from Reviewer #1.**

### Reviewer #2

#### Comments to the Author

Dr. Sethi and his colleagues provided a narrative review of “The use of nebulized pharmacotherapies during the COVID-19 pandemic.” The review is certainly helpful and gives a good overview of the literature; however, there are some points that need to state more clearly. The authors should also add several current publications to this manuscript. Please see below for more information.

#### Response:

- **We appreciate the reviewer’s evaluation of the manuscript. Please find responses to your specific comments below.**

INTRODUCTION: The introduction should provide an objective evaluation of nebulizers and current literature.

Page 3, Line 18-25: A few organizations and recently published papers that did not recommend using nebulizers in COVID-19. Please add them to the paper to provide a more objective review. I copy them below for your convenience.

The Canadian Paediatric Society Practice Point. Paediatric asthma and COVID-19. 2020 May 25, 2020]; Available from: <https://www.cps.ca/en/documents/position/paediatric-asthma-and-covid-19>

Global Initiative for Asthma. [www.ginasthma.org](http://www.ginasthma.org) COVID-19: March 25 2020.  
<https://ginasthma.org/covid-19-gina-answers-to-frequently-askedquestionson-asthma-management/>.

Mei-Zahav M, Amirav I. Aerosol treatments for childhood asthma in the era of COVID-19. *Pediatric pulmonology*. 2020.

Amirav I, Newhouse MT. Transmission of coronavirus by nebulizer: a serious, underappreciated risk. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2020; 192:E346.

Ari A. Practical strategies for a safe and effective delivery of aerosolized medications to patients with COVID-19. *Respiratory medicine*. 2020; e-pub ahead of print.

Ari A. Use of aerosolised medications at home for COVID-19. *Lancet Respir Med*. 2020

**Response:**

- **We thank the reviewer for providing the above references. We cited the Canadian Paediatric Society and Global Initiative for Asthma in the Introduction section (page 3/paragraph 2/lines 3-5) and revised the text as follows: “The Canadian Paediatric Society and the Global Initiative for Asthma have both advised against the use of nebulized treatment unless absolutely necessary.”**
- **The references (Amirav I, Newhouse MT *CMAJ* 2020 and Mei-Zahav M, Amirav I *Pediatr Pulmonol* 2020) were added as citations in the introduction section following this sentence “Despite the lack of evidence, there is currently a heightened concern regarding the potential risk of transmission of SARS-CoV-2 in the form of aerosolized respiratory droplets from patients with COVID-19 undergoing nebulized treatment.”**
- **We do not believe the references (Ari A. *Lancet Respir Med* 2020 and Ari A. *Respir Med* 2020) specifically recommended against nebulization in the treatment of COVID19. In the paper Ari A. *Lancet Respir Med* 2020, the author proposes protective measures (eg, use of HEPA filters, negative pressure rooms, personal protective equipment) if nebulized treatment is indicated in patients with COVID-19. Similarly, in the paper Ari A. *Respir Med* 2020, the author recommends protective measures in the home setting if patients require nebulized therapy (eg, carrying out nebulization near open windows/areas of increased air circulation, avoiding nebulization in the presence of other people, and stringent nebulizer hygiene). We discuss these concepts in the Protective measures section, and added both citations to this section (Ari A. *Lancet Respir Med* 2020 and Ari A. *Respir Med* 2020).**

SELECTION OF ARTICLES FOR REVIEW

Page 4, Line 14-23 I am surprised to see that some of the references that I listed above were missed by the authors. Please update this section as more paper has been published since May 11.

**Response:**

- **We thank the reviewer for bringing these references to our attention. We updated the PubMed search to July 7, 2020. (Selection of articles for review/page 4/paragraph 1/line 2)**

OVERVIEW OF THE TRANSMISSION ROUTES OF RESPIRATORY VIRUSES

Page 4, Line 37: Please cite the following sentence “These generally travel no further than 1 meter before settling.” After reading the study conducted by Tang et al, I believe that it is not true for jet nebulizers. Please revise this section based on the article below and add it to your references.

Tang JW, Kalliomaki P, Varila TM, Waris M, Koskela H. Nebulisers as a potential source of airborne virus. *J Infect*. 2020

**Response:**

- **Please note that this sentence refers to large droplets in relation to the transmission of viruses and does not refer specifically to nebulizers. The references Tellier R, et al. *BMC***

*Infect Dis* 2019 and Kutter J, et al. *Curr Opin Virol* 2018, support the following sentence “These generally travel no further than 1 meter before settling,” and these were added as citations. (Overview of the transmission routes of respiratory viruses/page 4/paragraph 1/line 7)

- We further discussed the Tang JW, et al. *J Infect* 2020 reference in the Nebulization and viral transmission section (page 6/paragraph 1/lines 12-21 & page 7/paragraph 1/lines 1-2). We added the following text “Another study by Tang and colleagues simulated a spontaneously breathing adult patient receiving nebulized therapy with a jet nebulizer and a face mask. Air samples obtained from three separate locations indicated 612 viruses per liter near the head, 174 viruses per liter near the abdomen, and 118 viruses per liter near the feet using a live attenuated influenza vaccine as a surrogate virus tracer. The findings of this experimental study showed that the aerosols spread at a decreasing concentration with increasing distance from the patient. It is possible that the jet nebulizer with the facemask increased the risk of transmission because viral secretions can enter into the nebulizer’s reservoir. To reduce viral transmission, jet nebulizers need to be used with the mouthpiece, and HCP should attach filters or one-way valves to the large bore tubing of the nebulizer to prevent emissions during aerosol therapy. Another option would be to use a mesh nebulizer combined with the mouthpiece and a filter to the other end of the mouthpiece to minimize viral spread to the environment.”

#### REVIEWS ON THE TRANSMISSION OF CORONAVIRUSES

Page 5, Line 3-5: The following statement is not correct based on the study above. Please revise. “The concentration of SARS-CoV-2 RNA detected in aerosols in isolation wards and ventilated patients’ rooms was very low”

Response:

- We would like to clarify that the sentence in the Reviews on the transmission of coronaviruses section (page 5/paragraph 1/lines 1-2) “The concentration of SARS-CoV2 RNA detected in aerosols in isolation wards and ventilated patients’ rooms was very low” refers to a separate study in two Wuhan hospitals. We cited the reference “Liu Y, et al. *Nature* 2020” following this sentence.

Page 7, Line 19-20, and Line 26. I don’t agree with these statements. I also believe that it is important to provide an objective evaluation on nebulizers. Therefore, please remove these sentences from the paper. It is also important to add the following references to explain issues with hand-held jet nebulizers and exhaled air dispersion due to external gas flow used to operate the hand-held jet nebulizer. Also, Tang’s study is a piece of evidence that hand-held nebulizers may increase viral transmission even in isolated rooms.

D. Ciuzas, T. Prasauskas, E. Krugly, et al., Characterization of indoor aerosol temporal variations for the real-time management of indoor air quality, *Atmos. Environ.* 118 (2015) 107–117.

J. McGrath, M. Byrne, M. Ashmore, A. Terry, C. Dimitroulopoulou, A simulation study of the changes in PM2.5 concentrations due to interzonal airflow variations caused by internal door opening patterns, *Atmos. Environ.* 87 (2014) 183–188.

Rau JL, Ari A, Restrepo R. Performance comparison of nebulizer designs: Constant-output, breath-enhanced, and dosimetric. *Respiratory Care* 2004; 49(2): 174-179

Ari A. Jet, mesh and ultrasonic nebulizers: An evaluation of nebulizers for better clinical practice. Eurasian Journal of Pulmonology. 2014

**Response:**

- We thank the reviewer for his/her comments. For the initial statement mentioned above (Nebulization and viral transmission/page 7/paragraph 3), we amended the text as follows: *“Overall, the evidence to date has not been definitive in determining whether a direct link exists between nebulization and increased coronavirus transmission. Thus, further research is required to confirm whether this association exists.*
- For the second statement mentioned above (Handheld inhalers and viral transmission/page 7/paragraph 1/line 1), we amended the text as follows: *“At present, there does not appear to be a concern with handheld inhalers and viral transmission.”*
- In relation to the Tang et al. *J Infect* 2020 study and the other publications suggested by the reviewer (Ciuzas D, et al. *Atmos Environ* 2015; McGrath J, et al. *Atmos Environ* 2014; Rau JL, et al. *Respir Care* 2004; Ari A. *Eurasian J Pulmonol* 2014), we added the following text to the Nebulization and viral transmission section (page 6/paragraph 1/lines 12-21 & page 7/paragraph 1/lines 1-2) *“Another study by Tang and colleagues simulated a spontaneously breathing adult patient receiving nebulized therapy with a jet nebulizer and a face mask. Air samples obtained from three separate locations indicated 612 viruses per liter near the head, 174 viruses per liter near the abdomen, and 118 viruses per liter near the feet using a live attenuated influenza vaccine as a surrogate virus tracer. The findings of this experimental study showed that the aerosols spread at a decreasing concentration with increasing distance from the patient. It is possible that the jet nebulizer with the facemask increased the risk of transmission because viral secretions can enter into the nebulizer’s reservoir. To reduce viral transmission, jet nebulizers need to be used with the mouthpiece, and HCP should attach filters or oneway valves to the large bore tubing of the nebulizer to prevent viral emissions during aerosol therapy. Another option would be to use a mesh nebulizer combined with the mouthpiece and a filter to the other end of the mouthpiece to minimize viral spread to the environment.”*

**THE RIGHT TOOL FOR THE RIGHT PATIENT & PROTECTIVE MEASURES**

These sections are nicely written. Some of the concepts were introduced in the previous publications listed below. Please cite them in this section.

**Response:**

- We thank the reviewer for their encouraging comment. We included the following text in the Protective measures section (page 10/paragraph 2/lines 9-10): *“In order to minimize viral transmission, it is recommended that nebulizers are used with a mouthpiece and a filter.”*