

Peer Review File

Article information: <http://dx.doi.org/10.21037/atm-20-4633>

Reviewer A

Comment 1: In my opinion, the title does not reflect appropriately the topic of the paper (the evidence regarding the non-pharmacological management of SARS-CoV-2 infection). Please, amend it.

Reply 1: We changed the title as suggested. **Page 1, Lines 2-3**

Changes in the text: Changed title to “A Narrative Review of Non-Pharmacological Management of SARS-CoV-2 Respiratory Failure: A Call for an Evidence based Approach”

Comment 2: The paper is focused on the respiratory failure in patients infected by SARS-CoV-2. Therefore, the pathophysiological mechanisms leading to lung injury should be briefly reported (DOI: 10.1152/ajplung.00189.2020).

Reply: We have added relevant pathophysiological mechanisms as suggested. Added the relevant citation to the text. **Page 4, Lines 63-68.**

Changes in the text: Added “The renin-angiotensin system (RAS) arm disequilibrium caused by SARS-CoV-2 has been hypothesized to be the pathophysiological hallmark of the disease. Binding of the SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) causes its functional downregulation, thereby enhancing the classic RAS and attenuating the anti-RAS arm. This disequilibrium leads to an intense inflammatory response resulting in leaky pulmonary capillaries and eventual fibrosis.”

Comment 3: In the section regarding corticosteroids, the preliminary results of the RECOVERY trial on COVID-19 should be mentioned (DOI: 10.1056/NEJMoa2021436).

Reply: We have changed our position on corticosteroids based on the recently conducted RECOVERY trial, as suggested by the Reviewer A. [Page 12, Lines 237-243.](#)

Changes in the text:

“A large randomized control trial conducted by RECOVERY Collaborative Group showed that the patients infected with SARS-CoV-2, who received dexamethasone had a significantly lower 28-day mortality (21.6% vs 24.6%; $P < 0.001$), the effect being more pronounced in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%; $P < 0.001$) and supplemental oxygen (21.5% vs. 25.0%; $P = 0.022$) (49). Based on this overwhelmingly positive evidence, we suggest the routine use of dexamethasone in patients with COVID-19 who present with respiratory failure requiring supplemental oxygen or mechanical ventilation.”

Comment 4: Figure 1 should be cited in the text.

Reply: Figure 1 cited as instructed. [Page 5, line 86.](#)

Changes in the text: Added (Figure 1)

Reviewer B

Comment 1: line 49: “Global mortality has been reported at 4.7% with case fatality ratio (CFR) at 1.4 %.” “>> how are these numbers estimated or defined in the studies mentioned?”

Reply 1: We have updated the CFR based on the recent trend. The latest data has been taken from <https://ourworldindata.org/mortality-risk-covid#>, they have estimated CFR based on the total number of confirmed cases of COVID-19 and the total number of deaths, for each country or region that had at least 100 confirmed cases. [Page 3, lines 49-52](#)

Changes in the text:

Depending upon the country the case fatality rate (CFR) ranges from 0.25% to 10%, (4). However, due to the lack of standardized criteria for testing and for the recording of deaths, the

real mortality rate and CFR will be unknown and will likely change once the actual prevalence of the disease becomes apparent.

Comment 2: 69: “.. rising death toll...” > use comma not semicolon

Reply 2: changed to comma, [page 4 line 75](#)

Changes in the text: ; changed to ,

Comment 3: “A cultural shift away from evidence based medicine...”>> This sentence appears crucial for the paper: therefore, it should be made more explicit, not only referring to another paper having the same conclusion. Or, give examples.

Reply 3: We appreciate the reviewer’s suggestion. In order to bring in more clarity we have highlighted few of the examples. [Pages 4-5 lines 80-83](#)

Changes in the text: Changed the text to “Casting aside lessons learned over two decades of ARDS management in favor of anecdotal therapies (interleukin receptor 6 antagonists, inhaled nitric oxide, empiric anticoagulation etc.) or management strategies (liberalization of tidal volume, low positive end expiratory pressure or PEEP, delayed intubation etc.), however well intentioned, does not augur well for our patients or the practice of critical care.”

Comment 4: Put a comma after ‘failure’ and before HFNC

Reply 4: added comma after ‘failure’ and before HFNC. [Page 6, Line 106](#)

Changes in the text: added ,

Comment 5: Put a comma after ‘failure’ and before HFNC

Reply 5: changed hypoxemic respiratory failure to AHRF and added comma after AHRF and before HFNC. [Page 6, Line 110](#)

Changes in the text: AHRF,

Comment 6: “NIPPV may also aggravate lung injury in these patients (...)” >> Also this sentence is crucial for the author’s narrative: therefore, give additional support by providing some numbers or statistics (even when the information is derived from another source!).

Reply 6: We have substantiated our narrative with the data from a recent publication in ATS. [Page 6, lines 113-117](#)

Changes in the text: text changed to “A recent study found that in patients with moderate or severe AHRF on NIPPV, the median swing in esophageal pressure was 34 cmH₂O and the median exhaled tidal volume was 11 mL/kg of predicted body weight (PBW) (22). Such large swings in transpulmonary pressures, generating unsafe tidal volumes, can further aggravate the lung injury (23).”

Comment 7: “Anecdotal reports of delaying intubation by instituting this therapy are prevalent among clinicians.”>> Numbers??

Reply 7: Per the reviewer’s earlier suggestion in being explicit about the data and recently published newer evidence we have extensively revised the whole paragraph. We have deleted the anecdotal comment due to lack of consistent data. The general theme of the paragraph to avoid delays in intubation remains the same. [Page 7, lines 122-137](#)

Changes in the text: Paragraph has been revised to

“A recently published study prior to the COVID-19 pandemic (n=20) showed that early application of awake prone positioning with HFNC prevented intubation in patients with moderate ARDS (25). Since the pandemic, multiple studies have tried to evaluate the effect of

awake proning in AHRF patients with COVID-19. In a study on 50 non intubated patients with COVID-19, Caputo and colleagues(26) found a statistical increase in SpO2 5 minutes after awake proning (preproning: 84%; interquartile range [IQR], 75%-85%; postproning: 94%; IQR, 90%-95%; P = .001). Sartini and colleagues showed improvement in respiratory rates (P < .001) and SpO2 and PF ratios (P < .001) after awake proning in patients who were hypoxemic despite being on NIPPV(27). In another observational study, awake proning improved oxygenation in only 25% of the patients(28). Finally, Thomson et al had similar findings of improvement in SpO2 1 hour after initiation of prone position in spontaneously breathing patients with COVID-19 severe AHRF(29). Although early improvement in physiological parameter like oxygenation looks promising, none of the studies were randomized and did not evaluate patient centered or long term mortality outcomes. Relevant concerns have been raised that the use of awake proning could potentially delay the intubation(30), which has been associated with increased mortality in patients with ARDS(31). The safety of this procedure in diverse populations and the overall rates of eventual intubation are also significant safety end points that have not been adequately studied at this time. So, in the absence of a randomized trial, this evidence is weak at best with insufficient evidence in support its efficacy or safety. Due to the rapid fulminant progression of this disease, intubation should not be delayed for a trial of such unproven therapies.”

Comment 8: “Based on the evidence we have;..” > use comma not semicolon.

Reply 8: changed to comma **Page 8, line 150**

Changes in the text: changed ; to ,

Comment 9: Check syntax: finite verb is missing.

Reply 9: We rephrased the whole line to bring the clarity to our message. **Page 8, Lines 162-165**

Changes in the text: text is changed to “Instead, surrogate measures of the respiratory system mechanics (i.e. plateau pressure, driving pressure and compliance) as calculated on the ventilators

should be used to set inflation pressures while being mindful of the twin dictates of ventilator management in ARDS, namely limiting volutrauma and barotrauma.”

Comment 10: “(...) or there is evidence of flow starvation (...)” > missing word ‘if’?

Reply 10: Added “if” [Page 9, line 171](#)

Changes in the text: added “if”

Comment 11: Put a comma after ‘shock’.

Reply 11: Comma added. [Page 10, line 187](#)

Changes in the text: added ,

Comment 12: “Neuromuscular blocking agents (NMBA)...” > which one? Give name of substance or product name, not only a title from the reference list (difficulty to check what is meant)

Reply 12: We have rephrased the paragraph with the names of the agents. [Page 11, lines 213-219](#)

Changes in the text: changed to “Neuromuscular blocking agents (NMBA) like cisatracurium were previously employed as continuous infusions for management of patients with ARDS(44). However, current literature(45) has questioned that use. We advocate the use of NMBAs, if ventilator dyssynchrony persists despite optimal use of analgesia and sedation. NMBA boluses like rocuronium, with deliberate attempts at ventilator manipulation to offset the dyssynchrony should be considered as the initial treatment of choice as opposed to a continuous infusion(15).

Comment 13: “Patients with suspected myocardial (...) should a 12-lead EKG ..” >> (finite) verb is missing.

Reply 13: added get. **Page 14, line 281.**

Changes in the text: added “get”

General Comment: ... However, at several occasions, the paper should become more transparent when specific cases - or particular examples -, as well as statistical analysis, or significant effects on mortality rates would be given, and not only a reference to the literature

Reply: we have added statistics with reference to mortality or outcomes where ever necessary

Changes in the text: with paragraphs and lines are as follows:

(9RCTs; n=2093; RR 0.85, 95% CI 0.74–0.99)- **Page 6; Line 107-108**

(Odds Ratio 3.1; 95% CI 1.4- 6.8)- **Page 6; Line 118**

(14.6±0.5 days vs. 12.1±0.5 days, P<0.001)- **Page 9; line 185-186**

(13.4±0.4 days vs. 11.2±0.4 days, P<0.001)- **Page 9; line 186**

with no difference in 90-day mortality (42.5% vs 42.8% , 95% CI –6.4 to 5.9; P=0.93)- **Page 11; lines 215-216**

(meta-analysis- 34% vs 47% ; RR 0.73 [95% CI 0.58–0.92]; p=0.008)- **Page 12; lines 230-231**

Updated the word count to 3125- **Page2; Line 22**