Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Should inhaled nitric oxide be used in patients with COVID-19?

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RECOMMENDATION

We recommend against the use of nitric oxide among patients with COVID-19. *(Low certainty of evidence; Strong recommendation)*

Consensus Issues
A strong recommendation against the use of nitric oxide was unanimously given on the basis of low certainty of currently available evidence (non-peer reviewed pre-print article with small population and imprecision of effect estimates) to justify its use and the high cost of the intervention.

Key Findings

One open-label randomized controlled trial showed that the administration of inhaled nitric oxide as an adjunct to standard-of-care among hospitalized patients with moderate COVID-19 infection had no significant difference in 28-day mortality, need for mechanical ventilation, intensive care unit length of stay, hospital length of stay, viral clearance, and two-point WHO Ordinal Scale improvement when compared to standard-of-care alone. The incidence of methemoglobinemia was also not significantly different among patients who were given inhaled nitric oxide compared to those who received standard-of-care. The certainty of evidence was low due to lack of allocation concealment and serious imprecision of effect estimates.

Introduction

COVID-19 is an ongoing pandemic from the SARS-COV-2 virus. While vaccines have been made available to protect against the deadly disease, to date, there has been no specific drug identified to treat the infection as it continues to spread around the globe. Nitric oxide (NO), a free radical that has bronchodilator and vasodilator effects, has been shown to inhibit viral replication and inactivate viruses as previous studies from the 2004 SARS-CoV infection demonstrated.[1,2] In addition, NO plays a key role in vascular function and regulating the inflammatory cascade which, when excessively activated, can lead to acute respiratory distress syndrome (ARDS) and acute lung injury (ALI).[3,4] Knowing its pathophysiology and its potential role in mitigating viral infections, NO is currently being suggested as a potential therapy for severe and critical COVID-19 patients.

Review Methods

A search was done through PubMed of available studies to search for the best evidence of the role of nitric oxide in COVID-19 patients. The following search terms were used: “inhaled nitric oxide”, “therapy”, “COVID 19 treatment”. A total of 30 studies were retrieved after data search. After duplicates were removed, a total of 28 studies were screened with 7 articles excluded after title/abstract screening due to different primary outcome of interest (pulmonary hypertension

reversal), use of another intervention on top of inhaled nitric oxide (veno-venous ECMO) and population of interest (mild COVID patients treated in OPD setting). After review of inclusion criteria, a total of 8 studies were included in the final review and a randomized controlled trial was included in the final evidence summary.

Results

A single randomized control trial [5] was included in the final evidence review (n = 25, low certainty of evidence). The study was a phase II open label, randomized controlled trial done in a tertiary hospital in India. A total of 29 patients with moderate COVID (SpO_2 <94%, Respiratory Rate> 24) were enrolled with 25 patients completing the trial (treatment group = 14, control group = 11). Inhaled nitric oxide (iNO) was given via pulse in a crescendo-decrescendo pattern twice daily for 3 consecutive days. Primary outcome was decline in viral load, and cycle threshold was measured pre-, during and post-treatment.

Mortality and need for invasive mechanical ventilation

A total of 4 patients died in the control group (4/11, 36%) while none died in the iNO group. Moreover, 4 other patients in the control group also required mechanical ventilation.

Other important outcomes

Longitudinal analysis of viral loads collected on days 0, 3, 5, 7 and 10 show reduction in viral load in the iNO group with increased viral efficiency compared to the control group, which was not statistically significant (RR 1.37, 95% CI 0.96-1.97; p> 0.05 at Day 7). Other important outcomes including average length of ICU stay (MD -2.08 days, 95% CI -5.75-1.59; p>0.05), average length of hospital stay (MD -2.29 days, 95% CI -8.99-4.41; p>0.05), viral load decline at 7 days (RR 1.37, 95% CI 0.96-1.97; p >0.05) and 2 point improvement in WOS at 7 days were also not significant between the two groups (RR 1.05, 95% CI 0.74-1.49, p >0.05). None of the patients administered iNO demonstrated increase methemoglobin >3% throughout treatment.

Ongoing Studies

There are currently 10 ongoing randomized clinical trials [6-15] registered in the clinicaltrials.gov assessing the efficacy of inhaled nitric oxide for COVID-19 among adult patients.

Evidence to Decision

A study evaluating the cost effectiveness of inhaled nitric oxide in pediatric ICU patients was done in 2015 showing that the direct cost was $100 per hour regardless of dose without a statistically significant difference in mortality.[17] In the Philippines, nitric oxide is used as a biomarker of inflammation and is measured as fraction of exhaled nitric oxide (FeNO).[19] In the Philippines, FeNO has been studied for obstructive lung diseases.[20, 21] No local studies to date evaluate cost, feasibility and efficacy of FeNO for COVID-19 patients.

Recommendations from Other Groups

The Society of Critical Care Medicine recommends against the routine use of iNO in patients with COVID 19 pneumonia.[16] Instead, they recommend a trial of iNO only in mechanically ventilated patients with severe COVID ARDS and hypoxemia despite other rescue strategies. Meanwhile, the Philippine Society for Microbiology and Infectious Diseases states that there is no current evidence to support its use for patients with COVID-19.[18]

Research Gaps

Most studies on the utility of inhaled nitric oxide are observational studies and clinical trials are still ongoing to assess efficacy and safety of the intervention for COVID-19 patients.[6-15]

References

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion: inhaled nitric oxide (N=9)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)				• NO plays a key role in vascular function and regulating inflammatory cascade which when excessively activated can lead to acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) [3,4].
Benefits	Large	Moderate (2)	Small (3)	Uncertain (4)		• Significant reduction in viral load in iNO group ($p < 0.002$, $n = 23$) • Outcome of improvement ≥ 2 points in the WHO ordinal scale (WOS) for severe acute respiratory infections was also observed in the iNO group. • SOFA, total length of stay in the ICU and hospital were insignificant between the two groups.
Harm	Large	Small (7)	Uncertain	No response		• None of the patients administered iNO demonstrated increase methemoglobin > 3% throughout treatment.
Certainty of Evidence	High	Moderate	Low (7)	Very low (2)		
Balance of effects	Favors drug	Does not favor drug	Uncertain (6)			• Limited RCTs evaluating the efficacy and safety of inhaled nitric oxide for COVID-19

Values	Important uncertainty or variability	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability	No important uncertainty or variability			• No research evidence found
Resources Required	Uncertain (1)	Large cost (5)	Moderate Cost (3)	Negligible cost	Moderate savings	Large savings	• Direct cost was $100/h regardless of dose without a statistically significant difference in mortality [17].
Certainty of evidence of required resources	No included studies (5)	Very low (4)	Low	Moderate	High		• Cost is based on economic burden of disease from a study in 2015 from pediatric ICU patients. No studies were retrieved on adult patients during the evidence review.
Cost effectiveness	No included studies (8)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (7)	Reduced	Probably no impact	Increased			
Acceptability	Uncertain (7)	No (2)	Yes				
Feasibility	Uncertain (6)	No	Yes				

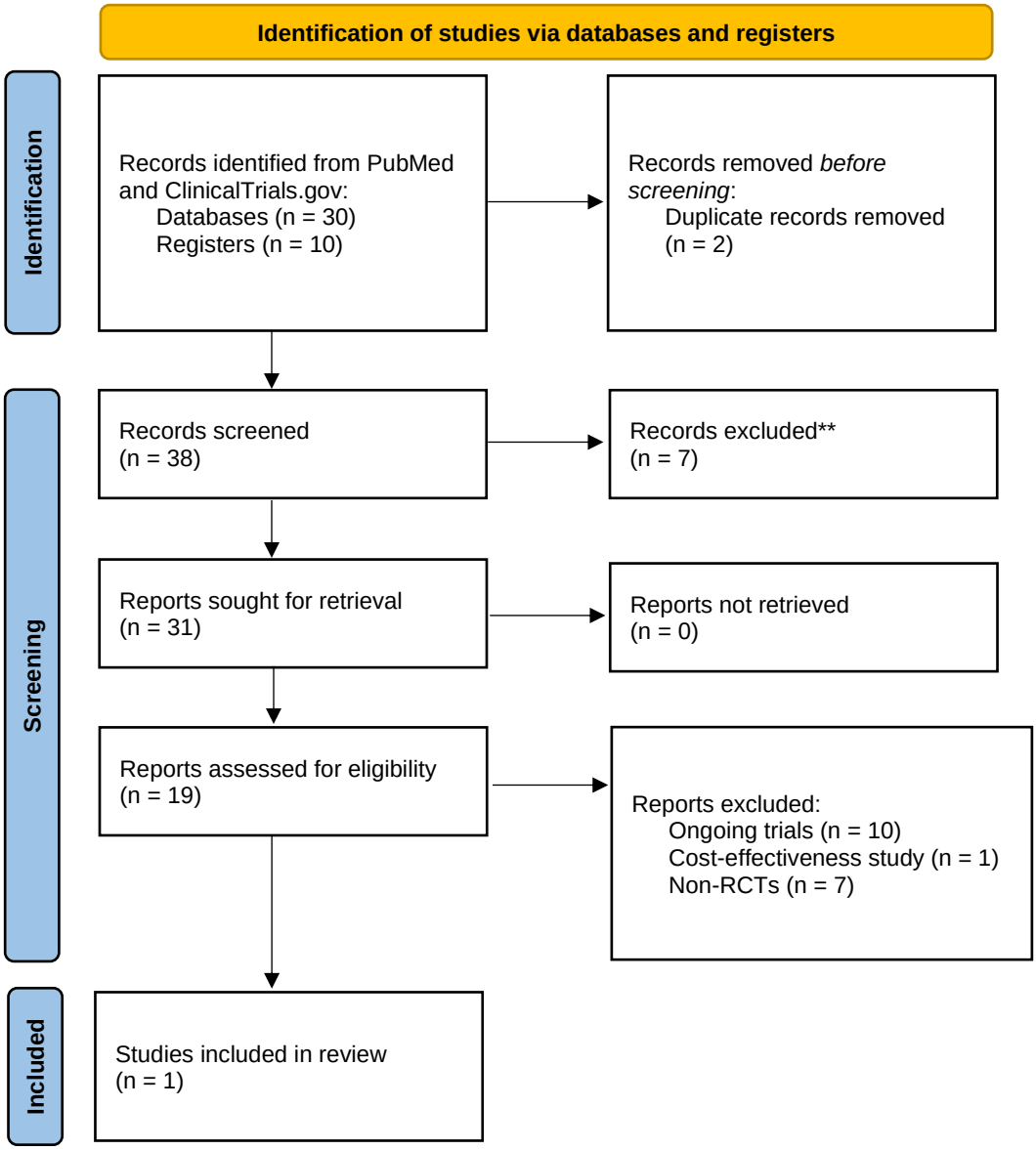
Appendix 2. Search Yield and Results

Hand searching, Google Scholar and PUBMED

Search	Query	Results
#4	#1 AND #2 AND #3 **((inhaled nitric oxide AND therapy [MeSH]) AND (COVID 19 treatment [MeSH])) AND (inhaled nitric oxide AND COVID 19)**	30
#3	**inhaled nitric oxide AND COVID 19** ("administration, inhalation"[MeSH Terms] OR ("administration"[All Fields] AND "inhalation"[All Fields]) OR "inhalation administration"[All Fields] OR "inhalant"[All Fields] OR "inhalability"[All Fields] OR "inhalable"[All Fields] OR "inhalants"[All Fields] OR "inhalated"[All Fields] OR "inhalation"[MeSH Terms] OR "inhalation"[All Fields] OR "inhal"[All Fields] OR "inhalations"[All Fields] OR "inhale"[All Fields] OR "inhaled"[All Fields] OR "inhaling"[All Fields] OR "inhalational"[All Fields] OR "inhalative"[All Fields] OR "inhalatively"[All Fields] OR "inhalent"[All Fields] OR "inhaler s"[All Fields] OR "inhales"[All Fields] OR "nebulizers and vaporizers"[MeSH Terms] OR ("nebulizers"[All Fields] AND "vaporizers"[All Fields]) OR "nebulizers and vaporizers"[All Fields] OR "inhalator"[All Fields] OR "inhalators"[All Fields] OR "inhaler"[All Fields] OR "inhalers"[All Fields]) AND ("nitric oxide"[MeSH Terms] OR ("nitric"[All Fields] AND "oxide"[All Fields]) OR "nitric oxide"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))	70

#2	**COVID 19 treatment [MeSH]** ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND "therapeutics"[MeSH Terms]	23,147
#1	**inhaled nitric oxide AND therapy [MeSH]** ("administration, inhalation"[MeSH Terms] OR ("administration"[All Fields] AND "inhalation"[All Fields]) OR "inhalation administration"[All Fields] OR "inhalant"[All Fields] OR "inhalability"[All Fields] OR "inhalable"[All Fields] OR "inhalants"[All Fields] OR "inhalated"[All Fields] OR "inhalation"[MeSH Terms] OR "inhalation"[All Fields] OR "inhal"[All Fields] OR "inhalations"[All Fields] OR "inhale"[All Fields] OR "inhaled"[All Fields] OR "inhaling"[All Fields] OR "inhalational"[All Fields] OR "inhalative"[All Fields] OR "inhalatively"[All Fields] OR "inhalent"[All Fields] OR "inhaler s"[All Fields] OR "inhales"[All Fields] OR "nebulizers and vaporizers"[MeSH Terms] OR ("nebulizers"[All Fields] AND "vaporizers"[All Fields]) OR "nebulizers and vaporizers"[All Fields] OR "inhalator"[All Fields] OR "inhalators"[All Fields] OR "inhaler"[All Fields] OR "inhalers"[All Fields]) AND ("nitric oxide"[MeSH Terms] OR ("nitric"[All Fields] AND "oxide"[All Fields]) OR "nitric oxide"[All Fields]) AND "therapeutics"[MeSH Terms]	3,975

Search Yield and Results



PRISMA 2020 Flow Diagram

Appendix 3. Characteristics of Included Studies

(1) – randomized controlled trial

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Moni M et al. 2021 A feasibility trial to evaluate the composite efficacy of inhaled nitric oxide in the treatment of COVID-19 pneumonia: impact on viral load and clinical outcomes	RCT	India	COVID confirmed with moderate symptoms (sPO2 <94% and RR > 24)	inhaled nitric oxide given in pulse for 3 days	standard of care	Primary outcome: Viral load Secondary outcomes: 28 day all cause mortality, need for invasive ventilation, length of hospital/ICU stay, change in SOFA score, methemoglobin levels > 3%

Appendix 4. Characteristics of Excluded Studies

(7) – observational studies

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Longobardo A et al. 2021 Inhaled nitric oxide produces minimal improvement in oxygenation in COVID-19 related ARDS	Retrospective case control (single center)	London, UK (ICU)	ICU patients with ARDS COVID and non COVID	inhaled nitric oxide given to COVID 19 patients in ARDS (n = 27)	inhaled nitric oxide patients given to non-COVID 19 patients in ARDS (n = 20)	- Improvement in PaO2:FiO2 ratio - Conclusion: more than half of patients with refractory hypoxemia secondary to COVID 19 ARDS did not show increase PF ratio in response to iNO; response much

						lower compared to cohort with non-COVID ARDS
Safaee F et al. 2021 Inhaled nitric oxide is a safe and effective respiratory treatment in spontaneous breathing hospitalized patients with COVID-19 pneumonia	Interventional study (single arm) comment: RCT protocol but did not reach target patients	Massachusetts, USA	Symptomatic non-intubated adults admitted for COVID 19	inhaled nitric oxide + standard of care iNO twice daily at 160 ppm for 30 mins x 14 days (n = 29)	no comparator	- Mortality, need for invasive ventilation, time to clinical recovery, hospital length of stay, viral shedding - Conclusion: acute improvement of systemic oxygenation in hypoxemic patients and reduced respiratory rate
Tavazzi G et al. 2020 Inhaled nitric oxide in patients admitted to intensive care unit	Interventional study (single arm)	Pavia, Italy	COVID-19 mechanically ventilated patients with refractory hypoxemia (ARDS)	inhaled nitric oxide + standard of care iNO at 25 ppm for 30 minutes (n = 16)	no comparator	- Improvement in hypoxemia and hemodynamic parameters - Conclusion: iNO did not improve oxygenation in COVID-19 patients with refractory hypoxemia
Benjamin G et al. 2020 Potential for personalized application of inhaled nitric oxide in COVID-19 pneumonia	Interventional study (single arm)	London, UK	COVID-19 mechanically ventilated patients with refractory hypoxemia (ARDS)	inhaled nitric oxide + standard of care iNO at 20 ppm for an average of 146.4 hours (n = 35)	no comparator	- Improvement in hypoxemia (PF ratio) - Conclusion: iNO may be helpful in patients with COVID-19 with refractory hypoxemia

Lotz C et al. 2020 Effects of inhaled nitric oxide in COVID-19 induced ARDS – is it worthwhile?	Retrospective observational study	Wurzburg, Germany	COVID-19 mechanically ventilated patients with refractory hypoxemia (ARDS)	inhaled nitric oxide + standard of care iNO at 20 ppm x 15-30 mins for as long as deemed necessary (n = 7)	no comparator	- Hemodynamics, hypoxemia - Conclusion: non-significant pulmonary vasodilation with significant improvement in arterial oxygenation
Ferrari M et al. 2020 Inhaled nitric oxide in mechanically ventilated patients with COVID-19	Interventional study (single arm)	Milan, Italy	COVID-19 mechanically ventilated patients with refractory hypoxemia (ARDS)	inhaled nitric oxide + standard of care iNO at 20 ppm x 30 mins – continue as deemed necessary if with initial improvement in hypoxemia after 30 mins (n = 10)	no comparator	- Improvement in hypoxemia - Conclusion: No significant improvement in arterial oxygenation
Abou-Arab et al. 2020 Inhaled nitric oxide for critically ill COVID-19 patients	Interventional study (single arm)	Amiens, France	COVID-19 mechanically ventilated patients with refractory hypoxemia (ARDS)	inhaled nitric oxide + standard of care iNO at 10 ppm x 30 mins (n = 34)	no comparator	- Improvement in respiratory parameters (PEEP, respiratory compliance, driving pressures, PF ratio) - Conclusion: 65% response rate to iNO administration

Appendix 5. Characteristics of Ongoing Studies (10)

Study ID	Study Design	Setting	Population	Intervention	Comparator	Outcomes
Inhaled nitric oxide for preventing progression in COVID-19 (NO-COVID-19)	RCT	USA	COVID-19 confirmed with high risk for mortality	iNO	standard of care	- Prevention of progressive systemic de-oxygenation
High dose inhaled nitric oxide for COVID-19 patients	RCT	Toronto, Canada	COVID-19 critical patients	iNO	standard of care	- Viral load and ICU admission
Nitric oxide inhalation therapy for COVID-19 infections in ED (NO COV-ED)	RCT	USA	COVID-19 patients in ED	iNO	standard of care	- Inpatient hospitalization, rates of intubation, rates of mortality
NO prevention of COVID-19 for healthcare providers	RCT	USA	healthcare workers in COVID-19 areas	iNO	no intervention	- COVID-19 diagnosis, RT PCR positive test, total number of quarantine days
Nitric oxide gas inhalation in severe acute respiratory syndrome in COVID-19 (NOSARSCOVID)	RCT	USA	hypoxic COVID-19 confirmed patients	iNO	standard of care	- Improvement in oxygenation, mortality
Nitric oxide gas inhalation therapy for mild/moderate COVID-19 (NoCOVID)	RCT	USA	COVID-19 confirmed with mild to moderate illness	iNO	standard of care	- Reduction in the incidence of patients with mild/moderate COVID-19 requiring invasive ventilation
Inhaled NO for the treatment of COVID-19 caused	RCT	USA	COVID-19 confirmed patients with sPO2 <93% on room air	iNO	standard of care	- Time to deterioration

by SARS-COV-2 (US trial)						
Nitric oxide therapy for COVID-19 patients with oxygen requirement	RCT	Russia	COVID-19 confirmed patients needing oxygen support	iNO	standard of care	- Change in methemoglobin levels, improvement in oxygenation, time to clinical recovery
Prevent viral exposure and transmission study: a SARS-COV2 PEP study	RCT	USA	non-confirmed COVID patients with exposure to known COVID positive patients	iNO	standard of care	- Incidence of newly confirmed COV-2 infection in previously uninfected household members
A study to assess efficacy and safety of RESP301 plus standard of care to standard of care alone in hospitalized participants with COVID 19	RCT	United Kingdom	COVID-19 confirmed patients	iNO	standard of care	- Proportion of participants who progress using WHO ordinal scale by day 14, desaturation

Appendix 6. GRADE Evidence Profile

Author(s): Mithi Kalayaan Zamora MD, Vaneza Leah Espino MD, Christopher G. Manalo MD
Question: Inhaled NO compared to standard of care for COVID-19 infection
Setting: Hospitalized COVID-19 patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	inhaled NO	standard of care	Relative (95% CI)	Absolute (95% CI)		
28-day Mortality												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/14 (0.0%)	4/11 (36.4%)	**RR 0.0889** (0.0053 to 1.4935)	**331 fewer per 1,000** (from 362 fewer to 179 more)	⨁⨁◯◯ Low	CRITICAL
Need for Mechanical Ventilation												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/14 (0.0%)	4/11 (36.4%)	**RR 0.0899** (0.0053 to 1.4935)	**331 fewer per 1,000** (from 362 fewer to 179 more)	⨁⨁◯◯ Low	CRITICAL
Average Intensive Care Unit Length-of-Stay (assessed with: Days)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	14	11	-	MD **2.08 days lower** (5.75 lower to 1.59 higher)	⨁⨁◯◯ Low	IMPORTANT
Average Hospital Length-of-Stay (assessed with: Days)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	14	11	-	MD **2.29 days lower** (8.99 lower to 4.41 higher)	⨁⨁◯◯ Low	IMPORTANT
Viral Clearance at Day 7 (N-Gene) (assessed with: CT Value >35)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	12/12 (100.0%)	8/11 (72.7%)	**RR 1.3750** (0.9575 to 1.9746)	**273 more per 1,000** (from 31 fewer to 709 more)	⨁⨁◯◯ Low	IMPORTANT
Viral Clearance at Day 7 (ORF1ab) (assessed with: CT value>35)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	inhaled NO	standard of care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	12/12 (100.0%)	10/11 (90.9%)	**RR 1.1000** (0.9125 to 1.3260)	**91 more per 1,000** (from 80 fewer to 296 more)	⨁⨁◯◯ Low	IMPORTANT
Incidence of Methemoglobin Levels >3%												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/14 (0.0%)	0/11 (0.0%)	**RR 0.8000** (0.0171 to 37.4368)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	IMPORTANT
Two-point Improvement in WOS at Day 7												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2/14 (14.3%)	2/11 (18.2%)	**RR 1.0476** (0.7374 to 1.4884)	**9 more per 1,000** (from 48 fewer to 89 more)	⨁⨁◯◯ Low	IMPORTANT
Two-point Improvement in WOS at Day 14												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	11/14 (78.6%)	4/11 (36.4%)	**RR 2.1607** (0.9438 to 4.9465)	**422 more per 1,000** (from 20 fewer to 1,000 more)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Lack of allocation concealment
b. Confidence interval crosses line of no effect