COVID-19 Critical Intelligence Unit

Evidence check

20 May 2021

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP)

Evidence check question

- 1. What is the evidence that continuous positive airway pressure (CPAP) and/or bilevel positive airway pressure (BiPAP) are aerosol generating?
- 2. What are the implications of CPAP and/or BiPAP use in planes and quarantine settings during COVID-19?

In brief

Question 1

 There is limited evidence on the topic of CPAP and/or BiPAP as aerosol generating procedures. Some publications, which include a systematic review of clinical guidelines, five small studies, two literature reviews and a commentary, describe CPAP and BiPAP as potential aerosol generating procedures involved in nosocomial virus transmission.(1-9) A systematic review in 2012 found nonsignificant results for transmission of acute respiratory infections for CPAP.(10)

Evidence for SARS-CoV-2

- Two recent systematic reviews found that non-invasive ventilation (NIV), including CPAP and BiPAP, was associated with an increased risk of severe acute respiratory infection. These reviews included patients with SARS-CoV-1, SARS-CoV-2, MERS-CoV and severe acute respiratory infection.(11, 12)
- Small single centre observational studies suggest that CPAP may be associated with the nosocomial transmission of SARS-CoV-2, after healthcare workers and other patients tested positive to SARS-CoV-2 following exposure.(13-16)
- Experimental simulations found nasal high-flow therapy, CPAP and NIV are associated with virus aerosolization, however the studies were small, experimental and had limitations.(5, 17-20)
- The World Health Organization included NIV as an aerosol generating procedure in March 2020. (21)



- Regulators and medical device companies recommend healthcare professionals use personal protective equipment when using CPAP on COVID-19 patients due to the potential risk of transmission.(22, 23)
- There is limited advice on the use of CPAP in community settings during COVID-19.

Question 2

- All Australian states, where information was available, have banned the use of nebulisers in quarantine facilities. Pressure breathing machines, including CPAP and BiPAP, have been banned in NSW and Victoria. (24-29) Whilst they are permitted in Western Australia, individuals must not open their door or have any face-to-face contact within 30 minutes of switching the machine off. (24)
- Internationally, similar policies do not seem to exist, with New Zealand permitting nebulisers in managed isolation and quarantine facilities. (30)

Limitations

Evidence on this topic, particularly around the implications for use in planes and quarantine settings during COVID-19, is still emerging. Risk assessment may be different for quarantine centres and health care settings. Question two was limited to grey literature with limited information specific to CPAP and BiPAP. There was however some information on nebulisers, so where available this has also been included.

Background

CPAP and BiPAP are both modes of NIV. CPAP provides a constant steady pressure to keep the lungs expanded, generally used for obstructive sleep apnoea. BiPAP delivers two distinct pressures, one for inhalation and the second for exhalation, which leads to air flow in and out of the lungs.(22) There have been some concerns around the potential for transmission in quarantine settings following an outbreak in Victoria.(29, 31)

Methods (Appendix 1)

For the updated search, PubMed and Google were searched on the 11 March and 12 March 2021, respectively. A supplementary search was run on 30 March 2021 to include the term non-invasive ventilation.



Results

Table 1a. CPAP and BiPAP as an aerosol generating procedure: Peer reviewed

Source	Summary
Peer reviewed sources	
Aerosol generation from the respiratory tract with various modes of oxygen delivery Gaeckle, et al. 2020 (8)	 This study measured the size and concentration of aerosols and droplets generated from 10 healthy participants, exposed to various oxygen delivery devices, during talking and breathing. Results Cough significantly increased the number of particles from 0.041 to 0.168 particles/cm³. Aerosol concentration slightly increased from 1.02 to 1.53µm with the use of humidified high-flow nasal cannula or non-invasive positive pressure ventilation. Humidified high-flow nasal cannula and non-invasive positive pressure ventilation do not increase aerosol generation in healthy participants.
The use of non-invasive ventilation in COVID-19: A systematic review Wang, et al. 2021 (6)	 Systematic review Compared the clinical recommendations of guidelines regarding safety issues on NIV. Twenty-six guidelines, focused on the management of NIV for COVID-19 patients, were reviewed. Results Methodological quality of guidelines was low. Almost half of the guidelines (n=13) provided recommendations on NIV safety issues. Suggested the use of NIV would increase the risk of aerosol generation for virus transmission, though the National Health Service, China considered NIV was mainly a droplet-generating procedure.
Risk of COVID-19 infection in healthcare workers exposed during use of non-invasive ventilation in a tertiary care hospital in Oman Al Lawati, et al. 2021 (13)	 Retrospective study Describes the association between NIV and transmission of SARS-CoV-2. Thirty-eight healthcare workers and 28 patients exposed to a SARS-CoV-2 patient using NIV in a high dependency unit, were tested with real time polymerase chain reaction. Results



Source	Summary
	 Forty-six (69.7%) healthcare workers and patients tested positive for SARS-CoV-2.
	 NIV poses a significant risk for SARS-CoV-2 transmission if appropriate infection control measures are not taken.
Oxygen therapy and risk of infection for health care workers caring for patients with viral severe acute respiratory infection: a systematic review and meta-analysis Cournoyer, et al. 2021 (11) Protecting healthcare workers from SARS-CoV-	 Systematic review and meta-analysis Fifty publications between January and April 2020 reviewed. Results BiPAP is considered as an aerosol generating procedure due to air and droplet dispersion. Air dispersion distance observed for BiPAP was 5L/min. CPAP and BiPAP were associated with an increased risk of infection (odds ratio, 3.96; 95% confidence interval, 2.12-7.40). Recommendations
<u>SARS-Cov-</u> <u>2 infection: practical</u> <u>indications</u> Ferioli, et al. 2020 (3)	 Aerosol generating procedures expose healthcare workers at high risk of contagion. The World Health Organization recommends NIV procedures to be performed in negative rooms with a minimum of 12 air changes per hour per patient in facilities with natural ventilation. CPAP and NIV support methods are high risk aerosol dispersion procedures, especially in unprotected environments.
High-flow, noninvasive ventilation and awake (nonintubation) proning in patients with coronavirus disease 2019 with respiratory failure Raoof, et al. 2020 (2)	 Literature review Describes precautionary measures required for using high-flow and non-invasive ventilatory procedures. The World Health Organization recommends the use of appropriate personal protective equipment when using CPAP or non-invasive ventilatory procedures. CPAP via an oronasal mask and NIV with a helmet are the preferred ventilatory procedures that allow minimum room air contamination.
Transmission of severe acute respiratory syndrome coronavirus 1 and severe acute respiratory syndrome coronavirus 2 during aerosol-generating procedures in critical care:	 Systematic review and meta-analysis Assessed the risk of transmission to healthcare workers performing aerosol generating procedures, including CPAP and BiPAP Seventeen studies reviewed by seven reviewers against pre-determined eligibility criteria Results:



Source	Summary
<u>a systematic review and</u> <u>meta-analysis of</u> <u>observational studies</u> Chan, et al. 2021 (12)	 Aerosol generating procedures significantly increase the odds of healthcare workers contracting SARS-CoV-1 and 2 (odds ratio 3.65; 95% confidence interval, 1.86-7.19; p<0.001). Aerosol generating procedures should only be performed when clinically indicated, and personal protective equipment must be worn.
<u>Use of high-flow nasal</u> <u>cannula and noninvasive</u> <u>ventilation in patients with</u> <u>COVID-19: A multicenter</u> <u>observational study</u> Duan, et al. 2020 (4)	 Retrospective study Compared the effect of using high-flow nasal cannula and NIV as first line therapy in 36 patients, also reported the outcome of strict safety measures for preventing aerosol transmission. Results It was considered that NIV generates more aerosols than high-flow nasal cannula due to higher pressure. No healthcare staff were infected with strict training on the use of full personal protective equipment.
COVID-19: minimising contaminated aerosol spreading during CPAP treatment Donaldsson, et al. 2020 (18)	 Experimental simulation study Attaching a filter to the expiratory limb of a CPAP machine reduces, but does not eliminate, the risk of aerosol spread. Personal protective equipment should be worn by caretakers at all times.
Transmission of COVID- <u>19 to health care</u> <u>personnel during</u> <u>exposures to a</u> <u>hospitalized patient –</u> <u>Solano County, California,</u> <u>February 2020</u> Heinzerling, et al. 2020 (14)	 Case study on healthcare worker exposure to the first community-acquired COVID-19 patient in the USA (n=121). Three healthcare workers developed COVID-19. Exposure during nebuliser treatments and BiPAP was more common among workers who developed COVID-19.
Viable virus aerosol propagation by positive airway pressure (PAP) circuit leak and mitigation with a ventilated patient hood Landry, et al. 2020 (17)	 Experimental simulation study on COVID-19 virus propagation from CPAP mask leak. Results Aerosols containing viable virus can escape from PAP system leak and are detected on surfaces at least 3.68m away from source. Using a hood and high-efficiency particulate air filter containment structure eliminated viral spreading. Conclusion: Mask leak from PAP therapy can lead to viable virus aerosol propagation.



Source	Summary
Aerosol generation related to respiratory interventions and the effectiveness of a personal ventilation hood McGain, et al. 2020 (5)	 Human volunteer study on aerosol generation from respiratory interventions and reduction using a personal ventilation hood. Results NIV generated moderate aerosols and nebulisation high aerosols. Personal ventilation hood reduced aerosol counts by at least 98%.
Recommended approaches to minimize aerosol dispersion of SARS-CoV2 during noninvasive ventilatory support can deteriorate ventilator performances: a benchmark comparative study Patout, et al. 2021 (32)	 Preproof Simulation study on modifications to NIV and CPAP circuits to reduce risk of aerosolization. Nasal high-flow therapy, CPAP and NIV are associated with virus aerosolization. Limitations: No assessment of aerosol dispersion.
Position paper for the state-of-the-art application of respiratory support in patients with COVID-19 Pfeifer, et al. 2020 (33)	 Position statement Evidence on oxygen therapy, nasal high-flow therapy, CPAP and NIV is limited in terms of comparability e.g. different approaches and different room conditions. Staff can perform inhalation therapy, nasal high-flow therapy, CPAP or NIV wearing personal protective equipment without increased risk of infection. NIV and intermittent nasal high-flow therapy increase aerosol formation.
Preclinical validation of occupational and environmental safety of an isolation system for noninvasive ventilation in COVID-19 and other aerosol-transmitted infections Quadros, et al. 2020 (19)	 Simulation study on an isolation system for aerosol-transmitted infections. Aerosolized markers were contained within the isolation system under CPAP and high-flow nasal oxygen conditions.



Source	Summary
Helmet CPAP revisited in COVID-19 pneumonia: a case series	 Case series report single-centre experience of COVID-19 patients (n=3) managed with helmet non-invasive positive pressure ventilation.
Rali, et al. 2020 (16)	 Traditional non-invasive positive pressure ventilation delivered by facemask can lead to aerosolization of infectious respiratory pathogens.
	 Helmet non-invasive positive pressure ventilation reduces risk of particle aerosolization.
Risk following a severe	Letter
acute respiratory <u>coronavirus virus 2</u> (SARS-CoV-2) exposure	 Reported the delayed diagnosis of a COVID-19 patient who used his CPAP during nocturnal dialysis.
from a nocturnal hemodialysis patient utilizing continuous	 Eleven patients and 12 healthcare workers in the same dialysis pod were exposed to SARS-CoV-2, where personal protective equipment was not required.
positive airway pressure (CPAP)	 All 23 people did not develop COVID-19 symptoms after day 33 of follow up.
Lowe, et al 2020 (15)	 Transmission was likely mitigated by existing infection prevention and control precautions, such as hand hygiene, on the haemodialysis unit.
Nosocomial transmission of emerging viruses via aerosol-generating medical procedures Judson, et al. 2013 (7)	 Literature review Potential aerosol generating procedures involved in nosocomial virus transmission include NIV, such as CPAP, BiPAP, and high frequency oscillation ventilation. The mechanism is via possible mechanical dispersal of aerosols, and via the respiratory tract.
Exhaled air dispersion	Simulation study
during high-flow nasal cannula therapy versus cpap via different masks	 Exhaled air dispersion during high flow nasal cannula and CPAP via different interfaces is limited provided there is good mask interface fitting.
Hui, et al. 2019 (34)	 Gas flow rates and mask interface fitting seem to dictate how much air and aerosol escape upon exhalation.
Exhaled air dispersion	Simulation study
during noninvasive ventilation via helmets and a total facemask	 Examined exhaled air dispersion by two different helmets via a ventilator and a total facemask with a bi-level positive airway pressure device.
Hui, et al. 2015 (35)	 During NIV via a total facemask for mild lung injury, air leaked through the exhalation port to 618 and 812mm when inspiratory



Source	Summary
	pressure was increased from 10 to 18cm H_2O , respectively, with the expiratory pressure at 5cm H_2O .
Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review Tran, et al. 2012 (10)	 Systematic review Procedures that are believed to generate aerosols and droplets as a source of respiratory pathogens include positive pressure ventilation (BiPAP and CPAP), but when pooled the procedures were not significant.
Hospital management of adults with severe acute respiratory syndrome (SARS) if SARS re- emerges Lim, et al. 2004 (36)	 Guideline Procedures that might promote the generation of aerosols should be avoided where possible to reduce the risk to healthcare workers, this list includes NIV and CPAP.
Exhaled air dispersion distances during noninvasive ventilation via different respironics face masks Hui, et al. 2009 (37)	 Simulation study Substantial exposure to exhaled air occurs within a 1m region, from patients receiving non-invasive positive pressure ventilation via the ComfortFull 2 mask and the Image 3 mask, with more diffuse leakage and room contamination from the latter, especially at higher inspiratory positive airway pressure. Healthcare workers should take adequate precautions when providing non-invasive positive pressure ventilation support to patients with pneumonia of unknown aetiology complicated by respiratory failure.
Transmission of severe acute respiratory syndrome during intubation and mechanical ventilation Fowler, et al. 2004 (9)	 Retrospective cohort study Examined the occurrence of transmission rates to 122 healthcare workers caring for seven patients with SARS, who required various modes of ventilatory support. Results Physicians and nurses performing endotracheal intubation had a greater risk of developing SARS (risk ratio 13.29; 95% confidence interval: 2.99-59.04; p=0.003). The relative risks of nurses caring for patients receiving non-invasive positive pressure ventilation and high-frequency oscillatory ventilation were not statistically significant. Many forms of ventilatory support may be associated with increased dispersal of respiratory droplets in SARS patients.



Health

Source	Summary
Evaluation of droplet dispersion during non- invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for	 Study to evaluate the characteristics of droplets/aerosol dispersion during NIV, oxygen therapy, nebuliser treatment and chest physiotherapy. Three groups of participants: 12 controls, 11 patients with coryzal symptoms; and 21 inpatients with infective exacerbation of chronic lung disease.
practice: implications for management of pandemic influenza and other airborne infections Simonds, et al. 2010 (1)	 Results NIV and chest physiotherapy are droplet-generating procedures, not aerosol, producing droplets of >10µm in size. Oxygen therapy did not increase droplet count in any size range. Nebulised saline did not increase large-size droplet count. Healthcare workers providing NIV and chest physiotherapy working within one metre of an infected patient should have a higher level of respiratory protection to limit aerosol spread. Study results may have infection control implications for other contagious airborne infections such as SARS.

Table 1b. CPAP and BiPAP as an aerosol generating procedure: Grey literature

mmary
 Fact sheet COVID-19 contaminated droplets may be spread in the air through CPAP use. The air pressure from CPAP increases droplet production and spread and aerosolized virus particles may remain in the air for an hour or more. Contaminated CPAP masks and tubing can also spread COVID-19 through direct contact. CPAP machines should be used in a separate bedroom where possible. Equipment must be cleaned after every use. Similar concerns apply to BiPAP machines.



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Source	Summary
Infection prevention and control during health care	 Interim guidance on infection prevention and control strategies for caring people with suspected COVID-19.
when novel coronavirus World Health Organization 19 March 2020 (21)	 'Some aerosol-generating procedures have been associated with an increased risk of transmission of coronavirus (SARS-CoV and MERS-CoV), such as tracheal intubation, non-invasive ventilation'
	 Recommendations for healthcare workers performing aerosol generating procedures:
	 Perform procedures in a ventilated room with air flow of at least 160L/s per patient or in a negative pressure room.
	 Use a disposable particulate respirator such as N95 or equivalent with good facial fit.
	 Protect eyes with googles or a face shield.
	\circ Wear a long-sleeved impermeable gown and gloves.
	\circ $$ Minimise access to room and limit visitor numbers.
Aerosol emission from the respiratory tract: an analysis of relative risks from oxygen delivery	 Preprint Twenty-five health volunteers and eight COVID-19 hospitalised patients had aerosol emissions measured during breathing, speaking and coughing.
systems Hamilton, et al. 2021 (20)	Results
	 CPAP with an exhalation port filter generates less aerosols.
	 High-flow nasal oxygen produces aerosols but mainly from the machine, not the patient.
	 Coughing produced higher aerosol emissions compare with speaking and breathing.
	 Aerosol transmission of SARS-CoV-2 is likely to be high in all areas where COVID-19 patients are coughing.
Ventilators and COVID- <u>19. Information on</u> <u>applications in the</u> <u>treatment of patients with</u> <u>COVID-19</u> ResMed 2020 (22)	 Evidence suggests that NIV procedures are more likely to produce large droplets (>10µm) rather than aerosols, and that these are largely confined to within one metre due to their large mass. Therefore the risk of droplet dispersion as a result of use of non- invasive ventilation or bi-level devices may not be that different to that of any COVID-19 patient in the hospital who is coughing or sneezing.



Source	Summary
Consensus statement on the safe use of respiratory therapy and sleep studies to minimise aerosolisation of COVID-19 Australasian Sleep Association March 2020 (23)	 Consensus statement The use of nebulisers, high flow oxygen and NIV all pose a risk of transmission of viral infection to staff and patients. Healthcare workers should use positive airway pressure in isolation or single rooms and wear personal protective equipment. Minimise transmission risk by limiting the use of high-risk therapies (nebulisers, high flow oxygen, and NIV) where clinically possible. Nebulisation of respiratory medications should be replaced by metered dose inhaler with a spacer. Well-fitted high flow nasal prongs are considered less aerosol dispersing when oxygen flow rates <6Litres per minute. NIV used in acute clinical settings is recommended for non-COVID-19 suspected or confirmed patients. Non-comorbid patients with suspected or confirmed COVID-19 should be assessed individually for the need of NIV. NIV used at home is considered safe if patients are not suspected or confirmed With COVID-19. Physicians need to weight the benefit and risk of NIV therapy for suspected or confirmed COVID-19 patients (adult and paediatric) with suspected or confirmed COVID-19 patients (adult and paediatric) with suspected or confirmed until recovered (up to 14 days). Bilevel NIV users with suspected or confirmed COVID-19 should continue home therapy unless advised by treating respiratory or sleep physicians. Discontinue laboratory and home CPAP sleep studies to minimise risk of community spread of COVID-19.
Emergency use of ventilators during the COVID-19 pandemic USA Food and Drug Administration 2020 (39)	 A positive pressure breathing device may expose others to aerosols that could be contagious.



Table 2a. CPAP in planes and quarantine settings during COVID-19: Peer review

Source	Summary
Peer reviewed sources	
Use of helmet-based noninvasive ventilation in air medical transport of coronavirus disease 2019 patients	 Case report on air medical transfer (air medical crew and patient only on board) of COVID-19 positive patient. Helmet NIV used as ventilator for the patient. Does not specifically describe transmission however concludes bolmet NIV is a viable option for air transport of COVID 19
Beckl 2020 (40)	helmet NIV is a viable option for air transport of COVID-19 patients.

Table 2b. CPAP in planes and quarantine settings during COVID-19: Grey literature

Source	Summary
Grey literature	
COVID-19: information for people requiring hotel quarantine NSW Ministry of Health March 2021 (27)	 Nebulisers and positive pressure breathing machines including CPAP are not allowed in quarantine facilities.
Hotel quarantine for returned overseas travellers Victorian Government March 2021 (29)	 CPAP and BiPAP machines, nebulisers and humidifiers are prohibited in quarantine.
Position statement: nebulisation and COVID-19 Australian Commission on Safety and Quality in Health Care April 2020 (41)	 Nebulisers can rapidly spread SARS-CoV-2 and aerosol transmission may be increased during nebulisation.
Frequently asked questions Western Australia Department of Health 2021 (24)	 Nebulisers are banned in hotel quarantine in Western Australia as they may produce aerosols that transmit COVID-19. Sleep machines are permitted but individuals must not open their door or have any face-to-face contact within 30 minutes of switching the machine off.



Source	Summary	
Grey literature		
NT bans nebulisers at guarantine centres Bunch February 2021 (26)	The Northern Territory has banned the use of nebulisers at quarantine facilities due to a Victorian COVID-19 outbreak suspected to have been caused by the device.	
State bans nebulisers in COVID-19 hotels after Melbourne outbreak Cosenza 2021 (25)	 Nebulisers are banned in South Australian quarantine hotels after link to Melbourne outbreak. 	
<u>'Quick out of the blocks': Qld</u> <u>Health pounces on</u> <u>Melbourne visitors</u> Layt, et al. February 2021 (28)	 People in hotel quarantine in Queensland will no longer be able to use a nebuliser to treat asthma or other lung conditions following the outbreak in Melbourne. 	
Doctors say more care must be taken around nebulisers in NZ MIQ facilities 1 News February 2021(30)	 Nebulisers are permitted in managed isolation and quarantine facilities in New Zealand if certain conditions are met. Clear clinical evidence that nebuliser required. Good ventilation in room. Strict personal protective equipment protocols in place. 	

Appendix

PubMed search terms (update 1)

("CPAP"[All Fields] OR "continuous positive airway pressure"[All Fields] OR "bipap"[All Fields] OR "Bilevel Positive Airway Pressure"[All Fields]) AND ("aerosol*"[Title/Abstract] OR "agp"[Title/Abstract] OR "exhale*"[Title/Abstract] OR "droplet*"[Title/Abstract] OR "airborne infection*"[Title/Abstract] OR "air dispersion"[Title/Abstract] OR "transmi*"[Title/Abstract] OR "hospital infection"[Title/Abstract] OR "nosocomial infection"[Title/Abstract]) AND 2019/12/01:2021/12/31[Date - Publication]

68 hits on 11 March 2021

PubMed search terms (update 2)

((((("CPAP"[All Fields] OR "continuous positive airway pressure"[All Fields] OR "bipap"[All Fields] OR "Bilevel Positive Airway Pressure"[All Fields])) OR ((Noninvasive Ventilation[MeSH Terms] OR Noninvasive Ventilation[Title/Abstract] OR NIV[Title/Abstract]))) AND (("aerosol*"[Title/Abstract] OR "agp"[Title/Abstract] OR "exhale*"[Title/Abstract] OR "droplet*"[Title/Abstract] OR "airborne infection*"[Title/Abstract] OR "air



dispersion"[Title/Abstract] OR "transmi*"[Title/Abstract] OR "hospital infection"[Title/Abstract] OR "nosocomial infection"[Title/Abstract]))) AND (2019/12/01:2021/12/31[Date - Publication])) NOT (("CPAP"[All Fields] OR "continuous positive airway pressure"[All Fields] OR "bipap"[All Fields] OR "Bilevel Positive Airway Pressure"[All Fields]) AND ("aerosol*"[Title/Abstract] OR "agp"[Title/Abstract] OR "exhale*"[Title/Abstract] OR "droplet*"[Title/Abstract] OR "airborne infection*"[Title/Abstract] OR "air dispersion"[Title/Abstract] OR "transmi*"[Title/Abstract] OR "hospital infection"[Title/Abstract] OR "nosocomial infection"[Title/Abstract]) AND 2019/12/01:2021/12/31[Date - Publication] AND (english[Filter]))

76 hits on 30 March 2021

Google and Twitter search terms (update)

Hotel quarantine and CPAP

Hotel quarantine and nebulisers

Inclusion and exclusion criteria

Inclusion	Exclusion
Population: Humans	Animal experiments
Intervention: CPAP and/or BiPAP use	Not about CPAP or BiPAP
 Outcomes: Aerosol generation or spread during use; transmission of virus due to use of CPAP or BiPAP; preventative measures 	 Irrelevant outcomes, i.e. adherence to correct use, outcomes in relation to condition management, device design and safety evaluations.

Original search 1 April 2020	Updates
12 March 2021	 Search re-run Question on use in quarantine or travel settings added Question on use as a substitute for ventilators removed New relevant publications added to table In-brief updated to reflect new evidence



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