VENTILATION TECHNIQUES AND RISK FOR TRANSMISSION OF CORONAVIRUS DISEASE, INCLUDING COVID-19

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ABSTRACT

Background: Mechanical ventilation is used to treat respiratory failure in coronavirus disease 2019 (COVID-19). Purpose: To review multiple streams of evidence regarding the benefits and harms of ventilation techniques for coronavirus infections, including that causing COVID-19. Data Sources: 21 standard, World Health Organization–specific and COVID-19–specific databases, without language restrictions, until 1 May 2020. Study Selection: Studies of any design and language comparing different oxygenation approaches in patients with coronavirus infections, including severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), or with hypoxemic respiratory failure. Animal, mechanistic, laboratory, and preclinical evidence was gathered regarding aerosol dispersion of coronavirus. Studies evaluating risk for virus transmission to health care workers from aerosol-generating procedures (AGPs) were included. Data Extraction: Independent and duplicate screening, data abstraction, and risk-of-bias assessment (GRADE for certainty of evidence and AMSTAR 2 for included systematic reviews). Data Synthesis: 123 studies were eligible (45 on COVID-19, 70 on SARS, 8 on MERS), but only 5 studies (1 on COVID-19, 3 on SARS, 1 on MERS) adjusted for important confounders. A study in hospitalized patients with COVID-19 reported slightly higher mortality with noninvasive ventilation (NIV) than with invasive mechanical ventilation (IMV), but 2 opposing studies, 1 in patients with MERS and 1 in patients with SARS, suggest a reduction in mortality with NIV (very-low-certainty evidence). Two studies in patients with SARS report a reduction in mortality with NIV compared with no mechanical ventilation (low-certainty evidence). Two systematic reviews suggest a large reduction in mortality with NIV compared with conventional oxygen therapy. Other included studies suggest increased odds of transmission from AGPs. Conclusion: Indirect and low-certainty evidence suggests that use of NIV, similar to IMV, probably reduces mortality but may increase the risk for transmission of COVID-19 to health care workers.

Keywords: ventilation techniques, risk for transmission of coronavirus disease, covid-19

INTRODUCTION

As of 18 May 2020, the ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected more than 4.8 million individuals worldwide and caused over 300 000 deaths (1). SARS-CoV-2 spreads from person to person through close contact and causes coronavirus disease 2019

(COVID-19); most deaths are caused by development of hypoxemic respiratory failure and severe acute respiratory distress syndrome (ARDS).

Noninvasive ventilation (NIV), invasive mechanical ventilation (IMV), and supportive therapies are the mainstays of treatment of ARDS. Noninvasive ventilation is associated with fewer adverse outcomes for patients than is IMV. However, NIV creates risks for the health care workers (HCWs) caring for these patients, because of SARS-CoV-2 transmission via aerosols (2). The magnitude of this risk is not well explored in COVID-19. In contrast, IMV typically uses a closed system and thus carries a much lower risk for transmission via aerosols. Countries with a large number of patients with COVID-19 requiring mechanical ventilation have experienced shortage of ventilators and have relied on NIV, which includes continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), and high-flow oxygen by nasal cannula (HFNC). Guidelines vary considerably in their recommendations on the role and optimal method of NIV, reflecting differences in assumed effectiveness balanced with the risk for infection to HCWs from aerosols.

Hypoxemic respiratory failure and ARDS are common in COVID-19, but the ideal way of providing ventilation and the effect of NIV on HCWs is uncertain. Although they are different from other causes of ARDS, severe acute respiratory syndrome (caused by SARS-CoV-1) or Middle East respiratory syndrome (caused by MERS-CoV) may resemble ARDS in COVID-19 (3, 4). Thus, evidence from SARS and MERS may be useful to explore the effects of NIV.

Commissioned by the World Health Organization (WHO) to inform their guidance documents, we urgently but systematically reviewed evidence to assess the benefits and harms of alternate noninvasive and invasive ventilation strategies in acute hypoxemic respiratory failure in patients with COVID-19. This included searching for indirect evidence (for example, that related to SARS and MERS) and for evidence on the effect of virus transmission on HCWs.

RESEARCH METHOD

By agreement with WHO on 3 April 2020, we performed an urgent systematic review to compare the effect of different ventilation techniques on important patient outcomes and the risk for transmission for coronavirus disease, including COVID-19. We adhered to Cochrane systematic review methods, rated the certainty of evidence by following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, prospectively registered the review on PROSPERO (registration number CRD42020178187) (Supplement 1), and followed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) reporting guidelines (5–9). We assembled a large international collaborative team of

researchers, frontline and specialist clinicians, epidemiologists, patients, public health experts, and health policy experts with expertise in systematic reviews. The review addresses the following 4 streams of evidence: 1) studies of any design that addressed NIV for individuals with acute hypoxic respiratory failure caused by coronavirus (COVID-19, MERS, SARS); 2) systematic reviews of randomized trials that assessed the efficacy of NIV approaches in patients with hypoxemic respiratory failure not due to coronavirus infection; 3) animal, mechanistic, laboratory, and preclinical evidence regarding aerosol dispersion of coronavirus; and 4) studies in adults evaluating risk for virus transmission to HCWs from aerosol-generating procedures (AGPs). When possible, results focus on information most relevant to SARS-CoV-2 and COVID-19. Information related to the first stream of evidence will be continually updated and maintained as a living systematic review for at least 1 year.

Without language restrictions, we searched MEDLINE (by using the OVID platform); PubMed; EMBASE; CINAHL (by using the EBSCO platform); the Cochrane Library; the COVID-19 Open Research Dataset, hosted by Kaggle and created by the Allen Institute and collaborators; the COVID-19 Research Database maintained by the WHO; Epistemonikos (by using its COVID-19 L·OVE [Living Overview of the Evidence] platform); the EPPI Centre's living systematic map of the evidence on COVID-19; ClinicalTrials.gov, the U.S. National Library of Medicine's register of clinical trials; and the WHO International Clinical Trials Registry Platform (Supplement 2). We also searched relevant documents on the websites of governmental and other relevant organizations and reference lists of the included papers and relevant systematic reviews. We also hand-searched preprint servers (bioRxiv, medRxiv, and preprints in The Lancet, part of Social Science Research Network First Look). Finally, we searched Chinese databases, including the WHO Chinese database, the China Biomedical Literature Service (SinoMed), the Chinese Scientific Journal Database (VIP), the Wanfang database, and the China National Knowledge Infrastructure (CNKI), until 1 May 2020 (Supplement 2).

The strategies combined Medical Subject Headings and keywords related to COVID-19, NIV, and IMV, as well as studies focusing on laboratory evidence related to virus spread via AGPs for the 4 streams described above. We developed separate search strategies for streams 1 (from 1 January 2002 to 1 May 2020), 2 (from 2017 to 1 May 2020), and 3 (inception to 1 May 2020) with a senior information specialist. We used the original search strategy (from inception to 2010) for stream 4 from a review by the Canadian Agency for Drugs and Technologies in Health (CADTH) (restricted to the MEDLINE and EMBASE databases and SARS-CoV-1, SARS-CoV-2, and MERS-CoV until 1 May 2020) (2). We included records addressing the following population, interventions, comparisons, outcomes, and study designs.

We sought studies on patients with confirmed or probable COVID-19 infection and hypoxemic respiratory failure. We planned to evaluate different subgroups (Supplement 1), including different age groups and patients with comorbidities.

Interventions

Eligible interventions included NIV, including BiPAP, CPAP, and HFNC; IMV via endotracheal tubes or tracheostomy; standard oxygen therapy; or no mechanical ventilation. We determined a priori to evaluate different types of interfaces (helmet, oronasal, or full-face mask).

Outcomes

Outcomes of interest were death, transmission of COVID-19 to HCWs and other people, length of hospital and intensive care unit stay, complications of therapy, secondary bacterial pneumonia, need for invasive ventilation, need for tracheostomy, time to recovery from COVID-19, aerosol generation and droplet dispersion of live virus at various distances and times, and contextual outcomes (acceptability, feasibility, resources use, effect on equity).

Study Designs

Stream 1 consisted of studies of NIV in people with any acute hypoxic respiratory failure caused by coronavirus (COVID-19, MERS, or SARS). Evidence was prioritized by study design addressing the question of interest as follows: 1) randomized controlled trials (RCTs); 2) nonrandomized comparative studies; 3) noncomparative studies (that is, case series); and 4) qualitative studies (for contextual outcomes). We excluded single case reports.

Stream 2 consisted of systematic reviews published in 2017 or later that synthesized randomized trial evidence from patients with acute hypoxic respiratory failure who were critically ill but had neither suspected or confirmed COVID-19, MERS, or SARS. We included only recent credible systematic reviews (assessed by using AMSTAR 2 [A Measurement Tool to Assess Systematic Reviews 2]) because we intended to focus on up-to-date indirect evidence, and older reviews would not have included the most recent studies. We summarized the results of those reviews that are most credible (moderate- or high-quality rating on AMSTAR 2).

In streams 3 and 4, to identify all evidence about the risk for transmission of SARS-CoV-2 through AGPs, we evaluated additional streams of evidence. In stream 3, we selected controlled studies (animal, human, mechanistic, laboratory, preclinical, and simulation, among others) evaluating aerosol dispersion to inform the evidence about transmission of virus in confirmed cases of COVID-19, MERS, or SARS. We focused on COVID-19 in summarizing evidence, but if that evidence was sparse, we decided a priori to summarize evidence for MERS and SARS. For stream 4, we included all primary studies dealing with SARS, MERS, or COVID-19 published

after 22 October 2010 (date of prior search) (2). This update focused on transmission of virus.

For all 4 streams, the reviewers pilot-tested a standardized title and abstract screening form by using the same citations. We then conducted calibration exercises by webinars for each stream. Once the form was calibrated, pairs of reviewers screened in duplicate and independently all titles and abstracts by using the eligibility criteria. Conflicts between reviewers were resolved by consensus or by a senior methodologist (H.J.S., D.C., E.A.A.). Reviewers pilot-tested a full-text screening form and participated in a webinar using the same 5 or more full-text articles. Once the form was calibrated, the pairs of reviewers screened the full texts independently and in duplicate and resolved any conflicts by discussion, or with the help of a senior methodologist (H.J.S., D.C., E.A.A.). We recorded the primary reason for exclusion at the full-text screening stage.

Data Extraction and Risk-of-Bias Assessment

For each of the 4 streams, we developed a standardized data abstraction form in Microsoft Excel and piloted it as part of calibration exercises with all reviewers. Teams of 2 reviewers extracted data in duplicate and independently; all extracted data were verified by 2 biostatisticians (A.K. and R.B.) and a senior reviewer (H.J.S., D.C., or E.A.A.). We extracted data on the following variables: study identifier; study design; setting; population, intervention, and comparator characteristics; outcomes (quantitative, if possible); source of funding and reported conflicts of interest; ethical approval; and study limitations or other important comments.

Two experienced reviewers performed the risk-of-bias assessment, and a senior methodologist (H.J.S. or E.A.A.) verified all assessments. We used the Newcastle-Ottawa Scale for nonrandomized studies (10, 11) and Cochrane Risk of Bias tool, version 2.0, for randomized trials (12). We assessed systematic reviews by using the AMSTAR 2 tool (13). We did not assess the risk of bias for studies identified in stream 3.

Data Synthesis and Analysis

We synthesized the data in both narrative and tabular formats. One reviewer (H.J.S.) graded the certainty of the evidence by using the GRADE approach, and 2 senior reviewers (R.B. and E.A.A.) verified all assessments. When applicable, we followed published guidance for rating the certainty in evidence in the absence of a single estimate of effect (14, 15). We used the GRADEpro (www.gradepro.org) app to rate the evidence and present it in GRADE evidence profiles and summary of findings tables (16, 17) using standardized terminology (18, 19).

For quantitative analyses, we only included comparative studies—those that allowed a comparison of at least 2 interventions on an outcome of interest—in our synthesis. Although we planned meta-analyses, most studies provided unadjusted data or data

that could not be combined in a meta-analysis. We therefore did not perform a meta-analysis and present raw numbers. We present adjusted odds ratios (ORs) when studies reported them, using RevMan (Cochrane).

Living Review and Literature Surveillance

We plan weekly literature surveillance through May 2021 for studies related to stream 1. This surveillance and updating will focus on studies in patients with COVID-19. We will use the search strategy for stream 1 (Supplement 1) and the selection, data abstraction, and quality and certainty assessment methods described above. We plan monthly updates or alerts that present search findings and describe new evidence. If substantive new literature emerges that changes our overall conclusions, changes the certainty of evidence (20), provides data on additional outcomes, or provides data that would be appropriate for meta-analysis with other studies, we plan submission of an updated manuscript.

Role of the Funding Source

This systematic review was commissioned by the WHO on 3 April 2020. The WHO helped define the scope of the question but otherwise had no role in study design, data collection, data analysis, data interpretation, or writing of the report or the decision to submit it for publication.

RESEARCH RESULTS

Stream 1: Systematic Review of Ventilation Strategies in Patients With Hypoxemic Respiratory Failure Due to Coronavirus Infection

Among 38 942 records, 123 studies were eligible (45 on COVID-19, 70 on SARS, 8 on MERS) in stream 1. Supplement 3 shows the PRISMA flow diagram. Of these, 121 studies did not provide adequate data for extraction—for example, because outcome data could not be attributed to a specific treatment group. Supplement 4 shows a description of these studies. Of the remaining 28 studies (11 on COVID-19, 15 on SARS, 2 on MERS) that had data for extraction (12, 21–47), 18 included NIV as a treatment of choice (Supplement 5). Only 5 studies (including 1 very small RCT) provided results that we judged as adequately adjusted for important confounders, such as comorbidities or severity of hypoxemia (3 on SARS, 1 on COVID-19, and 1 on MERS) (12, 21, 29, 31, 32). We considered the remaining 23 unadjusted studies as providing results at high risk of bias. This included the 10 studies in patients with COVID-19 that reported unadjusted results.

We judged the risk of bias (Supplement 4 and Supplement 5) as low for the cohort designs on the basis of the Newcastle-Ottawa Scale, but in our GRADE assessment, we accounted for the risks of selection and confounding bias due to the nonrandomized design, and we noted some concerns for the RCT. We judged the 23 unadjusted studies, including all COVID-19 studies, to be at moderate to high risk of

bias because any estimate of effect will be subject to strong confounding and selection bias. Furthermore, we identified studies for which there was no clear comparison, mostly defined as case series or case reports, which were generally at high risk of bias (Supplement 5).

Supplement 6 shows the results of the studies with extractable data. Five studies reported adjusted results, one of them in patients with COVID-19. In these latter studies, 3 studies compared NIV with IMV and 2 studies compared NIV with no mechanical ventilation. The respective results from the former 3 studies (Figure 1) differ and suggest an imprecise increase in mortality in NIV compared with IMV in 1 study (COVID-19: hazard ratio, 1.61 [95% CI, 0.84 to 3.09]) and a reduction in mortality in 2 studies (MERS and SARS: OR, 0.61 [CI, 0.23 to 1.6] and 0.24 [CI, 0.10 to 0.72], respectively) (very low certainty of the evidence secondary to the nonrandomized study designs and concerns about inconsistency) (21, 29, 31). We were unable to perform a meta-analysis because of differences in how authors reported the effect estimates. For NIV compared with no mechanical ventilation, the RCT (32) suggested a reduction in mortality, but there were only 3 events in 60 patients in total, causing imprecision, and the nonrandomized study by Xu and colleagues (12) also showed a reduction in mortality (OR, 0.21 [CI, 0.09 to 0.47]; low certainty, owing to very serious imprecision of the RCT and the nonrandomized study design of the other study)

The 10 additional studies in COVID-19 presented only unadjusted results. In the only study from Italy, Duca and associates (25) reported a higher death rate in patients receiving helmet CPAP or other NIV compared with IMV. For the 3 studies from China, Liao and coworkers (28) reported rates of recovery greater than 40% after 28 days of follow-up in patients who received NIV, HFNC, and conventional oxygen therapy. Wang and colleagues (29) found low rates of the need for IMV in patients receiving NIV or HFNC. Mortality was greater than 60% in the NIV group and was 100% in the IMV group in the study by Wu and associates (30). We did not calculate effect estimates for these latter studies, given the high risk for confounding and selection bias as well as other potential biases in these studies. We found only 1 study on contextual factors, which reported a 2.5-fold higher cost for patients with SARS treated with mechanical versus no mechanical ventilation from 2004. We found no studies that provided information on any of the contextual factors for decision making about NIV in COVID-19.

Stream 2: Overview of Systematic Reviews of Randomized Trials That Assessed the Efficacy of NIV Approaches in Patients With Hypoxemic Respiratory Failure Not Due to Coronavirus Infection

We identified 12 systematic reviews of indirect study populations that were judged to be credible on the basis of assessment with the AMSTAR 2 instrument (rating of moderate or high quality). Supplement 7 provides the full ratings, and Supplement 3 shows the PRISMA flow chart. Consultation with our 7 content experts who are involved in care of patients with hypoxemic respiratory failure, including those with COVID-19, identified no additional systematic review that would have superseded the identified reviews, but 5 of these reviews included study populations that we judged as too indirect on final review (48–52)—for example, because they were studies in postsurgery patients or those with cardiogenic pulmonary edema only (Supplement 7). We found no systematic review comparing IMV with NIV. We found no studies allowing us to draw conclusions about the indirect comparative efficacy of CPAP or BiPAP in COVID-19.

Two systematic reviews (53, 54) concluded that RCTs suggest a large reduction in mortality of NIV compared with conventional oxygen therapy for acute hypoxemic respiratory failure (Supplement 7). We included 4 systematic reviews of RCTs that compared HFNC, which is considered an NIV strategy by many content experts, with conventional oxygen therapy for adults (55–58) and 1 in children (59). The results overall suggested no reduction in mortality but a reduction in the need for IMV with the administration of HFNC. Compared with other NIV, 2 of the reviews of RCTs in adults (56, 57) suggested that HFNC had no effect on mortality or escalation of ventilatory support, including the need for intubation. The RCTs included in 1 review suggested that helmets are at least as efficacious as the use of facemasks in NIV (53). In children, the risk for treatment failure and mortality appeared to be increased with HFNC compared with CPAP (59) (Supplement 7).

Stream 3: Systematic Review of Mechanistic, Animal, Human, Foundational Science, Preclinical, and Other Studies Describing the Risk for Transmission From AGPs

To determine the risk for transmission of COVID-19, we conducted a systematic review of mechanistic, animal, human, preclinical, laboratory, and other studies and identified 25 102 citations; Supplement 3 shows the PRISMA flow chart for the included studies. We included 6 studies assessing the presence or transmission of the 3 coronaviruses in different environments: MERS-CoV (2 studies) (60, 61), SARS-CoV (1 study) (62), and SARS-CoV-2/COVID-19 (3 studies) (63–65). Wan and colleagues (62) studied droplet distribution of SARS-CoV when patients with SARS used a humidifier or a large-volume nebulizer and found that none of the air samples had SARS-CoV–specific DNA products. One study found that SARS-CoV-2 persisted up to 16 hours in airborne form (64), and another reported a higher rate of SARS-CoV-2 detection in the intensive care setting where patients were ventilated (67% of air outlet swab samples and 44% of swab surface samples) (65). Adhikari and coworkers (60) modeled the transmission of MERS-CoV to HCWs visiting an

index patient, other patients sharing the same room, and family visitors. The risk was highest among HCWs and mostly depended on the concentration of MERS-CoV in the saliva. Pyankov and associates (61) used a virus-containing suspension aerosolized to an experimental aerosol chamber to compare, under controlled laboratory conditions, particle size and viable concentration of MERS-CoV in 2 different environments. They found higher evaporation and lower survival under hot and dry climatic conditions. Similarly, Bae and colleagues (63) found that coughing induces dissemination of SARS-CoV-2 and masks did not prevent colonization at a distance of 20 cm.

Stream 4: Update of Systematic Reviews of Human Studies Evaluating the Effect of AGPs

In 2011, CADTH produced a rapid response report that systematically reviewed the risk for transmission of acute respiratory infection to HCWs exposed to patients undergoing AGPs (2). The review included 5 case–control studies and 5 cohort studies evaluating the risk for SARS transmission to HCWs during AGPs (Supplements 8, 9, and 10). Only 4 of these studies provided adjusted effect estimates. The studies found large increases in the odds of SARS-CoV infection among HCWs performing or being present during tracheal intubation, or in HCWs performing chest compressions (66–69). Unadjusted studies reported an increased risk for transmission with tracheal intubation, NIV, manipulation of a BiPAP mask, and manual ventilation before intubation. Other AGPs were not associated with transmission in that report: endotracheal aspiration, suction of body fluids, bronchoscopy, nebulizer treatment, administration of oxygen, high-flow oxygen, defibrillation, insertion of nasogastric tube, and collection of sputum (Supplement 11).

Our update of this review identified 15 new studies (6 on COVID-19 and 9 on MERS), but these studies had high risk of bias (Supplements 12 and 13; Supplement 3 shows the PRISMA flow diagram). Most studies used real-time polymerase chain reaction to ascertain presence of virus. Three studies found no cases of transmission to HCWs in the following AGPs: bronchoscope-guided endotracheal intubation through nasal insertion (70); tracheostomy (71); endotracheal intubation, extubation, or NIV; and exposure to aerosols in an open circuit (72). Two additional studies reported no important association between the proportions of HCWs contracting acute respiratory illness in high-risk exposure versus other exposure in COVID-19 (73, 74), but another found that being present during or assisting with AGPs (nebulizer treatment or BiPAP) was more common among HCWs with COVID-19 (75). One study found an 11% infection rate among anesthetists who had direct contact with patients with COVID-19 who received oxygen via nasal cannula (76). Hall and colleagues (77) reported no infection among HCWs reporting contact with

patients with MERS-CoV, although a proportion of them had been present during AGPs (airway suction, nebulizer treatment, sputum induction, bronchoscopy, and intubation). Alraddadi and associates (78) reported different rates of infection among HCWs in direct contact with patients and among those performing AGPs, and 2 case reports (79, 80) described infection with MERS-CoV after being present at cardiac resuscitations and having face-to-face contact with a febrile HCW. However, these findings need to be interpreted with great caution, owing to a probable confounding effect of personal protective equipment (PPE) use and variable methods and reporting (81–84).

DISCUSSION

This systematic review evaluating different ventilation strategies identified 28 original comparative studies in patients with SARS, MERS, and COVID-19. Although an additional 34 studies in patients with COVID-19 were found, their methods and reporting were too poor for us to synthesize data appropriately. Together, the indirect evidence, including 7 systematic reviews in other populations, suggests that NIV may reduce mortality or need for IMV, with similar effects to IMV. However, the use of NIV and the choice of the ventilation strategy must be balanced against the potentially increased risk for infection of HCWs resulting from these AGPs. One study in patients with COVID-19 that used CPAP with helmets, and RCTs included in 1 systematic review, suggested that helmets are at least as efficacious as masks in NIV (25, 54, 85), and they have been used in children (86). Very limited evidence suggests that helmets may reduce the risk for transmission. Two additional comprehensive searches identified evidence that suggests a risk for infection for HCWs with COVID-19, SARS, and MERS (2). Tables 1 and 2 provide GRADE evidence profiles for 2 key comparisons (NIV versus IMV and NIV versus no mechanical ventilation), synthesizing the evidence and rating the certainty across the different streams for the most direct evidence (COVID-19, SARS, and MERS). Overall, the certainty of evidence is very low to low based on the observational design, which raises concerns about risk of bias. We did not rate down the evidence from patients with SARS or MERS for indirectness, because these diseases are caused by viruses belonging to the same family and subtype as SARS-CoV-2.

We are not aware of systematic reviews on the best NIV strategies in patients with COVID-19 who have acute hypoxemic respiratory failure. The adherence to full systematic review methods, inclusion of all languages, use of the GRADE approach (7), consideration of indirect evidence, and use of different streams of evidence are strengths of our urgent review. We also retrieved a total of 660 guidelines, of which 9 focused on COVID-19 (Table 3) (88–96). Of note, HFNC is not recommended by NHS England, although it is recommended by the other guideline bodies. Besides the Australian and

New Zealand Guideline bodies and the American Association for Respiratory Care, most guideline bodies recommend CPAP conditionally in selected patients.

Our study has limitations. The included original studies had poor reporting quality and were mostly observational, with inappropriate control for confounding or selection bias or with only single arms. The sole adjusted study of NIV in patients with COVID-19 was imprecise and included an inappropriately large number of variables in the regression model to produce reliable results. Furthermore, studies had mixed approaches to using NIV. In some, IMV was unavailable, and in others, IMV was used when NIV failed, which can introduce severe selection bias. Although we identified many studies in COVID-19, the most robust studies were in patients with MERS or SARS.

In stream 3, the 6 identified mechanistic and laboratory studies of the risk for transmission from AGPs did not allow quantitative risk estimates. In stream 4, we noted, similarly to the CADTH review (2), a risk of bias related to confounding due to use of PPE, which investigators often did not adjust for (74, 79, 97, 98).

Although our data are largely observational (with the exception of 1 small RCT in patients with SARS) and the degree of indirectness still needs to be determined on the basis of new evidence emerging about the similarities of SARS, MERS, and COVID-19, prior systematic reviews could not evaluate the effect of NIV on important outcomes in patients infected with coronaviruses. At a minimum, our review serves as a snapshot of the best available evidence. Clinicians should consider using NIV only when appropriate PPE is available to protect HCWs from the infection.

It is important that researchers performing observational studies adhere to reporting standards, even during pandemics. What is needed to protect HCWs and prepare for the next pandemic are robust, well-reported studies on strategies to improve the outcomes of patients and protect those who care for them. Although pharmacotherapeutics and vaccines are in the limelight, simple process-of-care measures and common support strategies must be systematically documented and analyzed to adequately prepare for the future. Better studies are needed to inform practice guidelines and reduce inconsistency among their recommendations (ongoing studies are listed in Supplement 14).

CONCLUSION

In conclusion, our systematic review examined different streams of evidence, including original human studies evaluating different modalities of NIV, IMV, and HFNC in COVID-19, SARS, and MERS; systematic reviews in other populations; mechanistic and laboratory evidence; and studies of AGPs. We found low-certainty evidence that NIV may have similar effects as IMV but reduce mortality compared with no IMV in patients with COVID-19 (stream 1). Evidence in other populations with acute hypoxic respiratory failure suggests that NIV improves outcomes compared with conventional oxygen therapy and HFNC (stream 2). However, that evidence is indirect

and very limited in children. We searched for but did not identify well-done mechanistic and other laboratory studies that allow quantification of virus transmission risk (stream 3). However, evidence in stream 4 suggests an increased risk for transmission of coronaviruses with invasive procedures, such as intubation and NIV, but also that risk for transmission was difficult to quantify exactly. On the basis of this and other reviews, PPE may reduce for some the risk for transmission during AGPs, but it will not abolish it. The poor quality of conduct and reporting of studies on the effects of NIV on important outcomes in COVID-19 is striking.

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