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Review article

Respiratory care for the critical patients with 2019 novel coronavirus

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted through respiratory droplets, aerosols and close contact. Cross infections occur because viruses spread rapidly among humans. Nineteen percent (19%) of the infected patients developed severe pneumonia and acute respiratory distress syndrome (ARDS). Hypoxemia usually occurs and patients may require oxygen therapy or mechanical ventilation (MV) support. In this article, recently published clinical experience and observational studies were reviewed. Corresponding respiratory therapy regarding different stages of infection is proposed. Infection control principles and respiratory strategies including oxygen therapy, non-invasive respiratory support (NIRS), intubation evaluation, equipment preparation, ventilator settings, special maneuvers comprise of the prone position (PP), recruitment maneuver (RM), extracorporeal membrane oxygenation (ECMO), weaning and extubation are summarized. Respiratory equipment and device disinfection recommendations are worked up. We expect this review article could be used as a reference by healthcare workers in patient care while minimizing the risk of environmental contamination.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to upper respiratory tract infection and could rapidly spread down to the lower respiratory tract. When infection occurs, most of the patients were asymptomatic or only having a mild illness (81%). The most common symptoms reported were fever, fatigue, cough (with or without sputum production), anorexia, malaise, myalgia, sore throat, dyspnea, nasal congestion and headache. Less frequently, patients may also present with diarrhea, nausea and vomiting. Near 14% of the infected patients developed severe pneumonia and had fever or signs of respiratory tract infection. Patients also manifested one of the following conditions: tachypnea with the respiratory rate (RR) > 30 breaths/minute; severe

respiratory distress; or hypoxemia with peripheral oxygen saturation (SpO₂) ≤ 93% when breathing in ambient air and needed oxygen therapy. Approximately 5% of these patients progressed to hypoxemic respiratory failure. Acute respiratory distress syndrome (ARDS) [1–3], results from intrapulmonary ventilation-perfusion mismatching or shunting and usually requires mechanical ventilation (MV) support [4]. The incidence rate, disease severity of coronavirus disease 2019 (COVID-19) patients, measures and needs of respiratory therapy, and oxygenation goals are summarized in Table 1.

Providing these patients timely with optimal respiratory care devices and protecting healthcare workers from being infected are important issues. This article is a brief overview of optimal respiratory care for 2019-nCoV infected patients.

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Abbreviations	
ACH	air exchanges per hour
AGMP	aerosol-generating medical procedures
AHRF	acute hypoxemia respiratory failure
ApOx	apneic oxygenation
ARDS	acute respiratory distress syndrome
ARF	acute respiratory failure
BiPAP	bi-level positive airway pressure
BUHE	bed-up-head-elevated position
BVF	bacterial viral filter
BVM	bag-valve-mask
CARDS	COVID-19 ARDS
COPD	Chronic Obstructive Pulmonary Disease
COT	conventional oxygen therapy
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CRS	respiratory-system compliance
ECMO	extracorporeal membrane oxygenation
EtCO ₂	end tidal carbon dioxide
ETT	endotracheal tubes
FiO ₂	inspired oxygen fraction
FRC	functional residual capacity
H1N1	influenza A virus subtype H1N1
H5N1	influenza A virus subtype H5N1
HEPA	high efficiency particulate air
HFNC	high flow nasal cannula
HFOV	high frequency oscillatory ventilation
HH	heated humidity
HME	heat and moisture exchanger
HMEF	Heat moisture exchanger filters
HPS	human patient simulator
ICU	intensive care unit
IMV	invasive mechanical ventilation
IV	intravenous
LPVS	lung-protective ventilation strategy
LRT	lower respiratory tract
MDI	metered-dose inhalers
MERS-CoV	Middle East respiratory syndrome coronavirus
MMAD	mass medium aerodynamic diameter
MPPS	most penetrating particle size
MV	mechanical ventilation
NC	nasal cannula
NIRS	non-invasive respiratory support
NMBA	neuromuscular blocking agents
NRM	non-rebreather mask
NIPPV	non-invasive positive pressure ventilation
PaO ₂	arterial oxygen tension
PBW	predicted body weight
PIP	peak inspiratory pressure
PL	transpulmonary pressure
PEEP	positive end-expiratory pressure
PONV	post-operative nausea and vomiting
Pplat	plateau pressure
PP	prone positioning
PPE	personal protective equipment; PSILI: patient self-induced lung injury
RCT	randomized controlled trial
RF	respiratory failure
RM	recruitment maneuver
RNA	ribonucleic acid
RR	respiratory rate
RSI	rapid sequence of intubation
SaO ₂	arterial oxygen saturation
SARI	severe acute respiratory infection
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	2019 severe acute respiratory syndrome coronavirus 2
SBT	spontaneous breathing trial
SGA	supraglottic airway
SOPR valve	subambient overpressure relief valve
SpO ₂	peripheral oxygen saturation
SSC	Surviving Sepsis Campaign
TV	tidal volume
UV light	ultraviolet light
VILI	ventilator induced lung injury
VV ECMO	venovenous extracorporeal membrane oxygenation
WOB	work of breath

2. Modes of transmission of SARS-CoV-2

SARS-CoV-2 could be transmitted through the air via respiratory droplets, aerosols, direct or indirect physical contact with pathogens released from patients' secretions and often lead to cross infections [5].

2.1. Droplets

Respiratory droplets with a mass medium aerodynamic diameter (MMAD) > 5 µm. These particles could be suspended in the air for a limited time and usually precipitate within 1 m from the infectious source settle in the patient's tracheal-bronchial region. The virus is spread by infective respiratory droplets produced during cough or sneeze. Vulnerable mucosa (mouth, nose and conjunctiva) could be exposed to the potentially infective respiratory droplets if direct or indirect physical contact is within 1 m (m) [6,7].

2.2. Aerosol

Aerosol with MMAD ≤ 5 µm. These particles are significantly smaller, allowing them to remain suspended in the air for a longer period of time (5 µm aerosols could be suspended in the air for 1hr) and conveyed to the alveoli. Since these infectious particles could introduce

opportunistic airborne transmission, precautions should be adopted to prevent healthcare workers from being infected [6,7].

2.2.1. Aerosol-generating medical procedures (AGMP)

AGMP are generally divided into two categories. a) Induced aerosol procedures: aerosols produced during medical procedures including bronchoscopy, tracheal intubation, cardiopulmonary resuscitation and sputum induction. b) Mechanical aerosol procedures: procedures that can mechanically create and disperse aerosols, including MV, non-invasive respiratory support (NIRS), high frequency oscillatory ventilation (HFOV), nebulizer treatment, suctioning, laser plume and surgery [8].

2.2.2. Fomites [9]

Fomites may be introduced by toilet flushing and cause aerosolization of the virus-laden aerosol from the patient's excretions [10–14].

2.2.3. Deposition and resuspension

When virus aerosol has adhered to the protective apparel or floor surface, viral transmission could occur when it is resuspended [15].

Table 1
Incidence rate, disease severity, related respiratory therapy and oxygenation goals in COVID-19.

Incidence Rate	Disease Severity	Respiratory Therapy	Oxygenation Goal
81%	Mild illness	Oxygen therapy is usually not needed.	SpO ₂ 92–96%
14%	Pneumonia	Oxygen therapy is usually not needed.	PaO ₂ 55–80 mmHg or SpO ₂ 88–95%
	Severe pneumonia	1) Oxygen therapy (humidified oxygen should be avoided). 2) Nebulization of medications should be avoided (consider MDI). 3) Prudently applying NIRS with PPE.	
5%	Acute respiratory distress syndrome (ARDS) ^a	1) Timely, elective intubation with video laryngoscopy and HEPA filter. 2) Preoxygenation for 3–5mins in BUHE position (ApOx or Apneic CPAP recruitment-Avoid any manual ventilation). 3) If intubation failed, insert SGA. 4) Use the HEPA filter on BVM or mechanical ventilator. 5) Use an EtCO ₂ device to confirm tracheal intubation. 6) Use in-line catheters for airway suctioning 7) Add a HEPA filter between the suction device and canister. 8) Clamp endotracheal tube when circuit disconnection is required.	

SpO₂: peripheral oxygen saturation; MDI: metered-dose inhalers; NIRS: non-invasive respiratory support; PPE: personal protective equipment; ARDS: adult respiratory distress syndrome; HEPA: high-efficiency particulate air; PaO₂: arterial oxygen tension; BUHE: bed-up-head-elevated position; ApOx: apneic oxygenation; SGA: supraglottic airway; BVM: bag-valve mask; EtCO₂: end tidal carbon dioxide.

^a ARDS is defined by the Berlin criteria. If arterial blood gas data is unavailable, SpO₂/FiO₂ ≤ 315 could be used as a surrogate, suggests by Kigali modification of Berlin criteria in ARDS (including non-ventilated patients) [1,3].

2.2.4. Respirable particle aerosols via natural respiratory activities

Previous studies indicated that the transmission of respirable particles generated during natural respiratory activities, including coughing, sneezing, talking, and breathing, may remain airborne for a prolonged period of time [16,17]. Milton, D.K. *et al.* proposed that during normal breathing and coughing, small, virus-containing droplets are generated [18]. During normal breathing and speaking, 80–90% of the generated droplet sizes are <1 μm and can transport via aerosols [19]. Since breathing and speaking occur far more frequently than coughs and sneezes in asymptomatic individuals, these are the major routes of viral transmission [17]. Zhou and Tan *et al.* also reported that when compared with the symptomatic individuals, the duration of viral shedding is longer and infectivity is also higher in asymptomatic cases [20,21]. Stadnytskyi *et al.* showed that thousands of oral droplets could be produced per second, and within 1 min of loud speak, at least 1000 virus-containing droplet nuclei could remain airborne for more than 8 min [22]. Netz *et al.* applied the method of algebraic equations in physics. They demonstrated that the airborne virion emission rates during speaking could be estimated and mouth covering can help to contain the COVID-19 pandemic [23]. In animal models, several authors

have affirmed that SARS-CoV-2 infection can be transmitted through air, even in the absence of physical contact [24–27]. Ong’s study demonstrated that viral ribonucleic acid (RNA) could be isolated from a ceiling extractor fan in a patient’s negative pressure room even when no AGMPs were implemented [28]. All these results suggest that during natural respiratory activities, virus-containing aerosols could be spread and viral RNA was contained in these respirable fraction particles.

Regarding these contentions, Wilson *et al.* indicated that, rather than focusing on 5 μm diameters as a cut-off size to define droplet or aerosol spread, lung deposition should be considered as a continuum process. They suggest that close physical contact with critical patients and total exposure time predispose higher risk than the procedure per se. In fact, AGMPs may result in less pathogen aerosolization than the aerosol spread from a dyspneic and coughing patient [29]. The mode of transmission of SARS-CoV-2 and precautions are summarized in Table 2.

3. Oxygen therapy and non-invasive respiratory support (NIRS)

3.1. Oxygen therapy

When severe pneumonia develops, the patient’s work of breath (WOB) is significantly increased. Clinical manifestations include tachypnea with RR > 30 breaths/minute, severe respiratory distress and hypoxemia with SpO₂ ≤ 93% when the patient is breathing in ambient air. When oxygen therapy is applied, the recommended target of SpO₂ is 92–96% [4,30]. Oxygen therapy applied in COVID-19 patients is summarized in Table 3.

3.1.1. Nasal cannula (NC)

Discomforts usually occur when the oxygen flow setting is greater than 6–8 L/min. Initial oxygen flow is usually set at 5 L/min then gradually titrate to the target SpO₂ ≥ 93%. Humidified oxygen should be avoided whenever possible in order to reduce the risk of spreading the virus. When an input flow is greater than 4 L/min, the cold dry air could cause nasal mucosa injury and may induce epistaxis. Hui, D.S. *et al.* observed that, when a patient is receiving oxygen via nasal cannula, there is a substantial risk of exposure of the patient’s exhaled air if a person is within 1 m towards the end of the bed [31]. If the patient is highly contagious, the risk of infection in healthcare workers could be significantly increased. Another study showed that the expelled air dispersion along the median sagittal plane distance was 68 cm if no mask was wearing and the patient’s coughing. If the patient was wearing a surgical or N95 mask, the disperse distances were remarkably reduced to 30 and 15 cm respectively. In the laser light-sheet and images test, the results also revealed distinct leakage of the expelled air. Although the N95 mask provides better protection, it could also aggravate respiratory distress in patients with acute lung injury. Hence, when applying oxygen therapy with a nasal cannula, a surgical mask can be worn over the cannula but maintaining a distance of greater than 30 cm from the patient is advised [32]. They also found that the distance of exhaled air dispersion was different according to the dimension and ventilation

Table 2
Mode of SARS-CoV-2 transmission and precautions.

Particle	SARS-CoV-2 transmission	Precautions
Droplets >5 μm	1) Produced by cough or sneeze. 2) Vulnerable mucosa infected by droplets. 3) Close contact within 1 m. 4) Direct or indirect physical contact with pathogens from patients’ secretions.	Droplet and contact
Aerosol ≤5 μm	1) AGMPs (induced and mechanical type). 2) Fomites formed by toilet flushing. 3) Deposition and resuspension. 4) Respirable particle aerosols via natural respiratory activities	Airborne

AGMP: aerosol-generating medical procedures.

Table 3
Oxygen therapy in COVID-19 patients.

Device	Suggest Flow Rate	FiO ₂ Range	Attachment/Monitor	Target
NC	≤5 L/min	24–40%	1) Wear a surgical mask 2) Maintain safe distance >30 cm 3) ≥ 4 L/min nasal mucosa injury without the humidifier	1) Target SpO ₂ 92–96%. 2) PaO ₂ /FiO ₂ <300 mmHg or SpO ₂ /FiO ₂ <315 or distress, consider applying NIRS.
NRM	10–15 L/min	60–80%	1) Properly fitted 2) Exhalation: One-way valve and filter	
Hi-Ox	1) Without RF 5–6L/min 2) Distress 10–12 L/min	>8 L/min FiO ₂ greater than 80%	1) Properly fitted 2) Exhalation filter	

NC, nasal cannula; NRM, non-rebreather mask; Hi-Ox, high oxygen mask; RF, respiratory failure; FiO₂, inspired oxygen fraction; SpO₂, peripheral oxygen saturation; WOB: work of breathing; NIRS: non-invasive respiratory support.

system of the room. In this study, the distance of exhaled air dispersion was longer in a dimension of 4.1 × 5.1 × 2.6 m and the ventilator system was set at a pressure of −7.4 Pa and 16 air exchanges per hour (ACH), when compared with 2.7 × 4.2 × 2.4 m with a pressure of −5 Pa and 12 ACH. For instance, when a patient is receiving NC 5 L/min, the dispersion distances in these two rooms were 1 m and 0.45 m respectively. It should therefore be noticed that in isolation rooms, room dimension and air exchange rate are important factors in preventing contamination [31].

3.1.2. Avoid aerosol generating masks or masks with side vents

Devices providing 6 L/min or more of oxygen are categorized as high flow rate systems and we discourage using these devices if an airborne infection isolation room is unavailable [33]. Somogyi, R's study recommended that properly fitted masks should be applied whenever possible. When NRM and Venturi-type masks are used, plumes of exhaled droplets escaping from the side vents were detected [34]. Hui, D.S demonstrated that transmissible respiratory infections such as influenza A virus subtype H5N1 (H5N1) and severe acute respiratory syndrome (SARS), using these devices could be a potential source of aerosol transmitting infection [35]. The exhaled air dispersed in various respiratory devices is summarized in Table 4. Air leakage with different disperse distances could also be detected in other masks equipped with side vents. The distance of the exhaled air dispersed in the Venturi mask and the simple mask is 0.4 m. Somogyi, R found that if a device equipped with side vents is used, the exhaled air could leak through both the vents and along the sides of the mask during expiration. The extent of the plume might be increased with high oxygen flows and expiratory flows are augmented by coughing, sneezing, or hyperventilation [34]. Moreover, when a Venturi mask is used and double exhaust fans are turned off, the exhaled smoke can quickly fill up the medical ward within 5 min [36]. When providing oxygen therapy, masks equipped with side vents and aerosol generating devices should be avoided.

3.1.3. Non-rebreathing mask (NRM) and high oxygen (Hi-Ox) mask

These masks are usually applied in COVID-19 patients with higher oxygen demand. Although NRM is equipped with side vents, the air leak is probably negligible. Hui, D.S. et al. had demonstrated that the leaked air dispersion distance in NRM is < 0.1 m [36]. Therefore, we believe that these masks could be safely applied to COVID-19 patients. However, when NRM and Hi-Ox masks are used, these masks should be properly fitted and attached to exhalation filters. Furthermore, adherence to

Table 4
The exhaled air dispersion in various respiratory devices [31,32,36,76,167].

Device or procedure	Distance traveled of the exhaled air	Dimension/pressure/ACH
Normal cough	0.7 m towards the end of the patient's bed	4.1 × 5.1 × 2.6 m; −7.4 Pa; 16 ACH
No wear mask, surgical and N95 mask	Sideway leakage to 0.68 m, 0.3 m and 0.15 m (during patient's coughing)	
NC	1) 1 m towards the end of the patient's bed under 5 L/min 2) 0.3–0.42 m under 1,3 and 5 L/min	1) 4.1 × 5.1 × 2.6 m; −7.4 Pa; 16 ACH 2) 2.8 × 4.22 × 2.4 m; −5 Pa; 12 ACH
Hudson mask (Simple mask)	0.22–0.4 m lateral to the center of the mask under 6–10 L/min	7.1 × 8.5 m × 2.7 m room ventilation was temporarily suspended
Venturi oxygen mask	0.29–0.4 m under FiO ₂ 24% (4 L/min) and 40% (8 L/min) Exhaled smokes filled up the ward within 5 min (double exhaust fans off)	General medical ward with double exhaust fans for room ventilation and HEPA filter
NRM	<0.1 m	2.8 × 4.22 × 2.4 m; −5 Pa; 12 ACH
Jet nebulizer at 6 L/min	>0.8 m laterally from the patient	2.8 × 4.22 × 2.4 m; −5 Pa; 12 ACH
NIPPV	Between 0.4 to 1 m (depended on different brands of face masks, and increase by higher inspiratory pressures and use of a whisper swivel device)	2.8 × 4.22 × 2.4 m; −5 Pa; 12 ACH
Manual ventilation with a viral-bacterial filter by bagging	Reduce the exhaled air leakage forward but could increase the sideway leakage	Not available

NC, nasal cannula; NIPPV, non-invasive positive pressure ventilator; ACH, air changes per hour; HEPA: high-efficiency particulate air.

isolation policy and personal protective equipment (PPE) practices is recommended.

3.1.3.1. Non-rebreathing mask (NRM). Inspired oxygen fraction (FiO₂) ranges from 0.6 to 0.8. One-way valve with filter must be used in the expiratory ports and the mask should be properly fitted.

3.1.3.2. High oxygen (Hi-Ox) mask. Oxygen flow setting at 5–6 L/min is usually adequate in patients without respiratory failure but higher flows (10–12 L/min) may be required in patients with severe respiratory distress. Typically, FiO₂ could be maintained greater than 80% if the oxygen flow setting is 8 L/min but under the same flow rate settings, NRM could only provide 50–60% of FiO₂. Therefore, Hi-Ox appears to be more environmentally friendly. The advantages of the Hi-Ox mask are: a) it could provide high oxygen concentration with lower flow rates settings, b) air leakage could be reduced when the non-vented mask is equipped with two auxiliary straps, c) the exhaled aerosols is directed downward when an adaptor is used (the risk of healthcare workers, who were standing nearby the patient, from being infected could be decreased). The risk of transmitting microorganisms could further be reduced when combined with a HEPA (high-efficiency particulate air) filter [37].

In summary, low oxygen concentration therapy could be applied to NC if it is covered with a surgical mask. When a high oxygen concentration is needed, a properly fitted NRM or Hi-Ox mask with an attached exhalation filter should be used. All aerosol generating masks with side vents should be avoided.

3.1.4. Respiratory distress

For patients with persistent elevated RR and moderate to severe

hypoxemia, adjust a higher flow of oxygen is generally not recommended. BVM and aerosols should not be used because the risk of viral aerosolization and dispersion is high. Nebulized medications are discouraged and could be replaced by metered-dose inhalers (MDI) and NIRS can apply to improve oxygenation and dyspnea by reducing WOB for patients with hypoxemia and dyspnea with COVID-19 pneumonia [38].

3.2. Prudently applying non-invasive respiratory support (NIRS)

NIRS is defined as either non-invasive positive pressure ventilators (NIPPV) or HFNC (high flow nasal cannula). Physiological benefits could be provided by applying positive pressure, humidification, and fine-tuning of the FiO₂ apart. Kurtz *et al.* reported that NIRS implementation was independently associated with improved survival when compared with direct intubation even if NIRS fails [39]. Marini *et al.* proposed that NIRS could reduce patient self-induced lung injury (PSILI) by decreasing respiratory drive effort. NIRS may also relieve tissue stress by attenuating the elevation of pulmonary transvascular pressures, vascular flows, and fluid leakage [40]. However, potential risk of cross-infection could occur when implementing NIRS in COVID-19 patients, and others including, procrastinate intubation, rapid deterioration of lung injury. Gorman *et al.* proposed that NIRS could only delay rather than avoid, endotracheal intubation. Furthermore, large tidal volume (TV) breathing could lead to PSILI when NIRS was used [41]. The applications of NIRS in contagious diseases are discussed separately.

3.2.1. High flow nasal cannula (HFNC)

HFNC is an oxygen system that can deliver high (50–60 L/min), heated, and humidified oxygen flow. The system is widely used because there are many advantages including, nasopharyngeal carbon dioxide could be washed out more effectively, inspiratory resistance may be decreased, alleviation of dyspnea, and WOB, improved hypoxia and hypercapnia, better mucociliary clearance and tolerated [42–45].

Since the patient's tolerance of HFNC is usually better than NIPPV therefore, HFNC may be continuously used for a prolonged period of time. Furthermore, the adverse effects are fewer because the lung is less stretched so ventilator-induced lung injury (VILI) may be less apt to occur [46]. The application of HFNC is increasingly popular among patients with acute hypoxemia respiratory failure (AHRF) because the beneficial effects have been demonstrated by many studies. The HENIVOT trial observed no difference in respiratory-free support at 28 days between helmet NIPPV and HFNC in patients with COVID-19 and moderate to severe hypoxemia [47]. Grieco *et al.* suggested that HFNC could be used as an alternative to NIPPV and appeared to be an optimal strategy to administer oxygen to hypoxemic critically ill patients with high respiratory demand [48]. Messika, J *et al.* recommended that HFNC could be applied as first-line therapy for patients with acute respiratory failure (ARF), including ARDS [49]. In patients with ARDS or AHRF, HFNC appears to be the preferred NIRS based on available evidence [50].

However, a recent systematic review showed that HFNC may increase the complications including, thoracic and cervical discomfort, nasal irritation, device-induced heat, unpleasant smell and inability to tolerate [51]. Moreover, it should be cautious that HFNC may increase the risk of viral spread through aerosol generation and dispersion of infected droplets [52,53]. In a retrospectively designed observational study by Raboud, J. *et al.* HFNC did not increase the risk of SARS transmission [54]. J. Li *et al.* also indicated that the risk of bio-aerosol dispersion was low in COVID-19 patients when HFNC was applied [55]. In this study, the authors found that the exhaled smoke dispersion distance in HFNC was similar to the simple O₂ mask and was less than other O₂ devices including non-rebreathing and Venturi mask so they proposed that HFNC could be safely applied. The conclusion is summarized from the results of two in-vitro studies. However, it should be noticed that these two in-vitro study designs, modes, settings and

scenarios were disparate and they were 12 years in the gap. Misinterpretation of these results may exist because of the bias [56,57]. Moreover, if the loose connection happened when HFNC was applied, the exhaled smoke dispersion distance significantly increased from 17 to 62 cm, which is exceedingly greater than other O₂ devices [56]. In the real world, disconnection frequently happens so the risk of exposure among healthcare workers may be considerably high. Furthermore, the author also cited a study from Leung, C.C.H., *et al.* who reported that bacterial droplet spread was not increased in HFNC when compared with the simple mask so the safety of HFNC is again demonstrated. However, in this study, simple masks with side vents (which is not recommended for COVID-19 patients) were used in the control group and the total case number was small (only 19). Moreover, the study was focused on gram-negative bacteria so it may not be applicable in the scenario of viral transmission [58].

Since the risk of viral spread could not be totally excluded, the use of HFNC should be prudently used in COVID-19 patients. When applying HFNC treatment, correct placement of the nasal cannulas (which must be completely inserted in the patient's nostrils and secured with elastic bands around the patient's head to minimize lateral losses) must be ensured and place a surgical mask over the HFNC [59].

3.2.2. Non-invasive positive pressure ventilators (NIPPV): Bi-Level positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP)

NIPPV contains both BiPAP and CPAP. The end-expiratory positive airway pressure (PEEP) could increase functional residual capacity (FRC) and open collapsed alveoli, thereby improving lung compliance and reducing respiratory load. NIPPV provides pressure support which can assist respiratory muscles during inspiration, reducing WOB and dyspnea, improve hypoxemia and hypercapnia [46]. While NIPPV efficacy has been well validated in the context of cardiogenic pulmonary edema and Chronic Obstructive Pulmonary Disease (COPD) exacerbation but its role within AHRF and ARDS remains controversial [60]. Antonelli *et al.* reported a study that included 147 subjects, those who received NIPPV had a lower intubation rate and intensive care unit (ICU) mortality. Ferrer *et al.* also suggested that NIPPV could reduce intubation rate and mortality but only in certain carefully selected patients. However, a meta-analysis concluded that in ARDS patients, when NIPPV was used in addition to standard care, there's no reduction in either intubation rate or ICU mortality. Delclaux *et al.* not only found that there were no beneficial effects, but on the contrary, the adverse events that occurred in patients receiving NIPPV consisting of CPAP were higher [46]. NIPPV failure raises the risk of death in AHRF because of delayed intubation and predisposing lung stress which could induce PSILI. Because of the high treatment failure rate (averages 52%; from 14 to 70%) [46], poor tolerance and subsequent unfavorable prognosis, current guidelines do not recommend the use of NIPPV in this type of patients with hypoxemia and is conditionally recommended for hypercapnic acute-on-chronic ventilator failure [45]. Other drawbacks of NIPPV include, skin ulcer usually occurs after prolonged wearing of a tight-fitting mask and also leads to airway mucociliary clearance impairment. As for the healthcare worker, environmental contamination and cross infection are the major concerns. In a systemic review, NIPPV could increase the risk of transmitting hospital acquired respiratory tract infections [61]. Franco *et al.* found that approximately 11.1% (n = 42) of the healthcare workers were infected after providing NIPPV treatment for COVID-19 patients with ARDS [62]. The possible causes of contamination are discussed here.

- a) Aerosol-generating device: BiPAP/CPAP could generate aerosols and increase the risk of pathogen transmission [61].
- b) Leakage: Mask leak is an important source of contamination. In clinical practice, facial skin grease, postural changes, detained nasogastric tube, adjustment of mask strap and pressure sore are important causes of mask interface leakage and could lead to trigger flow compensation.

- c) Higher inspiratory pressures: The dispersion of infected respiratory droplets may be augmented with higher inspiratory pressures [63].
- d) Humidity: Heated humidity (HH) with temperature setting to 30 °C should be applied when NIPPV is used in order to mitigate nasal symptoms, reduce the accumulation of secretions in the patient's oral pharynx, and provide better tolerance [64]. However, HH may carry a greater risk of spreading virus containing aerosols and associated with increase cross-infection. Passive humidity (heat and moisture exchanger; HME) is a reasonable alternative but should be used with caution [65]. Lellouche, F, reported that the additional dead space in HME could impede carbon dioxide elimination, particularly in patients with hypercapnia [66]. HMEs with bacterial filtration effect (heat and moisture exchanger; HMEF) may be adopted to minimize environmental contamination. HMEF should be replaced periodically in order to maintain airway humidification (at least 30 mg H₂O/L). Insufficient airway humidification could lead to sputum impaction, causing difficult expectoration and increase the risk of pneumonia. Elliott, M. *et al.* have brought up the concerns on

the use of a bacterial viral filter (BVF), because the filters could be blocked by moist secretions so it should be applied with caution [67]. Rodriguez *et al.* reported that when there were excessive leaks, higher inspiration pressure and inspired oxygen fraction (higher than 60%) were required, the AH would significantly be decreased [68]. HH should be used cautiously in patients with predisposed insufficient airway humidification or increased airway resistance. Health-care workers should adopt appropriate protective measures whenever possible.

- e) Delayed intubation: The extensive use of CPAP/BiPAP may delay the awareness of rapid clinical deterioration and leads to emergent intubation. It could raise the chance of contamination when donning PPE because of flustering and incur infection among the working staff [69].

Previous studies have demonstrated that implementing NIPPV is an independent risk factor of super-spreading events. Although Cheung, T. M.T. reported that NIPPV was an effective measure in SARS patients

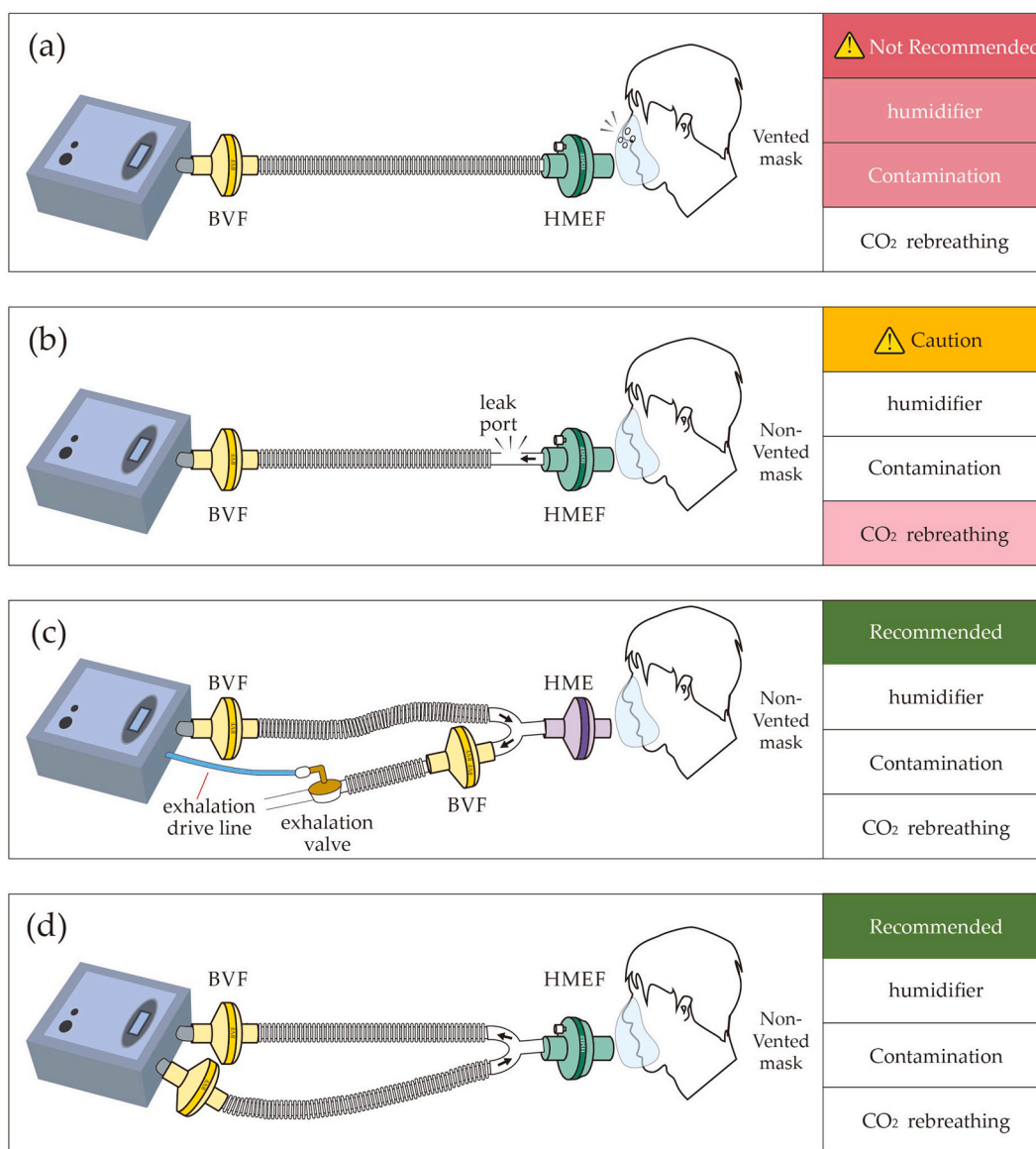


Fig. 1. The methods of different NIPPV circuits with BVF, HME and HMEF. Delorme *et al.* compared the effects on dead space and PETCO₂ in differently deployed NIPPV. In method b, pressure support levels had to be increased to 6 cmH₂O to compensate for the equipment dead space compare with method d [71]. A dual-limb circuit connected to a non-vented mask (d) is the best recommendation and (c) is recommended if a single-limb circuit was applying. NIPPV: non-invasive positive pressure ventilation; BVF: bacterial viral filter; HME: heat & moisture exchanging; HMEF: heat & moisture exchanging filter.

with ARF and was considered to be a safe device for healthcare workers. It should be noticed that the PPE and NIPPV used in their report were upgraded versions, Air-Mate HEPA Powered Air Purifying Respirator System (3 M Corporation; St. Paul, MN) [70]. Others had proposed that when the non-vented mask is equipped with two tube closed-circuit systems and viral filters, then NIPPV could be considered if it were applied in a negative pressure isolation room. However, when higher inspiratory pressure settings are required, mask leakage will be accentuated and leads to environmental contamination. It should be noticed that despite all the precautions, the risk of environmental contamination remains a major concern whenever NIPPV is used. We recommend that CPAP or BiPAP should be prudently used in COVID-19 patients. In situations when NIPPV must be applied, the non-vented mask with fully equipped viral filters according to different tubing may be considered. Furthermore, the instrumental dead space effect on alveolar ventilation should be pondered. In a bench study, Delorme *et al.* demonstrated that when the dual-limb circuit was connected to a non-vented mask with two filters placed both at the inspiratory and expiratory port of the ventilator, the dead space effect was low [71]. The disadvantages and advantages of different tubing systems equipped with BVF, HME and HMEF are shown in Fig. 1.

3.2.3. Helmet NIPPV

Helmet NIPPV comprises a transparent hood that covers the patient's head with a soft collar neck seal. It provides better comfort and allows speech communication, feeding, less difficulty to cough, and fewer skin and gastric complications. The major advantages of Helmet NIPPV also include higher levels of PEEP that could be applied without causing air leaks or patient-ventilator asynchrony and better patient tolerance. Oxygenation may be improved and prevent the progression of lung injury during spontaneous breathing [47]. Intubation and mortality rates may be reduced and the benefits of NIPPV may also be extrapolated to patients with ARDS. Patel, B.K., *et al.* has pointed out that, when compared with the face mask type NIPPV, the incidence of intubation and 90-day mortality in ARDS patients was lower if helmet NIPPV was applied [72]. Franco *et al.* found that when helmet NIPPV was used as a first line rescue measure in COVID-19 ARDS patients and only 25% of them needed invasive mechanical ventilation (IMV) after their initial treatment [62]. The HENIVOT trial also reported helmet NIPPV is successful management and could avoid intubation in a greater proportion of patients [47]. About the dispersion of exhaled air, Hui, D.S., *et al.* discovered that when the applied pressure was increased in NIPPV, the degree of leakage also increased among different interfaces. The distance of dispersion could reach 81.2 cm when facemask pressure was set to 20cmH₂O. However, the leakage of exhaled air was negligible when the helmet NIPPV connected to a two limb circuit equipped with filters and a good seal at the neck interface. When comparing with face masks or HFNC, helmet NIPPV significantly reduces SARS-CoV-2 aerosolization and exposure risk for healthcare workers in a recent report [73]. However, different degrees of exhaled air leakage could still be detected in helmets without a tight neck seal [63]. Therefore, when NIPPV is applied, the risk of cross infection among healthcare workers could be reduced by selecting an optimal interface. Potential problems also include, dead space ventilation may be strengthened by the increase of respiratory drive, minute ventilation and WOB that could lead to PSILI, fresh high flows are needed to avoid CO₂ rebreathing, noise, possible claustrophobia, armpits and neck skin injury, abdominal distension and eye irritation. Therefore, When increased respiratory drive, WOB, persistent dyspnea and the use of accessory muscles are present, IMV should be instituted as soon as possible [73].

3.2.4. Early detection of NIRS failure

Guidelines published from different regions on the use of NIRS in COVID-19 are generally inconsistent. Along with the rapid progression of the epidemic and because of limited medical resources, clinical management has changed to support or conditional recommendation

rather than not suggestion. However, clinical recommendations are relatively consistent on NIRS cross-over infection issues and emphasizing that attention must be paid during aerosol generating procedures [74]. Furthermore, prudent clinical judgment is needed during NIRS treatment and timely intubation should be considered if clinical conditions fail to improve [75].

Recently, several evaluation tools have been developed to predict NIRS failure, including the HACOR Scale and ROX Index. The HACOR Scale is calculated after 1 h of use of NIPPV with variables including heart rate, acidosis, consciousness, oxygenation, and respiratory rate. When the total score is > 5, timely intubation could improve hospital mortality. ROX Index is the ratio of SpO₂/FiO₂ to RR. It is evaluated continuously during HFNC treatment and has been tested and validated to predict treatment failure in HFNC. Patients with ROX Index <2.85, <3.47 and < 3.85 after two, six and 12 h of HFNC treatment are at high risk of treatment failure. The simple, readily available, physiological parameters may help to early distinguish patients with a high likelihood of treatment failure, in which prompt intubation and initiating invasive mechanical ventilation are mandatory [48]. The decision algorithm of pragmatic use of conventional oxygen therapy (COT), NIRS, and intubation for 2019-nCoV infected patients are presented in Fig. 2.

3. Timely, elective intubation with video laryngoscopy and HEPA filter.

During the major outbreak of SARS, medical procedures reported that could increase the risk of virus transmission were tracheal intubation, NIPPV, tracheotomy and manual ventilation before intubation [76]. There was a 13-fold increased risk of being infected during endotracheal intubations among the working staff [77]. When the patient's airway is opened, there is a considerably high level of viral shedding. The aerosols generated during resuscitation and intubation could induce virus transmission. It is of utmost importance to provide adequate protections for all the healthcare staff. The measures that are implemented in the rapid sequence of intubation (RSI) for COVID-19 patients are summarized in Table 5 [78–81].

4. Timely, elective intubation with video laryngoscopy and HEPA filter

4.1. Preparation and position

4.1.1. Patient's preparation

Timely decision and intubation: When respiratory distress fails to improve after NIRS is implemented presented by profound hypoxemia, compromised ventilation, loss of protective airway gag reflex, respiratory or cardiac arrest, airway bleeding, persistent vomiting and copious airway secretions, delayed or emergent intubation should always be avoided (Fig. 2).

4.1.2. Environmental preparation

- Full PPE, including N95 respirator, goggles, visor, safety coveralls, shoe cover, waterproof apron and gloves are required prior to intubation. Incomplete personal protection must be avoided even in an emergent rescue situation.
- The participated medical staff numbers should be minimized and medical procedures should be manipulated by experienced personnel in an isolation room.

4.1.3. SOAP-ME checklist

- Suction: Always use an in-line suction system with a HEPA filter placed in between the suction device and collecting canister. The viral spread could occur during vacuum suction either by in-wall or portable device.
- Oxygen: BVM, with HEPA filter, and PEEP Valves.

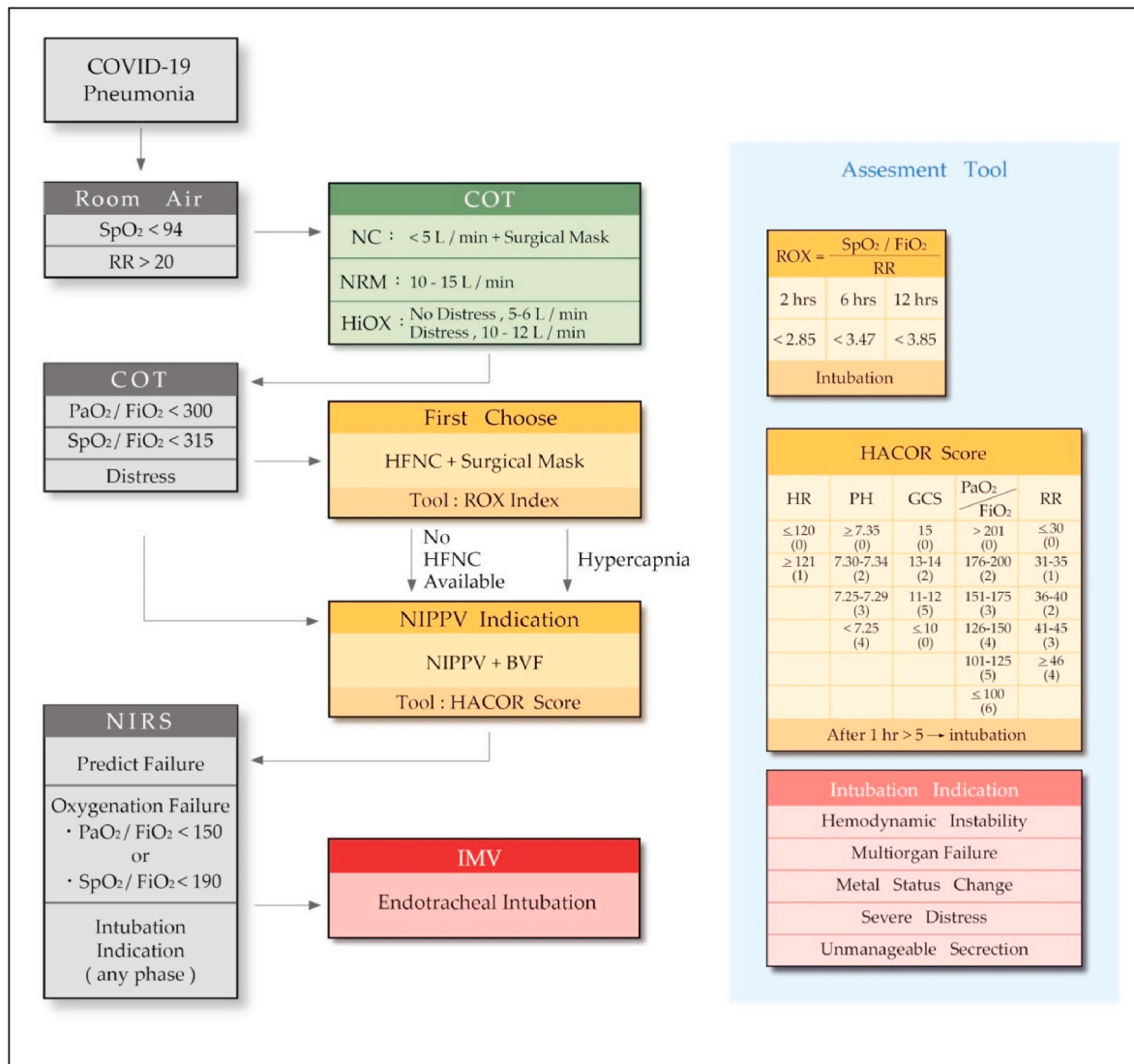


Fig. 2. The decision algorithm of pragmatic use of COT, NIRS, and intubation for 2019-nCoV infected patients. NIRS is defined as either NIPPV or HFNC. * NIPPV indication: CPAP for CHF and OSA, and BiPAP for COPD exacerbations, neuromuscular disease or OHS complicated by hypercapnic respiratory failure [25]. BiPAP support should be initiated at hospital admission for patients with acute on chronic hypercapnic respiratory failure [38]. COT: conventional oxygen therapy; NIRS: non-invasive respiratory support; NIPPV: non-invasive positive pressure ventilators; HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure; BiPAP: bi-level positive airway pressure; CHF: congestive heart failure; OSA: obstructive sleep apnea; COPD: chronic obstructive pulmonary disease; OHS: obesity hypoventilation syndrome; PaO₂: arterial oxygen tension; FiO₂, inspired oxygen fraction; SpO₂: peripheral oxygen saturation; NC: nasal cannula; NRM: non-rebreather mask; Hi-Ox: high oxygen mask; ROX index: respiratory rate-oxygenation index; BVF: bacterial viral filter; HACOR score: heart rate, acidosis, consciousness, oxygenation, and respiratory rate score; IMV: invasive mechanical ventilation; RR: respiratory rate.

c) Airway equipment:

Intubation equipment: laryngoscope or video laryngoscope, multiple sizes of endotracheal tubes (ETT), stylet/bougie, syringe and backup options (e.g., supraglottic airway; SGA and scalpel).

Mechanical ventilator:

- a) Use disposable tubing
- b) Protect the expiratory valve with a hydrophobic HEPA filter. Particle size larger than 3 μm is too large to pass through the filter holes or directly impact the filter fibers by inertia. In fact, smaller nanoparticles are easier to be captured because they do not travel in straight lines. Instead, these nanoparticles bounced off other molecules when they collide and travel in random patterns. According to the principle of Brownian movement, nanoparticles are trapped after hitting the filter fibers. Perry, J.L. et al. demonstrated that HEPA filters are highly effective and nearly 100% of nanoparticulate and

particles greater than 0.3 μm could be captured. Only around 0.3 μm particles, which is termed the most penetrating particle size (MPPS), are most difficult to catch. The effect of the HEPA filter is based on measuring the efficiency of capturing these particles, therefore, the environmental contamination may be further reduced. [82]; c) HEPA filter should also be used in the inspiratory circuit. It is because when ventilator malfunction occurs, in situations such as tubing occlusion or expiratory valve failure, circuit pressure will immediately increase and a backup pressure release safety countermeasure will be triggered. The subambient overpressure relief valve (SOPR valve) opens so the patient could still inhale ambient air. The interior components of the ventilator could then be contaminated by the patient's exhaled air. d) On the patient's end, HMEF should be applied and choose the type of absolute humidity at least 30 mg H₂O/L. When airway humidity is preserved, sputum clotting and lung injury could be avoided [83].

Table 5
Rapid sequence intubation (RSI) in COVID-19 patients.

The step of RSI	The item of covid-19 during intubation
Prepare and Position	1) Patient: Increased WOB, ventilation impairment, or hypoxemia, even if high FiO ₂ or NIRS was already applying. 2) Environment: PPE and isolation room. 3) SOAP-ME: - Suction: in-line suction and add a HEPA filter between the suction device and canister. - Oxygenation: BVM with HEPA filter, and PEEP Valves. - Airway: intubation equipment and preparing mechanical ventilator (Use single-use disposable, HEPA filters must be connected in both inspiratory and expiratory ends, HMEF >30 mgH ₂ O/L should be used in patient's end). - Position: BUHE position. - Monitor/meds: continuous monitoring devices and the meds of sedative or paralyzing agents. - Equipment: EtCO ₂ capnography or colorimetric CO ₂ detector.
Preoxygenation	1) Time: at least 3–5mins. 2) ApOx or apneic CPAP recruitment (if shunting is identified). 3) Avoid any manual ventilation.
Paralysis with induction	1) Induction agents: - Etomidate (0.2–0.6 mg/kg) or ketamine (1–2 mg/kg) plus low-dose midazolam is recommended. OR - Midazolam 1–2 mg is recommended for extremely anxious patients. Etomidate 0.2–0.3 mg/kg for patients with hemodynamic instability and propofol 1–1.5 mg/kg for those who are hemodynamic stable. Ketamine 1–2 mg/kg is recommended for cardiovascular instability patients. 2) Neuromuscular blocking agents: rocuronium with a dosage of at least 1.2 mg/kg.
Placement of ETT with video laryngoscopy	1) Intubation: video laryngoscopy and HEPA filter with NC 10–15 L/min (apneic oxygenation). 2) Intubation failure: do not use BVM, use a SGA attach with HMEF and ventilator settings in PC/AC mode (<20 cm H ₂ O).
Post-intubation management	1) EtCO ₂ device could be used to confirm tracheal intubation. 2) Ventilation tubing should always be attached to BVF. 3) Clamp ETT when disconnection.

RSI, rapid sequence intubation; WOB, work of breathing; NIRS: non-invasive respiratory support; PPE, personal protective equipment; HEPA, high efficiency particulate air filter; BVM, bag-valve mask; PEEP, positive end expiratory pressure; HMEF, heat and moisture exchangers filters; BUHE: bed-up-head-elevated position; EtCO₂, end-tidal carbon dioxide; ApOx, apneic oxygenation; CPAP, continuous positive airway pressure; SGA, supraglottic airway; BVF: bacterial viral filter; ETT: endotracheal tube.

- d) Position: BUHE (bed-up-head-elevated) position [84]. The patient should be kept in a bed-up position while providing preoxygenation. This position could increase the patient's FRC and oxygen reserves. Moreover, head-elevation is similar to sniffing position, which is adopted indirect laryngoscopy for the best glottis visualization and could facilitate intubation [85–88].
- e) Monitors and Medications: Continuous hemodynamic monitoring devices, sedatives (Ketamine, etomidate, midazolam, propofol) and paralyzing agents (rocuronium, succinylcholine).
- f) Equipment for confirmation: Continuous end tidal carbon dioxide capnography (EtCO₂; 35–45 mmHg) or calorimetric CO₂ detector is recommended to confirm successful intubation.

4.2. Preoxygenation

4.2.1. 100% oxygenation should be applied for at least 3–5 min

During preoxygenation, alveolar nitrogen is replaced by oxygen which could provide an oxygen reservoir [78,89] so the patient could

tolerate a longer period of apnea without manifesting desaturation.

4.2.2. Apneic oxygenation (ApOx) and apneic CPAP recruitment (if shunting is identified)

- a) ApOx is provided by NRM 15 L/min combined with NC 15 L/min. ApOx has been shown that could remarkably decrease the risk of hypoxemia during elective intubation. The principle is during apnea, the differential rate between alveolar oxygen absorption and carbon dioxide excretion generates a negative pressure gradient. If airway patency could be maintained, any measure of oxygen therapy via either oral or nasal route could deliver oxygen to the alveoli [90,91]. However, the risk of aerosol spread must be considered.
- b) Apneic CPAP recruitment by BVM 15 L/min with a PEEP valve of 10 cmH₂O, a HEPA filter and NC 15 L/min under spontaneous breathing. It could be applied in cooperative patients with a certain degree of shunting. In addition to oxygen therapy, applying 6–8 cmH₂O of PEEP could improve oxygenation in patients with severe pneumonia associated with shunting [92,93]. Environmental contamination could be reduced by tightly securing the BVM with both hands and use a HEPA filter.
- c) Avoid manual ventilation: Any measure of applying positive pressure ventilation prior to intubation could increase the risk of aerosol spread. If airway pressure is too high, the esophageal sphincter could be opened and cause vomiting [94,95]. The risk of aspiration and viral spreading is high.

4.3. Paralysis with induction

A sufficient dosage of induction and neuromuscular blocking agents must be used to ensure smooth intubation and reduce the spreading of viral containing aerosols. In one study, a total of 202 patients with COVID-19 who received emergent tracheal intubation were included in Wuhan. Propofol was the most frequently used (194 patients; 96%) medication for induction. The author explained that since propofol was easy to acquire in China so it might have been overused. They also pointed out that if other induction agents with less hypotensive effects were available, the use of propofol should be minimized. A combination of etomidate (0.2–0.6 mg/kg) or ketamine (1–2 mg/kg) plus a low-dose midazolam is recommended in one study [96]. In another study from Wuhan, midazolam 1–2 mg is recommended to be the drug of choice for extremely anxious patients. A smaller dosage of etomidate (0.2–0.3 mg/kg) is recommended for patients with unstable hemodynamics and propofol (1–1.5 mg/kg) could be used for patients with stable hemodynamics [97]. Etomidate should be avoided in severe adrenal insufficiency and immunocompromised patients. However, a single low dose of etomidate is considered to be safe for patients with a mild degree of adrenal insufficiency [96]. Ketamine 1–2 mg/kg is recommended for induction in patients with a high risk of cardiovascular instability [98]. Among neuromuscular blocking agents, rocuronium (≥ 1.2 mg/kg) would be the drug of choice for intubation in COVID-19 patients based on its rapid onset of action and fewer side effects. The longer duration effect of rocuronium also alleviates cough if intubation is expected to be prolonged. However, it should be noticed that rocuronium will take 60 s to take effect and should be waited before intubation [96,98].

4.4. Placement of endotracheal tube with video laryngoscopy and HEPA filter

4.4.1. Intubation

The use of video laryngoscopy could maintain a safe distance from the patient during intubation and thus decrease the risk of aerosol exposure. Lin, LW et al. also suggested using a closed system with the HEPA filter pre-attached to the ETT by HEPA-ETT (HE) or Swivel-HEPA-ETT (SHE)-bougie for intubation. The advantage of the system is that the aerosolization of viral droplets released from the larynx and trachea

during intubation and the ventilation could be reduced when a HEPA filter is combined with oral aerosol suction. The author also recommends simulation practice prior to actual manipulation because unacquaintance and nervousness could increase the risk of aerosolization [99]. Once intubation is initiated and NRM or BVM is removed, depending on the risk of hypoxemia, a nasal cannula with 10–15 L/min of flow may be used for apneic oxygenation. During intubation, a complete PPE is mandatory for all the working staff because they are exposed to a considerable quantity of virus aerosol. A barrier enclosure or clear plastic drape may be used for better protection [100–102]. However, since hand maneuvering could be limited, the appropriate training program should be completed in advance. Operators should be ready to remove the barrier should airway management prove difficult [103].

4.4.2. Intubation failure

The use of BVM is strongly discouraged. Instead, the use of a subglottic airway (SGA) connected to an HMEF with ventilator settings in PC/AC mode (<20 cmH₂O) is recommended. Volume controlled ventilation mode or BVM is not recommended because the unexpected increased airway pressure could cause the patient's esophagus to inflate and opens the cardiac sphincter. The risk of aspiration and viral spread is high.

4.5. Post-intubation management

- Use an EtCO₂ device to confirm tracheal intubation.
- Regardless of the ventilation mode, a HEPA filter and HMEF (at least 30 mgH₂O/L) must be connected to the ventilator and endotracheal tube respectively.
- Always clamp the endotracheal tube if disconnecting the ventilator circuit is required. Turbi, E *et al.* compared leak-preventing efficacy in three different clamps. Their results showed that the extracorporeal membrane oxygenation (ECMO) clamp had the best performance in preventing leak (volume loss) after circuit disconnection. The leakage results were ECMO clamp (15 ml/5s; 20 ml/30s), metal clamp (113 ml/5s; 423 ml/30s) and plastic clam (693 ml/5s; 692 ml/30s) respectively [104].

5. Ventilation strategies

In the pathology report of a patient who died from COVID-19, various degrees of diffuse alveolar damage with cellular fibromyxoid exudates and hyaline membrane formation were presented in ARDS lungs [105]. In a single-center study, 710 patients with SARS-CoV-2 pneumonia were included, and in these patients, 52 (7%) were critically ill. Among these critically ill patients, 35 (67%) developed ARDS and 37 (71%) patients required MV [106]. ARDS is a serious complication of SARS-CoV-2 infection and the median time from onset of symptoms to ARDS was 12 days. Patients usually deteriorated rapidly and respiratory failure ensued [21]. Bilateral patchy shadows or ground glass opacity were often manifested in chest radiology and MV was required in patients with profound hypoxemic respiratory failure and ARDS. Ventilation strategies recommended for COVID-19 patients with ARF are summarized in Table 6. Lung-protective ventilation strategy (LPVS) is widely adopted for ARDS patients and clinical studies have proven that LPVS could improve the prognosis of patients who developed ARDS by minimizing VILI. Ventilation strategies recommended in COVID-19 ARDS (CARDS) are summarized here.

5.1. Ventilator strategies

- LPVS, including a low TV and limited pressure setting [107,108].
 - Driving pressure <15 cm H₂O.
 - Limiting TV (4–8 ml/kg predicted body weight; PBW).

Table 6
Strategies of ventilation in COVID-19 patients with ARF.

Strategy	Suggest item
Ventilator strategy in ARDS	LPVS 1) Driving pressure <15 cm H ₂ O. 2) Limit TV (4–8 ml/kg PBW). 3) Limit inspiratory pressures (plateau pressure <30 cm H ₂ O). 4) Tolerate hypercapnia if pH > 7.2. Higher PEEP if PaO ₂ /FiO ₂ <200 mmHg, maintain PaO ₂ >60 mmHg.
Prone position RM	Maintain 12–16 h per day in ARDS. 1) Apply in the early phase of ARDS and stop in non-responder. 2) Avoid using staircase method
Ventilator strategy in ECMO	Ultra-protective ventilation: 1) TV < 4 ml/kg PBW or PIP between 20 and 25 cm H ₂ O. 2) Targets very low plateau pressure (<25 cmH ₂ O). 3) Limit the respiratory rates from 4 to 30 cycles/minute. Maintaining high PEEP ≥10cmH ₂ O. Decreasing FiO ₂ with optimal PEEP and maintain SaO ₂ >85%.
Extubation	Preparation: 1) Passed SBT. 2) Environment: PPE and isolation room. 3) Devices: extubation and emergent reintubation devices. Procedures: 1) Alleviate cough by 0.5–2 mg/kg lidocaine IV slowly (rapid onset, duration 10–20mins). 2) Use in-line suction and pre-oxygenation. 3) Inserting a rigid suction catheter or saliva ejector suction system in the patient's oral cavity. 4) Extubation under a barrier device. 5) A ventilator should be set to standby mode or turned off, keep in-line suction and filter engaged during cuff deflation. 6) Extubation without future suctioning and carefully disposed of. 7) Apply NRM/Hi-Ox mask immediately and shift to NC covered with a surgical mask if FiO ₂ could be tapered.

ARF, acute respiratory failure; ARDS, adult respiratory distress syndrome; RM, recruitment maneuver; ECMO, extracorporeal membrane oxygenation; LPVS, lung protective ventilation strategy; TV, tidal volume; PBW, predicted body weight; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; SBT, spontaneous breathing trial; PPE, personal protective equipment; IV, intravenous; HEPA, high efficiency particulate air filter; NRM, non-rebreather mask; Hi-Ox, high oxygen mask; FiO₂, Inspired oxygen fraction; NC, nasal cannula.

- Limiting inspiratory pressures (maintain plateau pressure; Pplat <30 cm H₂O).
- Permissible hypercapnia and maintaining blood pH > 7.2.
- b) Higher PEEP level could be applied if PaO₂/FiO₂ <200 mmHg with the target PaO₂ >60 mmHg [107].
 - PEEP level setting.
- a) Based on PEEP/FiO₂ tables recommended by the ARDS network [109].
- b) ARDS severity defined by the Berlin definition [1,110].
 - Higher PEEP (range 15–20cmH₂O) in severe ARDS.
 - Intermediated (range 10–15 cmH₂O) in moderate ARDS.
 - Lower PEEP (range 5–10cmH₂O) in mild ARDS.

Lung hyperinflation and VILI could still occur despite limited TV and plateau pressure was strictly adhered to because of the smaller aerated lung volume (the baby lung) [107,111]. Amato, M.B.P. *et al.* described that, in previous studies, calculating TV according to patient's PBW and normalizing TV regarding the patient's lung size could further minimize VILI. However, this may not represent the true functional size of the lung. In his study, normalizing TV to lower respiratory-system compliance (C_{RS}) and using this ratio, which is termed driving pressure (ΔP = TV/C_{RS}), is recommended as a surrogate index and indicating the true functional size of the lung. Their results also showed that there is a strong association between ΔP and survival even when all LPVS

ventilator settings were adhered to. They further observed that the reduction in TV or increases in PEEP level could be beneficial only if it is associated with a decrease in ΔP [112].

Marini, J.J. *et al.* have proposed corresponding respiratory care strategies regarding C_{RS} -based phenotypes [40]. The authors believe that understanding the correct pathophysiology is crucial in establishing the basis for appropriate treatment. They also claim that different respiratory treatments should be administered according to different phenotypes [113]. Others also concurred with their contentions from histopathological features, computed tomography scan with quantitative analysis and case reports [114–117]. Furthermore, the German Respiratory Society also suggests that different stages of lung damage (type L and type H) should be taken into consideration when providing respiratory support for ARF [118]. However, the LUNG-SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) and ESICM (European Society of Intensive Care Medicine) Trials Groups have shown that there's a wide range of C_{RS} and 13% of the mechanically ventilated non-CARDS patients had type-L phenotype ($C_{RS} > 50$ mL/cmH₂O). They challenged the concept of the two distinct phenotypes that were proposed in CARDS pathophysiology. Another study showed that CARDS and ARDS respiratory mechanics are remarkably overlapped so the standard ventilation strategy could be applied to these patients [119]. Naidoo *et al.* also found the clinical picture manifested in COVID-19 patients was largely consistent with classical ARDS so using traditional LPVS may be acceptable and do not warrant change at this stage. A prospective, observational study composed of 742 CARDS patients conducted by Ferrando *et al.* reported that lung pathophysiologic parameters including C_{RS} , Pplat, and driving pressure were similar to ARDS caused by other etiologies. The adherence with LPVS was high and mortality rate was also similar to other ARDS observational studies [120]. In summary, the contention of C_{RS} -based phenotypes remains controversial and further studies are needed to verify optimal respiratory care strategy.

5.2. Prevention of pneumothorax

COVID-19 patients who developed lung injury were predispose to barotrauma. Inappropriate ventilator settings (large volume ventilation and non-respond recruitment maneuvers) could increase the risk of pneumothorax. Yao, W. *et al.* incorporated 202 COVID-19 patients of emergent tracheal intubation and reported that the incidence of pneumothorax was 5.9%, which is remarkably higher than previous studies (approximately 2%). LPVS should be adhered to maintain a lower airway pressure and lung recruitment should be terminated in non-responders [121]. If pneumothorax happens and requires open drainage, direct air contact with the fluid must be avoided because viral aerosol dispersion could occur. The drainage bottle can be connected to a second collecting bottle prefilled with 1000 ppm of bleach to avoid direct air contact [122].

5.3. Prone positioning (PP)

Redistribution of consolidation from dorsal to ventral areas of the lung could improve alveolar ventilation and oxygenation by PP [107]. Previous studies have indicated that PP could reduce the overinflated lung areas while promoting alveolar recruitment [123] and prevent VILI by homogenizing the distribution of stress and strain within the lungs. Guerin, C clearly pointed out that early application of PP, for at least 16 h a day, could significantly decrease 28-day and 90-day mortality in patients with severe ARDS [124]. PP during invasive MV has been demonstrated to improve oxygenation and reduce mortality, in theory, these benefits may also be applied to non-intubated patients. Oldani *et al.* reported that in patient with SARS-CoV-2 pneumonia, awake PP leads to a quick improvement in arterial blood oxygenation by vascular changes in the alveolar septa and blood flow redistribution to the less damaged area [114]. Ding *et al.* also revealed that early PP combined

with NIRS may avoid the need for intubation in up to half of the patients with moderate to severe ARDS, and this procedure was safe and well-tolerated [125]. However, a systematic review that summarized the evidence on awake PP, in a total of 35 observational studies, 29 of these studies included COVID-19 patients. Although all studies reported an improvement in oxygenation during PP, improvements in oxygenation were lost once patients reverted to the supine position. Only one study showed a sustained improvement in oxygenation but NIRS was administered. Given the lack of randomization and control arms, only transient improvement in oxygenation, uncertainty about the safety of this intervention and its effect on patient-important outcomes, we were not able to issue a recommendation on the use of awake prone positioning [75,126].

5.4. Recruitment maneuver (RMs)

Oxygenation could be improved if the poorly aerated lung is reopened by transiently increasing transpulmonary pressure (PL) [127]. When RMs are applied, the aerated lung mass could be augmented. The maneuver may contribute to minimizing lung heterogeneity and increasing the size of the baby lung. Furthermore, the risk of VILI might also be reduced because the repeated opening and closing of the terminal respiratory units are attenuated [128,129]. Goligher, E. C. *et al.* reviewed six RCTs with a total of 1423 patients, they concluded that RMs were associated with lower mortality, better oxygenation and less need for rescue therapy [128]. However, RM could over-distend aerated alveolar units thus increase the risk of barotrauma and predispose to detrimental hemodynamic effects [130]. Grasso *et al.* had expressed that, in the early phase of ARDS and patients were receiving ventilators, RMs could improve oxygenation if chest wall mechanics were unimpaired. However, in the scenario of prolonged ventilation, RMs may be ineffective because of the altered chest wall and lung structure. Increased transpulmonary pressure could lead to hemodynamic instability and is potentially harmful [131]. Constantin, J.M. *et al.* also clearly pointed out that, RM should not routinely be applied in ARDS patients [130,132]. Moreover, Ball *et al.* did not agree on the concept of the adoption of a high PEEP strategy because it did not lead to substantial RM and might worsen respiratory mechanics [133]. Therefore, RM is recommended in the early phase of ARDS but the patient's response must be continuously monitored. If RM is used, we recommend against using the staircase method (incremental PEEP) and should be immediately terminated in non-respond COVID-19 patients [4,75].

5.5. Extracorporeal membrane oxygenation (ECMO)

When all the available measures were applied and refractory hypoxemia fails to improve, this indicates that most of the functional alveoli units for gaseous diffusion are severely damaged. Venovenous ECMO (VV ECMO), through a gas-exchange device that could remove carbon dioxide and oxygenate the blood, should be considered [107]. Tramm, R. *et al.* reviewed four RCTs, comparing ECMO with conventional support in a total of 389 patients and found that there were no statistically significant differences in mortality [134]. In a study that was focusing on MERS-CoV patients with refractory hypoxemia, implementing ECMO was associated with lower mortality when compared with convention support [135]. Two observational studies also showed that the use of ECMO had a better survival rate in influenza A virus subtype H1N1 (H1N1) patients with refractory hypoxemia [107,136,137]. American Thoracic Society-led International Task Force has proposed that ECMO could be considered in patients with severe COVID-19 pneumonia and refractory hypoxemia after prone ventilation was applied. However, others do not agree because operating ECMO requires significantly more medical resources in the period of the pandemic and the risk of cross-infection is high. WHO, CDC, and FDA have not addressed the recommendation of ECMO. The Surviving Sepsis Campaign made a weak recommendation for VV ECMO or referral to an ECMO center in patients

with refractory hypoxemia [138]. The benefit of ECMO remains controversial.

When VV ECMO is initiated, reducing VILI is the primary goal when setting ventilation mode. Dreyfuss, D. *et al.* had brought up the concept that mechanical ventilation could activate inflammation and aggravate pulmonary damage [139]. Schmidt, M *et al.* proposed that MV could be combined with the use of ECMO while reducing the risk of VILI through three mechanisms including limit alveolar strain, atelectrauma and reabsorption atelectasis [140]. Three solutions were described in this study.

- a) Limit alveolar strain by allowing “lung rest” or known as “ultra-protective ventilation”
 - TV < 4 ml/kg PBW [141,142] or peak inspiratory pressure between 20 and 25 cmH₂O [143].
 - Target a very low plateau pressure (<25 cmH₂O).
 - Limit the RR from 4 to 30 cycles/minute (RR may increase mechanical lung stress).

- When ECMO is implemented, it usually indicates that the lung is severely injured and oxygenation is exceedingly impaired [136,143]. There is only a small region of the lung that could be ventilated [144]. Under this serious condition, allowing lung rest by ultra-protective ventilation or limiting inspiratory pressure could reduce further lung injury from the strain. It should be noticed that high RR may also increase the risk of mechanical lung stress. Thus, it would be reasonable to limit RR with permissible hypercapnia while maintaining pH and combining optimal ECMO gas flow settings.

- b) Minimize atelectrauma by applying high PEEP ≥10cmH₂O:
 - Atelectrauma occurs during cyclic intra-tidal alveolar opening and closing.
 - Adhering ultra-protective ventilation strategy with very low TV combined with a high PEEP is recommended. Caironi, P. *et al.* had demonstrated the beneficial effects of high PEEP in reducing cyclic intra-tidal alveolar opening and closing [145].
- c) Oxygen toxicity should be minimized by optimizing FiO₂ and PEEP settings while maintaining arterial oxygen saturation (SaO₂) >85% [146].

5.6. Others rescue therapies

When the patient is receiving mechanical ventilation support but is still unable to maintain oxygenation then other supportive measures should be considered. The new Surviving Sepsis Campaign (SSC) COVID-19 Guideline has brought out some recommendations. On the issue of steroids and fluid management, systemic corticosteroids, dexamethasone is preferred and a conservative fluid strategy is recommended. In the point of neuromuscular blocking agents (NMBA), as-needed and intermittently used can facilitate protective lung ventilation. However, when there's patient-ventilator dyssynchrony, need for deep sedation, PP or progressively increased Pplat, then continuous NMBA infusion for up to 48 h is suggested. SSC recommends against the routine use of nitric oxide but could be used as rescue therapy and should be tapered off if there's no clinical response. The primary goal of ARDS treatment is to ensure adequate oxygenation while minimizing the risk of VILI. These therapies may be instituted on an individualized basis, local availability and medical expertise [75].

5.7. Extubation

When the patient's clinical condition has improved but SARS-CoV-2 infection is still unresolved, several precautions should be heeded. a) Extubation can induce irritative cough and generate massive aerosols. b) In situation of difficult extubation, when HFNC and NIPPV were applied. c) Reintubation. All of these processes carry a substantial risk of

aerosolization and leads to viral transmission. Preparation and procedures are listed below [147].

5.7.1. Preparation

- a) Passed spontaneous breathing trial (SBT) by the closed system.
- b) Environment: full PPE in airborne infection isolation room (same as intubation).
- c) Devices: reintubation devices should be readily available.

5.7.2. Procedures

- a) Depending on the patient's condition, cough could be alleviated by slow intravenous (IV) injection with 0.5–2 mg/kg of lidocaine. (Rapid onset, duration 10–20 min). The beneficial effects need to be balanced against negative impacts on blood pressure, respiratory drive, and neuromuscular function.

Multiple pharmacological strategies were developed to alleviate cough, including alkalization of intracuff lidocaine (topical and endotracheal application), intravenous injection of lidocaine, dexmedetomidine and remifentanyl [148]. Among these strategies, intracuff alkalized lidocaine facilitated diffusion across the ETT cuff membrane and is 20 times more effective than the non-alkalized lidocaine. The incidence of sore throat, hoarseness, postoperative nausea and vomiting (PONV) were also decreased. However, the beneficial effects on cough alleviation were inconsistent [149–151]. Remifentanyl and dexmedetomidine could cause bradycardia and hypotension and lead to hemodynamic instability [148]. In the studies focusing on lidocaine, Clivio, S. reported that 0.5–2 mg/kg lidocaine IV injection could prevent intubation, extubation and opioid-induced cough in both adults and children with the number needed to treat ranging from 8 to 3 [152]. Hu, S. *et al.* also found that both lidocaine and dexmedetomidine had equal effect on alleviating cough and attenuating hemodynamic changes during extubation. Nevertheless, dexmedetomidine could cause bradycardia and prolonged consciousness recovering time when compared with lidocaine [153]. Regarding COVID-19 patient care in Wuhan, Meng, L *et al.* recommended the use of either lidocaine (1–1.5 mg/kg) or alfentanil (15 mcg/kg) for cough reduction in extubation [97].

- b) Use in-line suction and pre-oxygenation.
- c) Inserting a rigid suction catheter or saliva ejector suction system in the patient's oral cavity could decrease droplet spreading [154] during extubation.
- d) Extubation under a barrier device (e.g. barrier enclosure, clear plastic drape or mask-over tube extubation technique, etc.) [155–158].
- e) Ventilator should be set to standby mode or turned off and keep the in-line suction catheter with filter engaged during cuff deflation.
- f) Extubation without further airway suctioning and carefully disposed of the removed device.
- g) Apply NRM/Hi-Ox mask immediately after extubation to minimize droplet dispersion. NC covered with a surgical mask could be used according to the patient's oxygenation status.

6. Disinfection of respiratory devices

Since SARS-CoV-2 could be transmitted through the respiratory droplets, contact and aerosols. AGMP based on the available evidence provides recommendations for respiratory device disinfection. Transmission-based precaution principles were adopted. In addition to routine precautions, contact, droplets, and aerosols precautions are also documented in detail. Disinfection of respiratory devices in COVID-19 patients is summarized in Table 7.

Table 7
Disinfection of respiratory devices in COVID-19 patients.

Stage	Items
General principle	<ol style="list-style-type: none"> 1) Device: disposable or single-use; clean and disinfect before reuse. 2) Avoid using equipment that could disturb the airflow. 3) After AGMP, wait least 20 min before re-entering the room. 4) BVF should be used in both the inspiratory and expiratory ends of the ventilator; HMEF should be attached to the patient's end and use an in-line suction system.
Daily	<ol style="list-style-type: none"> 1) Wipe clean the respiratory equipment from top-down. a) Control panel and exterior parts of ventilator: sodium hypochlorite 1000 ppm, 5000 ppm if contaminated by patient's blood or secretions. b) Monitor of ventilator: 70% ethanol. 2) BVF, HMEF and the close suction system must be changed routinely.
Terminal	<ol style="list-style-type: none"> 1) Inactivate virus-containing aerosols in the air and environment by ultraviolet light (for protecting sanitary personnel). 2) Respiratory equipment: discard removal parts, disinfect and wipe clean reusable components. 3) Inactivate virus-containing aerosols in the air and environment by ultraviolet light again (for final environmental disinfection). 4) If there is any concern about infection, the ventilator could be kept stilled and unused for at least 3 days before it is applied to the next patient.

AGMP, aerosol-generating medical procedures; BVF: bacterial viral filters; HMEF, heat and moisture exchanger filters.

6.1. General principles [159]

G. Kampf *et al.* proposed that applying surface disinfection with 70% ethanol, 0.1% or 0.5% sodium hypochlorite could significantly reduce coronavirus infectivity within 1 minute of exposure time. They recommend a dilution of 1:50 (1000 ppm) of standard bleach in the coronavirus setting [160].

- Equipment and devices should be single patient used. If the devices are shared among patients, they must be clean and disinfected between uses (e.g. by using ethyl alcohol 70%).
- Avoid operating airflow generating equipment because it could extend the suspension time of aerosol or resuspension of the surface particles (e.g. fan).
- After AGMP or any maneuver that could generate aerosols, space must be ventilated with the frequency of 12 times/hour for at least 23 min with the removal efficacy of 99% or 35 minute (if time is sufficient) with the removal efficiency of 99.9% [161], before entering the space and all healthcare workers must wear a complete PPE.
- HEPA filters must be used in both the inspiratory and expiratory circuits of the ventilator. HMEF should be attached to the patient's end and use an in-line suction system.

6.2. Daily clean and disinfection

- Respiratory equipment (including mechanical ventilator): Should be cleaned and disinfected at least once a day. Wipe clean the control panel, exterior parts (e.g. sodium hypochlorite 1000 ppm and 5000 ppm if contaminated by patient's blood or secretions) and monitor (e.g. 70% ethanol) of the equipment with specified disinfectants or hospital-grade disinfectants (labeled effective against SARS-CoV-2) daily.
- Wipe surfaces using the general strategies: Start with the clean part then the smirched area and from top to bottom.
- HEPA, HMEF and a close suction system that is used in the ventilator should be changed at recommended intervals.

6.3. Terminal clean and disinfection

- Ultraviolet (UV) light could be used for room disinfection. Virus-containing aerosols are inactivated by UV light and could decrease the risk of sanitary personnel being infected when disinfecting the room [162–165].
- Respiratory equipment:
 - Removable components: Disposable parts of the components, including ventilator circuits, oxygen devices and BVM should be discarded according to the hazardous waste regulation.
 - Reusable components: Clean with specified disinfectant recommended by the manufacturer's instructions.
 - Wipe clean the control panel, exterior and monitor of the equipment with specified disinfectants.
- UV light could be used as the last measure of environmental disinfection. Exposure time (usually range from 30 to 120 min) is directly related to the watt of the UV light bulb and the distance of the exposing objects.
 - Store the ventilator unused for at least 3 days before it is applied to the next patient. Doremalen, N. V *et al.* have reported that coronavirus could remain viable for 72 h on plastic and 48 h on steel surfaces [166]. If there is any concern about cross infection, extending the storing time should be considered.

7. Conclusions

SARS-CoV-2 is transmitted through respiratory droplets, close contact and aerosols. Viruses spread rapidly among humans with a 19% chance of developing severe pneumonia and ARDS. Patients may subsequently require oxygen therapy and MV support.

When oxygenation is compromised ($SpO_2 < 93\%$), oxygen therapy should be provided in a timely manner. The nasal O_2 cannula should be covered with a surgical mask and maintain at least 30 cm of distance from the patient. During oxygen therapy, avoid using a humidifier whenever possible. MDI device should be used instead of nebulization if inhaled bronchodilators are needed. High oxygenation concentration could be provided with a Hi-Ox mask or NRM. Aerosol generating oxygen mask equipped with side vent could be a potential viral transmitting source. HFNC is indicated in hypoxemic respiratory failure and BiPAP may be considered in certain patients with Type 2 respiratory failure. When NIRS is implemented, complete protection with PPE is mandatory. Safety issues including ensure correct mounting of the nasal cannulas covered with a surgical mask over the HFNC and selecting an optimal interface connecting to tubing systems with appropriate BVF should be checked. Patients must be continuously monitored and adopting HACOR Scale and ROX Index for treatment evaluation. Early detection of impending respiratory failure patients and timely intubation may avoid further lung injury.

During intubation, the aerosol that was generated could induce virus transmission and lead to cross infection in healthcare workers so proper donning of airborne grade PPE is mandatory. The use of video laryngoscopy and EtCO₂ devices is highly recommended. Prior to intubation, the patient should be pre-oxygenated for at least 3–5 min with either ApOx or apneic CPAP recruitment, and HEPA filters must be used when BVM and mechanical ventilator are applied. Manual ventilation should be avoided. The subglottic airway could be used as a contingency measure if intubation fails. After successful intubation, an in-line suction system should always be employed and HEPA filters must be connected in both inspiratory and expiratory circuits of the ventilator. Passive airway humidification with HMEF is recommended. Always clamp the endotracheal tube when circuit disconnection is required. Adherence to the LPVS is important in order to reduce the risk of VILI. When ARDS develops, a prone position could be implemented and should be maintained for 12–16 h a day. Apply RM (avoid using staircase method) in the early phase of ARDS but stop in non-responder. When VV ECMO support is operated, adhering to an ultra-protective ventilation strategy is

recommended to minimize VILI.

When the patient's clinical condition starts to improve, ventilator weaning may be initiated. Extubation must be meticulously evaluated even if the patient has passed SBT. Massive virus contaminated aerosols could be generated during and after extubation. Healthcare workers must be donned with complete PPE and extubation should be carried out in a negative pressure isolation room under a barrier device. Devices for emergent reintubation should be prepared and antitussive agents could be used if needed. After successful extubation, NRM/Hi-Ox mask should be applied immediately then shift to NC covered with a surgical mask when oxygenation improves. For disinfection of the respiratory devices, use disposable or single-use devices whenever available, and the used respiratory equipment should be cleaned at least once a day. HEPA, HMEF and close suction system must be replaced routinely. In the terminal clean and disinfection, UV light could be used to inactivate virus-containing aerosols. The disinfected mechanical ventilator should be stored unused for at least 3 days before it is applied to the next patient.

Authors' contributions

Yao-Chen Wang and Yia-Ting Li contributed to study conception, design and perform a literature review. Yao-Chen Wang, Min-Chi Lu and Yia-Ting Li contributed to drafting and editing the manuscript. Mauo-Ying Bien and Yi-Fang Chen revised the manuscript. Shun-Fa Yang and Yia-Ting Li provided study supervision. All authors read and approved the final manuscript.

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