



# Various Aspects of Non-Invasive Ventilation in COVID-19 Patients: A Narrative Review

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## Abstract

Non-invasive ventilation (NIV) is primarily used to treat acute respiratory failure. However, it has broad applications to manage a range of other diseases successfully. The main advantage of NIV lies in its capability to provide the same physiological effects as invasive ventilation while avoiding the placement of an artificial airway and its associated life-threatening complications.

The war on the COVID-19 pandemic is far from over. The present narrative review aimed at identifying various aspects of NIV usage, in COVID-19 and other patients, such as the onset time, mode, setting, positioning, sedation, and types of interface. A search for articles published from May 2020 to April 2021 was conducted using MEDLINE, PMC central, Scopus, Web of Science, Cochrane Library, and Embase databases. Of the initially identified 5,450 articles, 73 studies and 24 guidelines on the use of NIV were included. The search was limited to studies involving human cases and English language articles. Despite several reported benefits of NIV, the evidence on the use of NIV in COVID-19 patients does not yet fully support its routine use.

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## What's Known

- Over the last two decades, non-invasive ventilation (NIV) has dramatically changed the management of many diseases, such as chronic obstructive pulmonary disease and weaning failure.
- Routine use of NIV in the management of COVID-19 patients is still controversial.

## What's New

- NIV can be used under certain conditions and initiated based on the PaO<sub>2</sub>/FiO<sub>2</sub> ratio instead of SpO<sub>2</sub> alone.
- Key NIV recommendations: Select a mode based on the type of respiratory failure and comorbidities, the helmet interface is preferred, and enteral or parenteral feeding should be balanced against susceptibility to airway complications.

## Introduction

Non-invasive ventilation (NIV) is a procedure to support the respiratory system and breathing effort, improve gas exchange, and enhance patients' comfort using an oxygen delivery device with an easy-to-use interface.<sup>1</sup> NIV is well recognized as an effective strategy to avoid endotracheal intubation with adverse complications (e.g., ventilator-associated pneumonia) in patients with various forms of hypercapnic respiratory failure, immunosuppression, and specific postoperative conditions.<sup>2</sup> During the past few years, the main application of NIV has been in chronic obstructive pulmonary disease (COPD) exacerbations. In addition to being a weaning strategy for COPD patients from invasive mechanical ventilation (IMV), the use of NIV has resulted in a significant reduction in mortality rate, nosocomial pneumonia, and weaning failure.<sup>3, 4</sup> NIV is currently utilized in intensive care units (ICUs), emergency departments, and in the home setting.<sup>5</sup> However, the use of NIV in patients with severe respiratory failure is still controversial. A high rate of NIV failures has been reported to occur during the treatment of patients with Middle East Respiratory Syndrome (MERS).<sup>6</sup>

In December 2019, the first cases of the novel coronavirus were identified in Wuhan, China, and the infection was referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Shortly thereafter, the World Health Organization (WHO) called the virus the coronavirus disease 2019 (COVID-19). SARS-CoV-2 was considered highly contagious<sup>7</sup> to the extent that the WHO declared it as a global pandemic in March 2020.<sup>8</sup> COVID-19 may cause respiratory failure such that patients need respiratory support using NIV or IMV. According to guidelines on the treatment and management of patients with COVID-19, controlling the duration of hypoxemia is important for a favorable outcome.<sup>9</sup> However, clinicians resort to various protocols for using NIV. The present review is primarily aimed at identifying the effectiveness of NIV in COVID-19 patients. In addition, we investigated and compared different protocols from various national and international organizations on various aspects such as the onset and offset times, modes of ventilation, sedative drugs and dosage, patient positioning, types of interface, and nutritional management of patients receiving NIV support.

#### Search Strategy

A search was performed to identify suitable articles on NIV in COVID-19 patients using MEDLINE, PMC central, Scopus, Web of Science, Cochrane Library, and Embase databases. Publications from May 2020 to April 2021 were included, and a total of 5,450 articles were identified during the initial search. The search was limited to English language studies that included adults (age > 18 years), and those published in peer-reviewed journals to minimize possible sources of bias and exclude erroneous data.

The search strategy included a combination of keywords and terms: "coronavirus", "novel CoV", "SARS-CoV-2", "COVID-19", "acute respiratory failure"; "non-invasive mechanical ventilation", "NIV", "CPAP", "BiPAP", "onset", "position"; "sedation", "interface", "AHRF", "acute hypoxemic respiratory failure", "nutrition support", "enteral nutrition"; "parenteral nutrition", and "intensive care". The appropriateness of each article was determined based on the relevancy of its title and a detailed review of the reference list. The authors then independently reviewed the abstract and full-text of each article with a specific focus on NIV in COVID-19 patients. Accordingly, the final list of articles was made. In addition, we collected and compared the most important recommendations from prominent organizations on the application and management of NIV in patients with respiratory failure, including COVID-19 patients.

#### NIV Over the Years

During the past two decades, NIV has dramatically contributed to the treatment of patients with acute and chronic respiratory failure.<sup>10</sup> The concept of bellows-powered face masks dates back to the early 19<sup>th</sup> century, when Chaussier described the application of a device during resuscitation.<sup>11</sup> During the 1930s and 1940s, recommendations were made to use NIV in treating pneumonia, pulmonary edema, and asthma. However, these were not widely supported or accepted for several decades. In the 1980s, NIV was proposed for chronic conditions such as treating obstructive sleep apnea (OSA) using continuous positive airway pressure (CPAP). Eventually, in the 1990s, NIV was widely used in ICUs to treat chronic respiratory failure in patients with neuromuscular diseases.<sup>12</sup> It was then that manufacturers started to produce ventilatory support devices, including adjustable inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) or bi-level positive pressure (BiPAP).<sup>13</sup> Nowadays, NIV is an integral part of clinical equipment and used as the first-line treatment for patients with acute respiratory failure due to COPD, weaning from IMV,<sup>14, 15</sup> and immunocompromised conditions.<sup>11</sup>

Some studies have reported strong evidence in support of NIV usage, over IMV, in patients with cardiogenic pulmonary edema<sup>12</sup> and specific forms of acute respiratory failure.<sup>11</sup> The use of NIV in the United States has increased by 462% over the last 10 years, which led to a 42% reduction in IMV use and decreased in-hospital mortality.<sup>16</sup> Some specialists have proposed research concepts for the design of a more comfortable NIV interface for patients with *de novo* respiratory failure and to improve NIV settings for better patient-ventilator synchrony.<sup>3</sup>

COVID-19 has been shown to cause acute hypoxemic respiratory failure (AHRF), necessitating respiratory support.<sup>17</sup> A previous study reported a high mortality rate in patients with AHRF, who received IMV.<sup>18</sup> One of the reasons for the high mortality rate may be due to ventilator-induced lung injury, which is an IMV complication. As an alternative, NIV is a safe, feasible, and useful strategy for COVID-19 patients. However, there are different perspectives on the effectiveness of NIV in COVID-19 associated AHRF patients, and the data on its efficacy are still insufficient.<sup>19, 20</sup> Considering the high mortality rate in COVID-19 patients due to intubation,<sup>21</sup> clinicians tend to utilize NIV. However, there are uncertainties about its effectiveness and a lack of reported evidence on its use in COVID-19 patients.

### Different Perspectives

Supportive therapies such as NIV and IMV are essential in the management of COVID-19 respiratory failure. Although NIV has fewer adverse effects than IMV, it may put healthcare providers at risk of contracting the disease due to virus-laden aerosols.<sup>22</sup> This is probably the most controversial issue regarding the use of NIV in COVID-19 patients. Table 1 presents an overview of research studies with different perspectives and recommendations on the application of NIV in COVID-19 patients.

### NIV Interfaces

The success of the NIV procedure depends on several factors, the most prominent of which is the type of interface used, as it greatly affects the comfort of patients. The main disadvantages of NIV interfaces are air leakage, facial skin erythema, claustrophobia, eye irritation, skin breakdown, and acneiform rash.<sup>5</sup> There are many types of NIV interfaces, and new formats are in development. The most common types are oral interfaces (mouthpieces placed between the patient's lips and held in place by lip-seal

or teeth), nasal masks (cover the nose but not the mouth), nasal pillows (plug inserted into the nostrils), full-face masks (cover the mouth, nose, and eyes), oronasal masks (cover the nose and mouth), and helmets (cover the whole head and all or part of the neck without any contact with the face or head).<sup>29, 30</sup>

Unlike traditional masks, the helmet interface can be used in abnormal anatomical situations and is applicable to all patients. This interface is a transparent plastic hood that does not contact the patient's face, especially the nasal bridge, and thus prevents skin lesions. The fixation system is not as complex as traditional masks. A recently developed helmet interface features an annular openable ring placed underneath an inflatable cushion. This type reduces discomfort and axillary skin lesions caused by the padded armpit braces of a standard helmet. However, complications might occur in the neck area.<sup>31-33</sup> The main advantage of the helmet interface is minimal air leakage (i.e., no aerosol dispersion from the interface). It reduces the dispersion distance to 27 cm and becomes undetectable, if a leak-free seal is deployed. This range can go

**Table 1:** Recommendations of research papers regarding the use of non-invasive ventilation in COVID-19 patients

Organization	Author	Country	Recommendations and comments
Society of Critical Care Medicine (SCCM)	Alhazzani W et al. <sup>4</sup>	Multinational	Use NIV if HFNC is unavailable or in case of patient intolerance. Prompt intubation if no oxygenation improvement is observed after utilizing NIV for 1-2 hours.
Australian and New Zealand Intensive Care Society (ANZICS)	ANZICS group <sup>5</sup>	Australia and New Zealand	Not routine usage Use NIV and HFNC if health services are unable to provide invasive ventilation
Sociedad Española de Neumología y Cirugía Torácica, Spain	Raof S et al. <sup>23</sup>	Spain	Supportive of the use of NIV
Asociación Argentina de Medicina Respiratoria		Argentina	Supportive for the use of NIV. A short trial (one hour)
Associação Brasileira de Fisioterapia Cardiopulmonar e Fisioterapia em Terapia Intensiva		Brazil	Supportive of the use of NIV in certain situations. A short trial (30 min).
Italian Thoracic Society and Italian Respiratory Society		Italy	Supportive of the use of NIV.
Irish Thoracic Society		Ireland	Supportive of the use of NIV. Helmet interface suggested.
Sociedade Portuguesa de Pneumologia		Portugal	NIV can be used in specific patients and conditions. A short trial (one hour) using a facial mask is suggested.
European Society of Intensive Care Medicine and the Society of Critical Care Medicine 2020	Alhazzani W et al. <sup>24</sup>	Multinational	In adults with COVID-19 and acute hypoxemic respiratory failure, a short trial NIPPV with close monitoring is suggested, but only in the absence of urgent indication for endotracheal intubation and HFNC is not available.
ICM Anaesthesia <sup>25</sup>	-	United Kingdom	A short trial with a well-fitting interface (full face mask or helmet) is recommended as a bridge to invasive mechanical ventilation.
Military Medical Research	Jaber S et al. <sup>6</sup>	Multinational	In case of ineffectiveness of nasal cannula or mask oxygen therapy, HFNC or NIV can be considered. In the absence of improvement in respiratory failure or continuous worsening within one hour after HFNC or NIV, intubation should be performed straightaway.

National COVID-19 Clinical Evidence Taskforce	Shereen MA et al. <sup>7</sup>	Australia	NIV should only be considered in concomitant COPD with type 2 respiratory failure or cardiogenic pulmonary edema (CPE)
National Health Care System guidelines	Velly L et al. <sup>8</sup>	United Kingdom	NIV can be used for mild hypoxia and acute or chronic respiratory failure (selected patients). The use of NIV (BiPAP) should be reserved for those with acute hypercapnic respiratory failure or chronic ventilatory failure. CPAP is the preferred form of NIV support in the management of hypoxemic COVID-19 patients.
State Administration of Traditional Chinese Medicine in China and the National Health Commission	Suen CM et al. <sup>9</sup>	China	NIV is recommended and routinely use (invasive ventilation is recommended, only if NIV failed to enhance respiratory distress or hypoxemia).
World Health Organization	Scala R et al. <sup>10</sup>	Multinational	NIV usage: No recommendation for a pandemic viral illness (some confined data showed a high failure rate in patients with respiratory viral infections (MERS-CoV) receiving NIV). CPAP usage: For selected patients with close monitoring.
JAMA Clinical Guidelines Synopsis	Fakharian A et al. <sup>11</sup>		NIV usage: A trial period with close monitoring is recommended, but only if HFNC is not available.
The ÖGARI (Österreichische Gesellschaft für Anästhesiologie, Reanimation und Intensivmedizin), FASIM (Federation of Austrian Societies of Intensive Care Medicine) and ÖGIAM (Österreichische Gesellschaft für Internistische und Allgemeine Intensivmedizin und Notfallmedizin)	Pierson DJ et al. <sup>12</sup>	Austria	Consider a short trial only if HFNC is not suitable. When stabilization is not achieved within an hour, endotracheal intubation should be performed immediately.
Pakistan Chest Society	Bach JR et al. <sup>13</sup>	Pakistan	Against using NIV for COVID-19 patients.
Department Of Defense COVID-19 practice management guide	Ward NS et al. <sup>14</sup>	United States	Recommended avoiding NIV because of increased aerosolization generated by the face mask and lack of an exhalation filter. In exceptional cases, such as patients that chronically use NIV, isolation with airborne precautions is required regardless of ICU/acute care status.
European Respiratory Society (ERS)	MacIntyre N et al. <sup>15</sup>	Multinational	Recommended NIV as a preventive strategy for avoiding intubation in hypoxemic ARF only when performed by experienced teams in specifically selected cooperative patients with community-acquired pneumonia or early ARDS without any associated major organ dysfunction.
National Institutes of Health	Bellani G et al. <sup>26</sup>	United States	For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV)
Department of Biopathology and Medical Biotechnologies (DIBIMED), Section of Anesthesia, Analgesia, Intensive Care and Emergency, Policlinico P. Giaccone, University of Palermo, Palermo, Italy	Cortegiani A et al. <sup>27</sup>	Italy	Due to the lack of exhalation filters and aerosols generated for face mask ventilation, it is recommended to avoid NIV. Moreover, it is suggested that patients, who regularly receive NIV should be isolated regardless of ICU/acute care status.
China Medical Treatment Expert Group for COVID-19	Guan WJ et al. <sup>28</sup>	China	A preemptive NIV to prevent intubation in case of hypoxemic acute respiratory failure can be considered. Only when performed by experienced teams in specifically elected cooperative patients with community-acquired pneumonia or early ARDS without any associated major organ dysfunction.
The Northwell COVID-19 Research Consortium	Richardson S et al. <sup>18</sup>	United States	If conventional oxygen therapy does not improve oxygenation in acute hypoxemic respiratory failure in adults, HFNC oxygen may be preferred over NIPPV.

COVID-19: Coronavirus disease 2019, HFNC: High-flow nasal cannula, NIV: Non-invasive ventilation, NIPPV: Non-invasive positive pressure ventilation, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit

up to 91.6 cm with the addition of a face mask interface.<sup>34, 35</sup>

Previous studies have reported that using helmet NIV may improve the outcome in COVID-19 patients. In Italy, the most commonly used interface for COVID-19 patients is the helmet interface. Some studies have suggested that helmet NIV may be better than other traditional interfaces, as it prevents intubation and reduces the mortality rate in patients with hypoxemic respiratory failure.<sup>36, 37</sup> Other studies found that a helmet is generally well-tolerated, has fewer air leaks and pressure ulcer complications, is suitable for prolonged therapy, and may provide better tolerance with prolonged usage.<sup>38, 39</sup> A recent study by Raouf and colleagues recommended the use of helmet NIV in COVID-19 patients.<sup>23</sup> The results of a randomized controlled trial showed that the use of a helmet significantly reduced the intubation rate in patients with acute respiratory distress syndrome (ARDS) than the face masks (from 61% to 18%, respectively). Several supporting statements in favor of helmet interface have been reported, including its effectiveness, well-tolerated by patients,<sup>40</sup> fit-for-purpose, as it acts as a reservoir,<sup>41</sup> and being the interface of first choice.<sup>40-42</sup>

#### *NIV Modes and Settings*

The most common NIV modes are CPAP and BiPAP (or BPAP). These modes can provide respiratory support and a fraction of inspired oxygen ( $FiO_2$ ) equal to 100% in a closed-loop.<sup>6, 42</sup> CPAP is used to provide continuous positive airway pressure to patients with spontaneous breathing. This mode can support breathing at high flow rates of air or a mixture of air and oxygen as one set pressure, typically between 3 and 20  $cmH_2O$ .<sup>43</sup> By improving the ventilation-perfusion mismatch and respiratory compliance, CPAP reduces the degree of hypoxemia through alveolar recruitment. It has been shown that CPAP delivered by helmet interface is safer and more effective than a face mask, and is better tolerated over prolonged ventilation periods.<sup>44</sup>

BiPAP mode is considered when applying CPAP to non-intubated adult patients through different interfaces. It allows clinicians to control ventilation using two different pressures (IPAP and EPAP) to improve ventilation and make breathing easier. High inspiratory pressure offloads the patient's breathing effort, while the lower pressure preserves an acceptable alveolar volume and prevents the collapse of unstable alveoli during expiration. Pressure support (PS) is calculated by the difference between IPAP and EPAP, where the difference should be at

least 8  $cmH_2O$ .<sup>45, 46</sup> Early pressure setting for EPAP and IPAP is 3 and 10  $cmH_2O$ , respectively, followed by up-titration every 10-30 minutes to reach adequate chest expansion (maximum IPAP of 30  $cmH_2O$ ).<sup>47</sup> BiPAP is regularly used in treating COPD patients and thus may also benefit COVID-19 patients with comorbidities, as it improves their breathing.<sup>46, 48</sup> However, there is a potential risk of incorrect settings whereby a patient is given a tidal volume (VT) that is too large causing barotrauma and volutrauma.<sup>49</sup> Since COVID-19 patients have less lung compliance, they are at risk of developing barotrauma and pneumothorax. Since the condition of these patients can rapidly deteriorate, they should be closely monitored for early intervention.<sup>50</sup>

Some BiPAP ventilators include a 'ramp' or 'rise time' setting to slowly increase the pressure over the first few minutes of ventilation until the required pressure is reached. This has the benefit of preventing barotrauma and is less distressing to patients at the early stage of mechanical ventilation. By doing so, a 25% rise time will take up 25% of the total inspiratory time before the peak pressure is reached.<sup>49</sup> Respiratory support for COVID-19 patients is challenging due to differences in their lung pathologies and respiratory dysfunction. These patients require individualized lung-protective strategies to enhance outcomes. The setting and timing of respiratory support should be closely tailored to the specific demands of each patient, taking into account the phase and progression of the disease.<sup>51</sup>

Due to the lack of guidelines on how to manage a large number of COVID-19 patients with hypoxemic respiratory failure in a short time frame, an Emergency Department in Northern Italy proposed a procedure to standardize the process. They recommended the initiation of a CPAP trial of 120 minutes with the initial settings of positive end-expiratory pressure (PEEP) of 7.5  $cmH_2O$ , flow rate  $\geq 60$  L/min, titrating the  $FiO_2$  to reach pulse oximetry ( $SpO_2$ )  $\geq 94\%$ , and respiratory rate (RR)  $\leq 25$  bpm. They recommended that during the trial period, patients should be monitored closely, and all vital signs re-assessed every 30 minutes. In case of failure to reach the established target for RR, PEEP should be elevated by 2.5  $cmH_2O$  up to a maximum of 12.5  $cmH_2O$ . If the target is reached after the trial period, CPAP alternated with high-flow nasal oxygen should be continued, while vital signs are continuously monitored. In case of failure to reach the specified target after the CPAP trial, early intubation should be considered.<sup>44</sup>

Compared to CPAP, BiPAP is the preferred mode in patients with respiratory acidosis ( $p\text{CO}_2 > 40$  mmHg and  $\text{pH} < 7.35$ ), COPD, obesity, and respiratory muscle fatigue. The initial settings in BiPAP mode are PS of 5  $\text{cmH}_2\text{O}$ , PEEP of 5-10  $\text{cmH}_2\text{O}$ , and titrating the  $\text{FiO}_2$  to reach  $\text{SpO}_2 \geq 94\%$ ,  $\text{RR} \leq 25$  bpm, and a VT of 6 mL/Kg predicted body weight. Moreover, monitoring should be done every 30 minutes during the 60 minutes trial duration.<sup>44, 48, 52, 53</sup>

Novel modes of NIV are proportional assist ventilation (PAV), average volume assured pressure support (AVAPS), and assist/control. However, there is not enough evidence to support their application in COVID-19 patients with respiratory failure.<sup>38</sup>

#### *Sedation in Patients Receiving NIV*

Whether sedative medications can be used to improve NIV interface tolerance is still under debate. The goal of sedation is to reduce the patient's discomfort and reach a level of awake sedation without significant effects on respiratory drive, respiratory pattern, blood gases, minute volume, hemodynamics, and airway reflexes.<sup>54</sup> A small dose of sedation, while vital signs and oxygenation are closely monitored, could be considered on a case-by-case basis to help ease some of the adverse effects of the NIV interface and thus improve patient compliance.<sup>23</sup> Many physicians in Europe and North America oppose the use of sedatives, as they may interfere with their ability to protect airways or depress the respiratory system. However, to prevent NIV failure due to low patient tolerance, mild sedation is suggested in selected patients in the ICU provided close monitoring of the patient's airway and consciousness.<sup>54</sup>

Agitation is one of the most common causes of low tolerance to or failure of NIV. The term 'agitation' refers to a state of high anxiety that causes patients to become uncooperative. Agitation prevents patients from relaxing and synchronizing their breathing with the ventilator, and they often tend to remove the NIV interface. Agitation may also be related to the underlying delirium, a condition of inattention and disorientation, which becomes apparent, when a patient is stressed by the necessity to use NIV. In general, the management strategy in these patients focuses on non-pharmacological measures like verbal reassurance, giving the patient control over the mask, or improving comfort by frequent disconnection from NIV, if the respiratory insufficiency is not too severe.<sup>55, 56</sup> However, sedatives are also used to improve tolerance to NIV. The preferred agents are small doses of benzodiazepines (lorazepam or midazolam)

and/or narcotics (fentanyl or morphine sulfate). Other agents commonly used to calm patients with delirium to accept NIV include haloperidol, propofol, and dexmedetomidine. However, patients receiving propofol must be carefully observed for potential respiratory depression or apnea. In contrast, dexmedetomidine causes minimal respiratory depression and has sedative and analgesic sparing properties, but it is relatively expensive.<sup>30, 56, 57</sup> The Richmond agitation-sedation scale (RASS) is commonly used as an index for adjusting sedation levels. A score of +1 or higher on RASS is an indicator for sedation.<sup>58</sup> Patients are usually managed between -2 and 0 on the RASS during sedation. Sedation usually starts intermittently, but continuous administration is initiated, if the target sedation level is not reached.<sup>59</sup>

Prone ventilation can be performed with minimum effort, if sedatives (e.g., dexmedetomidine) are used. A previous study showed the benefits (e.g., mortality reduction and enhanced oxygenation) of prone position (PP) in patients with severe ARDS if applied early and for prolonged periods.<sup>60</sup> A case study on a COVID-19 patient in Canada likewise reported that PP prevented the use of IMV.<sup>61</sup> Another case series hypothesized an association between awake early self-proning in the emergency department and improved oxygen saturation in COVID-19 patients.<sup>62</sup>

Dexmedetomidine is a centrally acting, highly selective alpha-2 adrenoreceptor agonist that inhibits the release of norepinephrine from synaptic vesicles. It improves analgesic, anxiolytic, and sedative effects without depressing the respiratory system.<sup>63, 64</sup> A previous study compared the infusion of different loading doses of dexmedetomidine and midazolam over 24 hours in patients receiving NIV. Both agents were reported to be effective sedatives without significant differences in their effects on ventilation and oxygenation. However, dexmedetomidine required significantly fewer dosage adjustments to maintain adequate sedation, and patients receiving NIV were more cooperative.<sup>65</sup> Dexmedetomidine was also reported to be more effective than haloperidol in preventing delirium during NIV use with a lower incidence of intubation, NIV failure, and the requirement for supplementary sedation and analgesia. Dexmedetomidine was associated with a shorter hospital stay and lower incidence of respiratory tract infections.<sup>56</sup> A group of Italian physicians recommended bolus dosing of fentanyl or hydromorphone for analgesia and midazolam for sedation/anxiolysis as the best first-line agents in non-intubated patients. Additionally, they suggested dexmedetomidine

infusion as an effective alternative for medium sedation, particularly in the case of patients at risk of or already experiencing alcohol withdrawal symptoms.<sup>66</sup>

In the case of psychosis and/or unmanageable disruptive behavior, pharmacological treatment is required. Antipsychotic agents are suggested as the first-choice intervention. Existing guidelines vary in terms of the preferred first-line agents, but in general haloperidol, olanzapine, risperidone, and quetiapine are recommended.<sup>67</sup> The causes of delirium in COVID-19 patients are not clear. However, contributing factors include systemic inflammation and neuroinflammation, multi-organ failure, coagulation abnormalities, deep sedative strategies, mechanical ventilation, and social isolation.<sup>68</sup> The risks of delirium and coma in COVID-19 patients can be reduced by avoiding the use of deep sedative drugs. The type, duration, and depth of sedation also play an important role. The results of a multicenter cohort study, involving 69 adult ICUs across 14 countries, recommended the avoidance of benzodiazepines for a prolonged period, as it was associated with a 59% higher risk of developing delirium.<sup>69</sup>

The combined effects of inflammation and several other factors cause an increase in capillary permeability. These effects are not only confined to the lungs, but may also cause damage to the vascular endothelium, which in turn result in leakage from the vascular compartment into the interstitial tissues.<sup>70-72</sup> These variations increase the volume of distribution of water-soluble drugs and subsequently decrease their systemic exposure.<sup>73</sup> Sedative and analgesic agents with a low volume of distribution at steady-state (VD<sub>ss</sub>) such as midazolam (0.7-1.2 L/Kg) are prone to under-exposure linked to a hyper-inflammatory state. However, other drugs widely distributed in the extravascular space, such as propofol (1.8-5.3 L/Kg), sufentanil (VD<sub>ss</sub> 4.9 L/Kg), and fentanyl (VD<sub>ss</sub> 5.5 L/Kg), are theoretically less affected by these variations.

From the perspective of metabolic interactions, some combination drugs such as midazolam, extensively metabolized by cytochrome P450 3A4/5 (CYP3A4/5), can probably be modified by CYP inducers or inhibitors. This could be increased significantly by combining midazolam with lopinavir/ritonavir.<sup>74</sup> Therefore, it is important to adjust drug dosages since high doses or prolonged infusions of midazolam in patients receiving lopinavir/ritonavir may cause delayed recovery, long-lasting hypnotic effects, and respiratory depression. Propofol and fentanyl have a lower risk of metabolic interactions, as their clearance is dependent on hepatic blood

flow (not only on intrinsic metabolic activity), although they can be metabolized by CYP 3A4. However, fentanyl has a high hepatic extraction rate (0.7-0.8) and is therefore not affected by variations in metabolic enzyme activity. Since propofol and fentanyl clearance is dependent on hepatic blood flow, any reduction in hepatic blood flow in the event of circulatory insufficiency (e.g., ARDS) could increase systemic exposure to the molecules of these drugs.<sup>75-77</sup> The bradycardizing effects of dexmedetomidine must be taken into account in patients receiving azithromycin and hydroxychloroquine, as it may prolong the QT interval.<sup>74</sup> Accordingly, sedative and analgesic dosing should be adjusted to the patient's response in real-time. Based on clinical experience, COVID-19 patients may require higher doses of sedation than the patients with ARDS secondary to other etiologies (e.g., pneumonia).<sup>28</sup>

### *Positioning*

Previous studies have shown that awake PP in non-intubated COVID-19 patients with severe hypoxemic respiratory failure improves oxygen saturation than the supine position. Moreover, repositioning can improve the respiratory status and oxygenation in patients with normal mental status.<sup>62, 78</sup> It is recommended that patients change position every 30-120 minutes (e.g., right lateral recumbent, prone, left lateral recumbent, sitting upright at 60-90 degrees). During and immediately after every position change, the oxygen supply should be checked. Health care workers should evaluate patients' respiratory status and oxygen saturation about 10 to 15 minutes after each position change.<sup>79</sup> It has been reported that awake PP may improve oxygenation, ventilation/perfusion mismatch, and breathing.<sup>80</sup> Besides, the early application of PP with HFNC or NIV, particularly in patients with non-intubated moderate ARDS and with SpO<sub>2</sub>>95%, may reduce intubation incidence.<sup>81</sup> Another study recommended the semi-sitting or sitting position but avoiding the supine position in COVID-19 patients receiving NIV. These positions should be considered whenever possible and in close consultation with the medical team.<sup>81</sup> It is important to ensure that a patient has to exert as little effort as possible, even when maintaining a posture. Therefore, the use of cushions/pillows is recommended to allow a stable position without active use of muscles by the patient and to reduce shortness of breath and energy expenditure.<sup>41, 82</sup> Moreover, the position should be passive to reduce muscular activity and relax the accessory muscles to facilitate the ventilation/perfusion ratio.<sup>83</sup> Repositioning should be performed according

to clinical protocols to ensure its efficiency and patient safety.<sup>84</sup>

The results of an observational prospective study, conducted in patients with COVID-19 on helmet CPAP therapy, showed that only a small proportion of patients prone/lateral positioning resulted in a significant improvement in gas exchange. Additionally, a decrease in the alveolar-arterial oxygen gradient (A-a O<sub>2</sub>) of <20% (an important minimal but clinically relevant difference) was reported.<sup>85</sup> In another study, results showed that PP in conjunction with NIV can improve oxygenation in COVID-19 patients. This can be achieved without significant adverse effects, particularly in those with a sustained response, and may even avoid intubation. When used in a suitably monitored environment, with access to experienced clinicians able to facilitate IMV if required, PP alongside NIV may be a useful tool in treating COVID-19 patients with moderate AHRF. The reported change in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was 28.7 mmHg in PP without any notable change in heart or respiratory rate.<sup>86</sup>

#### Monitoring

Patients on NIV support should be monitored closely in order to take immediate action in case of NIV failure and to be able to switch to invasive ventilation. Health care providers should remain at the patient's bedside for constant monitoring of respiratory rate and breathing status. They should check arterial blood gases (ABG) every 30 min and alternate between CPAP and pressure support ventilation (PSV) to improve SpO<sub>2</sub> and reduce RR. Furthermore, patients should be checked, if administration of small doses of sedatives is needed and directly control delivered VT with high pressure.<sup>23, 47</sup> Another serious concern is the possible presence of 'happy or silent hypoxemia'. For clinicians, the presence of happy or silent hypoxemia in COVID-19 patients, despite marked arterial hypoxemia, can incorrectly lead to the conclusion that the patient is not in a critical condition. Such cases can quickly jump clinical evolution stages and suffer ARDS with the associated cardiorespiratory arrest and death.<sup>87</sup>

SpO<sub>2</sub> is used to measure oxygen saturation and to detect hypoxemia. However, SpO<sub>2</sub> levels should be interpreted cautiously in COVID-19 patients with hypoxemia. The sigmoid-shaped oxyhemoglobin dissociation curve moves to the left because of induced respiratory alkalosis (decrease in PaCO<sub>2</sub>) due to hypoxemia-driven tachypnea and hyperpnea. During periods of hypocapnia, the ionization of hemoglobin and thus oxygen saturation increases for a given

degree of PaO<sub>2</sub>. This explains why SpO<sub>2</sub> can be well-preserved in the face of a profoundly low PaO<sub>2</sub>.<sup>88</sup> Falsely high SpO<sub>2</sub> and low RR can be seen in COVID-19 patients due to secondary causes such as diarrhea, dehydration, and hypoalbuminemia. It is therefore recommended to initiate respiratory support based on the PaO<sub>2</sub>/FiO<sub>2</sub> ratio rather than SpO<sub>2</sub> levels alone.<sup>89</sup> It is suggested that the ratio should be above 150 mmHg, since NIV is associated with higher ICU mortality in patients with a ratio below this level.<sup>23</sup>

#### Nutrition

Oral intake of food and drinks by COVID-19 patients in the ICU remains inadequate due to disease-related loss of appetite, nausea, and loss of taste. NIV interface (full-face or helmet) also makes it difficult to eat and drink, and its removal will reduce arterial oxygen saturation. The English National Health Service has recommended the administration of opioids when using NIV interfaces to reduce the perception of breathlessness and high VT; however, it can negatively affect bowel motility.<sup>90</sup> <sup>91</sup> In COVID-19 patients at the risk of malnutrition due to insufficient oral nutritional intake, oral nutritional supplementation (ONS) should be initially considered and then enteral nutrition (EN) should be used. In case of restrictions through the EN route, peripheral parenteral nutrition (PN) may be considered in patients who fail to meet their energy-protein needs through ONS or EN.<sup>92</sup> In patients who cannot tolerate a full dose of EN during the first week in ICU, initiation of PN should be weighed on a case-by-case basis. PN should not be initiated until all strategies to maximize EN tolerance have failed. At every phase of disease progression, ICU patients with COVID-19 must be carefully evaluated for the risk of malnutrition and the need for nutritional support. Any delay will result in increased energy and protein deficiency, leading to extended hospitalization and rehabilitation of the surviving patients. Metabolism control and nutritional support play an important role in managing critically ill COVID-19 patients.<sup>93</sup>

Unlike IMV, patients treated with NIV have no airway protection and may experience airway-related problems (increased sputum, vomiting, atelectasis, and mucus plugging) and other complications such as discomfort, hypotension, pneumothorax, anxiety, and cardiac rhythm disturbances. EN may exacerbate these complications, especially those that are airway-related, and potentially lead to critical complications such as pneumonia and airway obstruction.<sup>94, 95</sup> Therefore, COVID-19 patients



receiving NIV support are predominantly fed with PN to avoid the gastrointestinal complications associated with EN.<sup>96</sup> However, liquid ONS is also given in an effort to meet energy needs, if it cannot be fulfilled with PN alone, and to maintain intestinal mucosal tropism.<sup>97</sup> An observational study found that inadequate oral intake was associated with prolonged NIV and hospital stay, whereby about 78% of patients received less than 80% of their energy requirements. Of the 150 patients receiving NIV support longer than 48 hours, 107 were unable to take oral nutrition to the extent that the medical staff had to opt for EN.<sup>59</sup>

EN is recommended as the preferred route for critically ill patients without contraindications, as it provides the required calories. However, EN may elevate residual gastric volume leading to bacterial colonization and increase the risk of aspiration pneumonia and ventilator-associated pneumonia (VAP).<sup>98</sup> In cases where patients receive both EN and NIV support, nasogastric (NG) tubes may undermine interface sealing and consequently, reduce the effectiveness of the ventilation. Moreover, NIV may cause abdominal distension due to positive air pressure in the stomach, which results in diaphragmatic dysfunction. Therefore, the use of EN on its own is associated with airway complications, prolonged NIV, and lengthy hospital stays.<sup>59, 24, 99</sup> It is recommended to initiate EN only during the first 48 hours of ICU stay, despite the risk of malnutrition and complications. Alternatively, peripheral or central PN may be considered.<sup>99, 100</sup>

Various measures have been proposed to minimize risks to patients receiving NIV in case of EN using NG tubes:

- Silicone dressings can be applied to tight-fitting masks to minimize air leakage and pressure on the skin.<sup>54</sup>
- If possible, a fine bore NG tube (size 8Fr) should be used for feeding.
- Position the patient in supine upright at an angle of 30-40 degrees during EN feeding. PP is not the preferred position.
- Use an EN pump for accurate and consistent delivery of feed, alternatively, gravity drip-feeding should be considered. The use of bolus feeding is not recommended, as it increases the risk of aspiration.<sup>91</sup>
- In the case of feeding intolerance, prokinetics metoclopramide (10 mg three times a day) and erythromycin (100-250 mg three times a day) can be used in patients without acute abdominal complication.<sup>97</sup>
- Use post-pyloric feeding in patients with gastric intolerance after treatment with prokinetic agents or in patients at risk of aspiration.
- The prone position does not show any

limitations or contraindications to EN.<sup>101</sup> Patients in the prone position should begin EN according to the preceding guidelines, keeping in mind that the prone posture is related to greater stomach residual volumes and an increased risk of vomiting. It is critical to examine the location of the NGT at the point of entry into the nasal cavity after placing the patient in the prone position to determine the possible risk of pressure damage.

- If the above procedures fail, use gastric aspiration to decompress the stomach and check feed absorption.<sup>97</sup>

PN support should be considered when EN and ONS are not effective, especially in those patients already suffering from malnutrition at admission.<sup>102</sup> This is also recommended in patients with long-term swallowing disorders for whom the re-introduction of an NG tube may reduce the rate of success of swallowing rehabilitation. An effective combination of new respiratory support strategies with a suitable route is suggested as nutritional therapy.<sup>103</sup> It should be noted that the use of peripheral PN (<850 mOsm/l) is not recommended as the first choice in patients receiving NIV due to its high fluid volume and low nutrition density.<sup>104</sup>

In all COVID-19 patients, critical or non-critical, carbohydrate intake should be reduced. High carbohydrate has been associated with deteriorating ARDS because of an increase in CO<sub>2</sub> production and subsequent hypercapnia.<sup>105</sup> Moreover, ESPEN guidelines on clinical nutrition in the ICU recommend a low-carbohydrate diet to avoid insulin resistance and hyperglycemia, as repeatedly observed in critically ill patients.<sup>97</sup> The guidelines also recommend 1.3 g protein equivalents per Kg body weight per day delivered progressively. However, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends 1.2-2 g/Kg of body weight.<sup>97, 106</sup> On a final note, one should be aware of using 0.9% saline as routine maintenance for COVID-19 patients, as it can increase sodium and chloride load, potentially cause bowel edema, and impair gastrointestinal function.<sup>107</sup>

## Conclusion

The application of NIV in the management of COVID-19 patients remains controversial. So far, the evidence on the use of NIV in patients with COVID-19 does not fully encourage its routine use. Some studies have revealed the benefits of using NIV in selected patients with respiratory failure. The main findings of our review are:

- NIV could be a useful respiratory support in the early stages of infection to prevent silent hypoxia as a complication of COVID-19.

- Patients receiving NIV support should be closely monitored during the trial period. Intubation should always remain an option, since any delay in intubation increases the risk of complications and may result in unfavorable outcomes.
- Early prone positioning can be deployed without significant adverse effects, mainly in patients with a sustained response, as it may help to increase oxygenation and thus avoid intubation.
- With close monitoring to prevent any complications, a small dose of sedation may be used in patients with agitation and delirium. The sedative dose should be adjusted for COVID-19 patients according to their response, as it is not a one-size-fits-all.
- Enteral feeding in patients receiving NIV support is associated with airway complications, prolonged NIV, and hospital stay, especially when initiated within the first two days of NIV use. However, it can still be considered for selected patients.
- Among all NIV interfaces, the helmet involves fewer complications and provides more comfort to patients.

Further studies are required to better understand the role and advantages of NIV in COVID-19 patients and to develop clear strategies (i.e., optimal settings, duration of therapy, sedation plane, and patient selection).

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### Authors' Contribution

M.M: Study concept and design, re-analyzed the clinical and statistical data, drafting and critical revision of the manuscript for important intellectual content; Z. H.K: Study concept and design, drafting and critical revision of the manuscript for important intellectual content; H.A.V: Study concept and design, statistical analysis and re-analyzed the clinical and statistical data, drafting and revising the manuscript; A.M.A: Study concept and design, re-analyzed the clinical and statistical data, drafting and critical revision of the manuscript for important intellectual content

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### References

- 1 Diurno F, Numis FG, Porta G, Cirillo F, Maddaluno S, Ragozzino A, et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *Eur Rev Med Pharmacol Sci.* 2020;24:4040-7. doi: 10.26355/eurrev\_202004\_20875. PubMed PMID: 32329881.
- 2 Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. *Eur Respir J.* 2010;36:362-9. doi: 10.1183/09031936.00123509. PubMed PMID: 20075052.
- 3 Lightowler JV, Elliott MW. Predicting the outcome from NIV for acute exacerbations of COPD. *Thorax.* 2000;55:815-6. doi: 10.1136/thorax.55.10.815. PubMed PMID: 10992530; PubMed Central PMCID: PMC1745614.
- 4 Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med.* 2020;48:e440-e69. doi: 10.1097/CCM.0000000000004363. PubMed PMID: 32224769; PubMed Central PMCID: PMC7176264.
- 5 Group AC-W. The Australian and New Zealand Intensive Care Society COVID-19 Guidelines (Version 1; 16 March 2020). 2020.
- 6 Jaber S, Michelet P, Chanques G. Role of non-invasive ventilation (NIV) in the perioperative period. *Best Pract Res Clin Anaesthesiol.* 2010;24:253-65. doi: 10.1016/j.bpa.2010.02.007. PubMed PMID: 20608561.
- 7 Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *J Adv Res.* 2020;24:91-8. doi: 10.1016/j.jare.2020.03.005. PubMed PMID: 32257431; PubMed Central PMCID: PMC7113610.
- 8 Velly L, Gayat E, Quintard H, Weiss E, De Jong A, Cuvillon P, et al. Guidelines: Anaesthesia in the context of COVID-19 pandemic. *Anaesth Crit Care Pain Med.* 2020;39:395-415. doi: 10.1016/j.accpm.2020.05.012. PubMed PMID: 32512197; PubMed Central PMCID: PMC7274119.
- 9 Suen CM, Hui DSC, Memtsoudis SG, Chung F. Obstructive Sleep Apnea, Obesity, and Noninvasive Ventilation: Considerations During the COVID-19 Pandemic. *Anesth Analg.* 2020;131:318-22. doi: 10.1213/ANE.0000000000004928. PubMed PMID: 32667157; PubMed Central PMCID:

- PMCPMC7202104.
- 10 Scala R, Accurso G, Ippolito M, Cortegiani A, Iozzo P, Vitale F, et al. Material and Technology: Back to the Future for the Choice of Interface for Non-Invasive Ventilation - A Concise Review. *Respiration*. 2020;99:800-17. doi: 10.1159/000509762. PubMed PMID: 33207357.
  - 11 Fakharian A, Hill NS. NIPPV: Where Are We Now? *Tanaffos*. 2013;12:6-8. PubMed PMID: 25191466; PubMed Central PMCID: PMCPMC4153252.
  - 12 Pierson DJ. History and epidemiology of non-invasive ventilation in the acute-care setting. *Respir Care*. 2009;54:40-52. PubMed PMID: 19111105.
  - 13 Bach JR. Mechanical exsufflation, noninvasive ventilation, and new strategies for pulmonary rehabilitation and sleep disordered breathing. *Bull N Y Acad Med*. 1992;68:321-40. PubMed PMID: 1586868; PubMed Central PMCID: PMCPMC1810174.
  - 14 Ward NS, Dushay KM. Clinical concise review: Mechanical ventilation of patients with chronic obstructive pulmonary disease. *Crit Care Med*. 2008;36:1614-9. doi: 10.1097/CCM.0b013e318170f0f3. PubMed PMID: 18434881
  - 15 MacIntyre N, Huang YC. Acute exacerbations and respiratory failure in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2008;5:530-5. doi: 10.1513/pats.200707-088ET. PubMed PMID: 18453367; PubMed Central PMCID: PMCPMC2645331.
  - 16 Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. *Am J Respir Crit Care Med*. 2012;185:152-9. doi: 10.1164/rccm.201106-1094OC. PubMed PMID: 22016446; PubMed Central PMCID: PMCPMC3297087.
  - 17 Guan L, Zhou L, Le Grange JM, Zheng Z, Chen R. Non-invasive ventilation in the treatment of early hypoxemic respiratory failure caused by COVID-19: considering nasal CPAP as the first choice. *Crit Care*. 2020;24:333. doi: 10.1186/s13054-020-03054-7. PubMed PMID: 32527302; PubMed Central PMCID: PMCPMC7289232.
  - 18 Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020;323:2052-9. doi: 10.1001/jama.2020.6775. PubMed PMID: 32320003; PubMed Central PMCID: PMCPMC7177629.
  - 19 Avdeev SN, Yaroshetskiy AI, Tsareva NA, Merzhoeva ZM, Trushenko NV, Nekludova GV, et al. Noninvasive ventilation for acute hypoxemic respiratory failure in patients with COVID-19. *Am J Emerg Med*. 2021;39:154-7. doi: 10.1016/j.ajem.2020.09.075. PubMed PMID: 33067061; PubMed Central PMCID: PMCPMC7527350.
  - 20 Sivaloganathan AA, Nasim-Mohi M, Brown MM, Abdul N, Jackson A, Fletcher SV, et al. Noninvasive ventilation for COVID-19-associated acute hypoxaemic respiratory failure: experience from a single centre. *Br J Anaesth*. 2020;125:e368-e71. doi: 10.1016/j.bja.2020.07.008. PubMed PMID: 32811662; PubMed Central PMCID: PMCPMC7373070.
  - 21 Hussain Khan Z, AbdulZahra Sasaa M, Mohammadi M, Alipour A, Hajipour A. Mortality Related to Intubation in Adult General ICUs: A Systematic Review and Meta-Analysis. *Archives of Neuroscience*. 2020;7:e89993. doi: 10.5812/ans.89993.
  - 22 Schunemann HJ, Khabsa J, Solo K, Khamis AM, Brignardello-Petersen R, El-Harakeh A, et al. Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19: A Living Systematic Review of Multiple Streams of Evidence. *Ann Intern Med*. 2020;173:204-16. doi: 10.7326/M20-2306. PubMed PMID: 32442035; PubMed Central PMCID: PMCPMC7281716.
  - 23 Raof S, Nava S, Carpati C, Hill NS. High-Flow, Noninvasive Ventilation and Awake (Nonintubation) Prone in Patients With Coronavirus Disease 2019 With Respiratory Failure. *Chest*. 2020;158:1992-2002. doi: 10.1016/j.chest.2020.07.013. PubMed PMID: 32681847; PubMed Central PMCID: PMCPMC7362846.
  - 24 Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020;46:854-87. doi: 10.1007/s00134-020-06022-5. PubMed PMID: 32222812; PubMed Central PMCID: PMCPMC7101866.
  - 25 England N, Improvement N. Clinical guide for the management of critical care for adults with COVID-19 during the coronavirus pandemic. *Icmanaesthesiacovid-19 Org* version. 2020;4:10-28.
  - 26 Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, et al. Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome. Insights from the LUNG SAFE Study. *Am J Respir Crit Care Med*.

- 2017;195:67-77. doi: 10.1164/rccm.201606-1306OC. PubMed PMID: 27753501.
- 27 Cortegiani A, Russotto V, Antonelli M, Azoulay E, Carlucci A, Conti G, et al. Ten important articles on noninvasive ventilation in critically ill patients and insights for the future: A report of expert opinions. *BMC Anesthesiol.* 2017;17:122. doi: 10.1186/s12871-017-0409-0. PubMed PMID: 28870157; PubMed Central PMCID: PMC5584318.
  - 28 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382:1708-20. doi: 10.1056/NEJMoa2002032. PubMed PMID: 32109013; PubMed Central PMCID: PMC7092819.
  - 29 Nava S, Navalesi P, Gregoretti C. Interfaces and humidification for noninvasive mechanical ventilation. *Respir Care.* 2009;54:71-84. PubMed PMID: 19111108.
  - 30 Elliott M, Nava S, Schönhofer B. *Non-invasive ventilation and weaning: principles and practice.* Florida: CRC Press; 2018. doi: 10.1201/9781315153643.
  - 31 Olivieri C, Costa R, Spinazzola G, Ferrone G, Longhini F, Cammarota G, et al. Bench comparative evaluation of a new generation and standard helmet for delivering non-invasive ventilation. *Intensive Care Med.* 2013;39:734-8. doi: 10.1007/s00134-012-2765-z. PubMed PMID: 23223773.
  - 32 Liu Q, Gao Y, Chen R, Cheng Z. Noninvasive ventilation with helmet versus control strategy in patients with acute respiratory failure: a systematic review and meta-analysis of controlled studies. *Crit Care.* 2016;20:265. doi: 10.1186/s13054-016-1449-4. PubMed PMID: 27549178; PubMed Central PMCID: PMC4994276.
  - 33 Pelosi P, Severgnini P, Aspesi M, Gamberoni C, Chiumello D, Fachinetti C, et al. Non-invasive ventilation delivered by conventional interfaces and helmet in the emergency department. *Eur J Emerg Med.* 2003;10:79-86. doi: 10.1097/00063110-200306000-00002. PubMed PMID: 12789060.
  - 34 Talan L, Altıntaş ND. COVID-19 and Intensive Care. *Asthma Allergy Immunology.* 2020;18:15-8. doi: 10.21911/aai.555.
  - 35 Montenegro F, Unigarro L, Paredes G, Moya T, Romero A, Torres L, et al. Acute respiratory distress syndrome (ARDS) caused by the novel coronavirus disease (COVID-19): a practical comprehensive literature review. *Expert Rev Respir Med.* 2021;15:183-95. doi: 10.1080/17476348.2020.1820329. PubMed PMID: 32902367.
  - 36 Ferrone G, Spinazzola G, Costa R, Gulli A, Scapigliati A, Antonelli M, et al. Comparative bench study evaluation of a modified snorkeling mask used during COVID-19 pandemic and standard interfaces for non-invasive ventilation. *Pulmonology.* 2021. doi: 10.1016/j.pulmoe.2021.05.009. PubMed PMID: 34217695; PubMed Central PMCID: PMC8185250.
  - 37 Rali AS, Howard C, Miller R, Morgan CK, Mejia D, Sabo J, et al. Helmet CPAP revisited in COVID-19 pneumonia: A case series. *Can J Respir Ther.* 2020;56:32-4. doi: 10.29390/cjrt-2020-019. PubMed PMID: 32844113; PubMed Central PMCID: PMC7427972.
  - 38 Rochweg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J.* 2017;50. doi: 10.1183/13993003.02426-2016. PubMed PMID: 28860265.
  - 39 Coppadoro A, Benini A, Fruscio R, Verga L, Mazzola P, Bellelli G, et al. Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak. *Crit Care.* 2021;25:80. doi: 10.1186/s13054-021-03502-y. PubMed PMID: 33627169; PubMed Central PMCID: PMC7903369.
  - 40 Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA.* 2016;315:2435-41. doi: 10.1001/jama.2016.6338. PubMed PMID: 27179847; PubMed Central PMCID: PMC4967560.
  - 41 Lazzeri M, Lanza A, Bellini R, Bellofiore A, Cecchetto S, Colombo A, et al. Respiratory physiotherapy in patients with COVID-19 infection in acute setting: a Position Paper of the Italian Association of Respiratory Physiotherapists (ARIR). *Monaldi Arch Chest Dis.* 2020;90. doi: 10.4081/monaldi.2020.1285. PubMed PMID: 32236089.
  - 42 Cinesi Gomez C, Penuelas Rodriguez O, Lujan Torne M, Egea Santaolalla C, Masa Jimenez JF, Garcia Fernandez J, et al. [Clinical consensus recommendations regarding non-invasive respiratory support in the adult patient with acute respiratory failure secondary to SARS-CoV-2 infection]. *Med Intensiva (Engl Ed).* 2020;44:429-38. doi: 10.1016/j.medin.2020.03.005. PubMed PMID: 32312600; PubMed Central PMCID: PMC7270576.
  - 43 Addala D, Shrimanker R, Davies MG. Non-invasive ventilation: initiation and

- initial management. *Br J Hosp Med (Lond)*. 2017;78:C140-C4. doi: 10.12968/hmed.2017.78.9.C140. PubMed PMID: 28898158.
- 44 Privitera D, Angaroni L, Capsoni N, Forni E, Pierotti F, Vincenti F, et al. Flowchart for non-invasive ventilation support in COVID-19 patients from a northern Italy Emergency Department. *Intern Emerg Med*. 2020;15:767-71. doi: 10.1007/s11739-020-02370-8. PubMed PMID: 32435934; PubMed Central PMCID: PMC7238716.
  - 45 Yarrarapu SNS, Saunders H, Sanghavi D. Average Volume-Assured Pressure Support. Treasure Island (FL): StatPearls; 2022. PubMed PMID: 32809435.
  - 46 Whittle JS, Pavlov I, Sacchetti AD, Atwood C, Rosenberg MS. Respiratory support for adult patients with COVID-19. *J Am Coll Emerg Physicians Open*. 2020. doi: 10.1002/emp2.12071. PubMed PMID: 32427171; PubMed Central PMCID: PMC7228246.
  - 47 Tabashi S, Mirkheshti A, Dahi M, Abtahi D, Vosoughian M, Sayyadi S, et al. Supplemental oxygen therapy and non-invasive ventilation in corona virus disease (COVID-19). *Journal of Cellular & Molecular Anesthesia*. 2020;5:27-31. doi: 10.22037/jcma.v5i1.29689.
  - 48 Duca A, Memaj I, Zanardi F, Preti C, Alesi A, Della Bella L, et al. Severity of respiratory failure and outcome of patients needing a ventilatory support in the Emergency Department during Italian novel coronavirus SARS-CoV2 outbreak: Preliminary data on the role of Helmet CPAP and Non-Invasive Positive Pressure Ventilation. *EClinicalMedicine*. 2020;24:100419. doi: 10.1016/j.eclinm.2020.100419. PubMed PMID: 32766538; PubMed Central PMCID: PMC7301102.
  - 49 Carter C, Aedy H, Notter J. COVID-19 disease: Non-Invasive Ventilation and high frequency nasal oxygenation. *Clinics in Integrated Care*. 2020;1:100006-. doi: 10.1016/j.intcar.2020.100006. PubMed Central PMID: PMC7261654.
  - 50 Floyd L, Stauss M, Storrar J, Vanalia P, France A, Dhaygude A. Using CPAP in COVID-19 patients outside of the intensive care setting: a comparison of survival and outcomes between dialysis and non-dialysis dependent patients. *BMC Nephrol*. 2021;22:144. doi: 10.1186/s12882-021-02341-x. PubMed PMID: 33882842; PubMed Central PMCID: PMC78059117.
  - 51 Cabrini L, Ghislanzoni L, Severgnini P, Landoni G, Baiardo Redaelli M, Franchi F, et al. Early versus late tracheal intubation in COVID-19 patients: a “pros/cons” debate also considering heart-lung interactions. *Minerva Cardiol Angiol*. 2021;69:596-605. doi: 10.23736/S2724-5683.20.05356-6. PubMed PMID: 33059400.
  - 52 Buheji M, Costa Cunha Kd, Barbosa Rocha RS. Ventilators in COVID-19, between scarcity and abundance mindset. *International Journal of Advanced Research in Engineering and Technology*. 2020;11.
  - 53 Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet*. 2009;374:250-9. doi: 10.1016/S0140-6736(09)60496-7. PubMed PMID: 19616722; PubMed Central PMCID: PMC7138083.
  - 54 Brill A-K. How to avoid interface problems in acute noninvasive ventilation. *Breathe*. 2014;10:230-42. doi: 10.1183/20734735.003414.
  - 55 Devlin JW, Nava S, Fong JJ, Bahhady I, Hill NS. Survey of sedation practices during noninvasive positive-pressure ventilation to treat acute respiratory failure. *Crit Care Med*. 2007;35:2298-302. doi: 10.1097/01.CCM.0000284512.21942.F8. PubMed PMID: 17717491.
  - 56 Akada S, Takeda S, Yoshida Y, Nakazato K, Mori M, Hongo T, et al. The efficacy of dexmedetomidine in patients with noninvasive ventilation: a preliminary study. *Anesth Analg*. 2008;107:167-70. doi: 10.1213/ane.0b013e3181732dc2. PubMed PMID: 18635484.
  - 57 Salluh JI, Dal-Pizzol F, Mello PV, Friedman G, Silva E, Teles JM, et al. Delirium recognition and sedation practices in critically ill patients: a survey on the attitudes of 1015 Brazilian critical care physicians. *J Crit Care*. 2009;24:556-62. doi: 10.1016/j.jcrc.2009.04.004. PubMed PMID: 19577412.
  - 58 Matsumoto T, Tomii K, Tachikawa R, Otsuka K, Nagata K, Otsuka K, et al. Role of sedation for agitated patients undergoing noninvasive ventilation: clinical practice in a tertiary referral hospital. *BMC Pulm Med*. 2015;15:71. doi: 10.1186/s12890-015-0072-5. PubMed PMID: 26164393; PubMed Central PMCID: PMC4499444.
  - 59 Kogo M, Nagata K, Morimoto T, Ito J, Sato Y, Teraoka S, et al. Enteral Nutrition Is a Risk Factor for Airway Complications in Subjects Undergoing Noninvasive Ventilation for Acute Respiratory Failure. *Respir Care*. 2017;62:459-67. doi: 10.4187/respcare.05003. PubMed PMID: 27923936.
  - 60 Kallet RH. A Comprehensive Review of Prone Position in ARDS. *Respir Care*.

- 2015;60:1660-87. doi: 10.4187/resp-care.04271. PubMed PMID: 26493592.
- 61 Slessarev M, Cheng J, Ondrejicka M, Arnfield R, Critical Care Western Research G. Patient self-proning with high-flow nasal cannula improves oxygenation in COVID-19 pneumonia. *Can J Anaesth.* 2020;67:1288-90. doi: 10.1007/s12630-020-01661-0. PubMed PMID: 32319029; PubMed Central PMCID: PMC7172385.
- 62 Caputo ND, Strayer RJ, Levitan R. Early Self-Prone in Awake, Non-intubated Patients in the Emergency Department: A Single ED's Experience During the COVID-19 Pandemic. *Acad Emerg Med.* 2020;27:375-8. doi: 10.1111/acem.13994. PubMed PMID: 32320506; PubMed Central PMCID: PMC7264594.
- 63 Cruz Salcedo EM, Rodriguez LM, Patel J, Seevaratnam AR. Use of Dexmedetomidine in Early Prone Positioning Combined With High-Flow Nasal Cannula and Non-Invasive Positive Pressure Ventilation in a COVID-19 Positive Patient. *Cureus.* 2020;12:e10430. doi: 10.7759/cureus.10430. PubMed PMID: 33062543; PubMed Central PMCID: PMC7556685.
- 64 Ju T, Lee CC, Chen W-c, Lin H-T. USE OF DEXMEDETOMIDINE IN CRITICALLY ILL PATIENTS RECEIVING NONINVASIVE VENTILATION: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. *Chest.* 2020;158:A577-A. doi: 10.1016/j.chest.2020.08.545. PubMed Central PMID: PMC7548602.
- 65 Senoglu N, Oksuz H, Dogan Z, Yildiz H, Demirkiran H, Ekerbicer H. Sedation during noninvasive mechanical ventilation with dexmedetomidine or midazolam: A randomized, double-blind, prospective study. *Curr Ther Res Clin Exp.* 2010;71:141-53. doi: 10.1016/j.curtheres.2010.06.003. PubMed PMID: 24683260; PubMed Central PMCID: PMC73967280.
- 66 Sorbello M, El-Boghdadly K, Di Giacinto I, Cataldo R, Esposito C, Falchetta S, et al. The Italian coronavirus disease 2019 outbreak: recommendations from clinical practice. *Anaesthesia.* 2020;75:724-32. doi: 10.1111/anae.15049. PubMed PMID: 32221973.
- 67 Meagher D, Adamis D, Timmons S, O'Regan NA, O'Keeffe S, Kennelly S, et al. Developing a guidance resource for managing delirium in patients with COVID-19. *Ir J Psychol Med.* 2021;38:208-13. doi: 10.1017/ipm.2020.71. PubMed PMID: 32460926; PubMed Central PMCID: PMC7520634.
- 68 Andrews LJ, Benken ST. COVID-19: ICU delirium management during SARS-CoV-2 pandemic-pharmacological considerations. *Crit Care.* 2020;24:375. doi: 10.1186/s13054-020-03072-5. PubMed PMID: 32576234; PubMed Central PMCID: PMC7309692.
- 69 Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, Raman R, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med.* 2021;9:239-50. doi: 10.1016/S2213-2600(20)30552-X. PubMed PMID: 33428871; PubMed Central PMCID: PMC7832119.
- 70 Brosnahan SB, Jonkman AH, Kugler MC, Munger JS, Kaufman DA. COVID-19 and Respiratory System Disorders: Current Knowledge, Future Clinical and Translational Research Questions. *Arterioscler Thromb Vasc Biol.* 2020;40:2586-97. doi: 10.1161/ATVBAHA.120.314515. PubMed PMID: 32960072; PubMed Central PMCID: PMC7571846.
- 71 Tagami T, Ong MEH. Extravascular lung water measurements in acute respiratory distress syndrome: why, how, and when? *Curr Opin Crit Care.* 2018;24:209-15. doi: 10.1097/MCC.0000000000000503. PubMed PMID: 29608455; PubMed Central PMCID: PMC6037282.
- 72 Opal SM, van der Poll T. Endothelial barrier dysfunction in septic shock. *J Intern Med.* 2015;277:277-93. doi: 10.1111/joim.12331. PubMed PMID: 25418337.
- 73 Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med.* 2009;37:840-51. doi: 10.1097/CCM.0b013e3181961bff. PubMed PMID: 19237886.
- 74 Lemaitre F, Solas C, Gregoire M, Lagarce L, Elens L, Polard E, et al. Potential drug-drug interactions associated with drugs currently proposed for COVID-19 treatment in patients receiving other treatments. *Fundam Clin Pharmacol.* 2020;34:530-47. doi: 10.1111/fcp.12586. PubMed PMID: 32603486; PubMed Central PMCID: PMC7361515.
- 75 Repesse X, Charron C, Vieillard-Baron A. Acute respiratory distress syndrome: the heart side of the moon. *Curr Opin Crit Care.* 2016;22:38-44. doi: 10.1097/MCC.0000000000000267. PubMed PMID: 26627538.
- 76 Goodlet KJ, Zmarlicka MT, Peckham AM. Drug-drug interactions and clinical considerations with co-administration of anti-retrovirals and psychotropic drugs. *CNS Spectr.* 2019;24:287-312. doi: 10.1017/S109285291800113X. PubMed PMID:

- 30295215.
- 77 Page M, Taylor S. Antiretroviral pharmacology. *Medicine*. 2018;46:287-92. doi: 10.1016/j.mpmed.2018.02.006.
  - 78 Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkowitz C, et al. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med*. 2008;359:677-87. doi: 10.1056/NEJMoa072771. PubMed PMID: 18703470.
  - 79 Long B, Liang SY, Hicks C, Gottlieb M. Just the Facts: What are the roles of oxygen escalation and noninvasive ventilation in COVID-19? *CJEM*. 2020;22:587-90. doi: 10.1017/cem.2020.396. PubMed PMID: 32398183; PubMed Central PMCID: PMC7261965.
  - 80 Roongta R, Ghosh A. Managing rheumatoid arthritis during COVID-19. *Clin Rheumatol*. 2020;39:3237-44. doi: 10.1007/s10067-020-05358-z. PubMed PMID: 32892311; PubMed Central PMCID: PMC7474575.
  - 81 Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. *Crit Care*. 2020;24:28. doi: 10.1186/s13054-020-2738-5. PubMed PMID: 3200806; PubMed Central PMCID: PMC6993481.
  - 82 Thomas P, Baldwin C, Bissett B, Boden I, Gosselink R, Granger CL, et al. Physiotherapy management for COVID-19 in the acute hospital setting: clinical practice recommendations. *J Physiother*. 2020;66:73-82. doi: 10.1016/j.jphys.2020.03.011. PubMed PMID: 32312646; PubMed Central PMCID: PMC7165238.
  - 83 Gampawar N, Surendran P, Jacob P, Karpouzis V, Haneef M, Aleef M, et al. Acute Care Physiotherapy Management of COVID-19 Patients in Qatar: Consensus-Based Recommendations. *Preprints*. 2020. doi: 10.20944/preprints202004.0417.v1.
  - 84 Woyke S, Rauch S, Strohle M, Gatterer H. Modulation of Hb-O<sub>2</sub> affinity to improve hypoxemia in COVID-19 patients. *Clin Nutr*. 2021;40:38-9. doi: 10.1016/j.clnu.2020.04.036. PubMed PMID: 32360083; PubMed Central PMCID: PMC7195129.
  - 85 Retucci M, Aliberti S, Ceruti C, Santambrogio M, Tammaro S, Cuccarini F, et al. Prone and Lateral Positioning in Spontaneously Breathing Patients With COVID-19 Pneumonia Undergoing Noninvasive Helmet CPAP Treatment. *Chest*. 2020;158:2431-5. doi: 10.1016/j.chest.2020.07.006. PubMed PMID: 32679237; PubMed Central PMCID: PMC7361047.
  - 86 Burton-Papp HC, Jackson AIR, Beecham R, Ferrari M, Nasim-Mohi M, Grocott MPW, et al. Conscious prone positioning during non-invasive ventilation in COVID-19 patients: experience from a single centre. *F1000Res*. 2020;9:859. doi: 10.12688/f1000research.25384.1. PubMed PMID: 33110499; PubMed Central PMCID: PMC7578762.
  - 87 Machado C, DeFina PA, Machado Y, Chinchilla M, Cuspineda E, Machado Y. Continuous positive air pressure (CPAP) should be used in all COVID-19 patients when the first and mild respiratory symptoms commence. *J Respir Dis*. 2020;2:1-6. doi: 10.15761/jrdm.1000124.
  - 88 Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. *Respir Res*. 2020;21:198. doi: 10.1186/s12931-020-01462-5. PubMed PMID: 32723327; PubMed Central PMCID: PMC7385717.
  - 89 Radovanovic D, Rizzi M, Pini S, Saad M, Chiumello DA, Santus P. Helmet CPAP to Treat Acute Hypoxemic Respiratory Failure in Patients with COVID-19: A Management Strategy Proposal. *J Clin Med*. 2020;9. doi: 10.3390/jcm9041191. PubMed PMID: 32331217; PubMed Central PMCID: PMC7230457.
  - 90 Turner P, Montgomery H, Stroud M, Grimbale G, Smith T. Malnutrition risk in hospitalised COVID-19 patients receiving CPAP. *Lancet*. 2021;397:1261. doi: 10.1016/S0140-6736(21)00447-5. PubMed PMID: 33743220; PubMed Central PMCID: PMC7969140.
  - 91 Reeves A, White H, Sosnowski K, Tran K, Jones M, Palmer M. Energy and protein intakes of hospitalised patients with acute respiratory failure receiving non-invasive ventilation. *Clin Nutr*. 2014;33:1068-73. doi: 10.1016/j.clnu.2013.11.012. PubMed PMID: 24321188.
  - 92 Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr*. 2020;39:1631-8. doi: 10.1016/j.clnu.2020.03.022. PubMed PMID: 32305181; PubMed Central PMCID: PMC7138149.
  - 93 Singer P. Nutritional and metabolic management of COVID-19 intensive care patients. *Journal of Intensive Medicine*. 2021;1:31-4. doi: 10.1016/j.jointm.2021.01.004. PubMed Central PMID: PMC7919505.
  - 94 Blaser AR, Starkopf J, Kirsimagi U, Deane AM. Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis.

- Acta Anaesthesiol Scand. 2014;58:914-22. doi: 10.1111/aas.12302. PubMed PMID: 24611520.
- 95 Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Crit Care Med. 1999;27:1447-53. doi: 10.1097/00003246-199908000-00006. PubMed PMID: 10470748.
- 96 Arkin N, Krishnan K, Chang MG, Bittner EA. Nutrition in critically ill patients with COVID-19: Challenges and special considerations. Clin Nutr. 2020;39:2327-8. doi: 10.1016/j.clnu.2020.05.007. PubMed PMID: 32425291; PubMed Central PMCID: PMC7227546.
- 97 Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38:48-79. doi: 10.1016/j.clnu.2018.08.037. PubMed PMID: 30348463.
- 98 Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371:1673-84. doi: 10.1056/NEJMoa1409860. PubMed PMID: 25271389.
- 99 Terzi N, Darmon M, Reignier J, Ruckly S, Garrouste-Orgeas M, Lautrette A, et al. Initial nutritional management during noninvasive ventilation and outcomes: a retrospective cohort study. Crit Care. 2017;21:293. doi: 10.1186/s13054-017-1867-y. PubMed PMID: 29187261; PubMed Central PMCID: PMC5707783.
- 100 Kagan I, Hellerman-Itzhaki M, Neuman I, Glass YD, Singer P. Reflux events detected by multichannel bioimpedance smart feeding tube during high flow nasal cannula oxygen therapy and enteral feeding: First case report. J Crit Care. 2020;60:226-9. doi: 10.1016/j.jcrc.2020.08.005. PubMed PMID: 32882605; PubMed Central PMCID: PMC7442574.
- 101 Chapple LS, Fetterplace K, Asrani V, Burrell A, Cheng AC, Collins P, et al. Nutrition management for critically and acutely unwell hospitalised patients with coronavirus disease 2019 (COVID-19) in Australia and New Zealand. Nutr Diet. 2020;77:426-36. doi: 10.1111/1747-0080.12636. PubMed PMID: 32945085; PubMed Central PMCID: PMC7537302.
- 102 National Collaborating Centre for Acute Care (UK). Nutrition Support for Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition. London: National Collaborating Centre for Acute Care (UK); 2006. PubMed PMID: 21309138.
- 103 Singer P, Rattanachaiwong S. To eat or to breathe? The answer is both! Nutritional management during noninvasive ventilation. Crit Care. 2018;22:27. doi: 10.1186/s13054-018-1947-7. PubMed PMID: 29409542; PubMed Central PMCID: PMC5801680.
- 104 Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M, Espen. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28:365-77. doi: 10.1016/j.clnu.2009.03.015. PubMed PMID: 19464090.
- 105 Cintoni M, Rinninella E, Annetta MG, Mele MC. Nutritional management in hospital setting during SARS-CoV-2 pandemic: a real-life experience. Eur J Clin Nutr. 2020;74:846-7. doi: 10.1038/s41430-020-0625-4. PubMed PMID: 32253375; PubMed Central PMCID: PMC7135971.
- 106 Thibault R, Seguin P, Tamion F, Pichard C, Singer P. Nutrition of the COVID-19 patient in the intensive care unit (ICU): a practical guidance. Crit Care. 2020;24:447. doi: 10.1186/s13054-020-03159-z. PubMed PMID: 32684170; PubMed Central PMCID: PMC7369442.
- 107 Li H, Sun SR, Yap JQ, Chen JH, Qian Q. 0.9% saline is neither normal nor physiological. J Zhejiang Univ Sci B. 2016;17:181-7. doi: 10.1631/jzus.B1500201. PubMed PMID: 26984838; PubMed Central PMCID: PMC4794509.