



# Non-pharmacological treatments for COVID-19: current status and consensus

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## Abstract

**Purpose** COVID-19 is a disease caused by SARS-CoV-2 (coronavirus type 2 of the severe acute respiratory syndrome), isolated in China, in December 2019. The strategy currently used by physicians is to control disease and to treat symptoms, including non-pharmacological treatments, as there is still no specific treatment for COVID-19. Thus, the aim of this article is to carry out a systematic review about non-pharmacological treatments used for COVID-19, addressing current status and consensus found in the literature.

**Methods** Three databases were consulted for evidence referring to the drugs indicated for COVID-19 (Cochrane Central, MEDLINE and Embase). The following terms and combinations were used: (“2019-nCoV” OR 2019nCoV OR nCoV2019 OR “nCoV-2019” OR “COVID-19” OR COVID19 OR “HCoV-19” OR HCoV19 OR CoV OR “2019 novel\*” OR Ncov OR “n-cov” OR “SARS-CoV-2” OR “SARSCoV-2” OR “SARSCoV2” OR “SARSCoV2” OR SARSCov19 OR “SARS-Cov19” OR “SARS-Cov-19”) OR “severe acute respiratory syndrome\*” OR ((corona\* OR corono\*) AND (virus\* OR viral\* OR virinae\*)) AND (“lung injury”) OR (“ventilation use”) OR (“respiratory injuries” OR prone)) AND (treatment)) NOT Drugs NOT medicines NOT antivirals.

**Results** A total of 28 articles were selected. These articles adopted one or more treatment methods for patients with severe cases of COVID-19, i.e., oxygen therapy, prone position, inhaled nitric oxide, intravenous infusion, passive immunotherapy, mesenchymal stem cells (MSC).

**Conclusion** There is still no specific treatment approved for patients with COVID-19. The available evidence is not able yet to indicate the benefits or harms of non-pharmacological treatments, but some studies show that some treatments can play an important role in relation to COVID-19. The current consensus among researchers is that several studies using a randomized clinical trial should be carried out to provide evidence of safety and efficacy of the proposed treatments.

**Keywords** Pandemic · COVID-19 · SARS-CoV-2 · Treatment

## Introduction

The World Health Organization (WHO), on March 11, 2020, decreed the pandemic by COVID-19 (corona virus disease) (WHO 2020c). This is an infectious disease caused by a coronavirus called SARS-CoV-2 (severe acute respiratory syndrome–corona virus) (WHO 2020a). Seven coronaviruses are known to cause human disease, three of which can cause severe respiratory syndromes (SARS-CoV, MERS-CoV, and SARS-CoV-2), while others usually cause mild symptoms

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such as common cold and diarrhea (HCoV-229E, HCoV-OC43, HCoV-HKU1, and HCoV-NL63) (Ye et al. 2020).

SARS was the first major pandemic caused by the coronavirus. The virus was transmitted to humans by animals, because in China there is a growing demand for animal protein in Chinese cuisine, including exotic animals such as civets. In addition to this, the lack of biosecurity measures in the Chinese markets, allowed the contamination of SARS-CoV, present in civets, by humans. During the epidemic in 2003, 8096 cases with 774 deaths occurred in more than 30 countries in five continents (Cheng et al. 2007). Subsequently to SARS-CoV contamination, many cases of the disease caused by the MERS-CoV virus (Middle East respiratory syndrome corona virus) were detected, which originated in the Arabian Peninsula in September 2012, and by November 2019, 2494 people were infected with a mortality rate of 37.1%. Outbreaks have occurred mainly in Saudi Arabia and South Korea (Farooq et al. 2020).

The first cases of COVID-19 were detected in December 2019 in Wuhan, Hubei province, China. Patients with pneumonia were diagnosed with SARS-CoV-2 infection. On March 3, 2020, the World Health Organization declared a Public Health Emergency of International Interest and also called it COVID-19 disease. At this stage of the pandemic, the mortality rate was 3.4%, with an incubation period of 3 to 6 days (Ye et al. 2020). Due to the similarity of the pangolin coronavirus to SARS-CoV-2, several authors suggest that the infection in humans may have occurred through contact with these animals, which would be the intermediate hosts (Lam et al. 2020).

These diseases have the common characteristic of transmission by airborne saliva droplets, which are spread when sneezing or coughing (Ye et al. 2020). Most people will be infected and experience mild to moderate form of respiratory disease and recover without the need for medical treatment. However, the elderly and people with comorbidities, such as cardiovascular disease, diabetes, chronic respiratory diseases or cancer, are more likely to develop the most severe form of the disease (WHO 2020a).

When a person has direct contact with someone who has been shown to be symptomatic, or with mild signs, occurring in more than 80% of cases, the recommendation is to stay in social isolation (predominant and exclusive stay in your own house), initially for 14 days and adopt respiratory and contact precautions (BRASIL 2020c). These precautions include avoiding contact with people with COVID-19, avoid touching the eyes, nose and mouth with unwashed hands and frequently washing hands with soap and water (BRASIL 2020c).

The mildest symptoms are usually fever, dry cough, sore throat and runny nose. The use of painkillers and antipyretics can control the temperature and relieve symptoms of general malaise. However, when dealing with serious cases, healthcare should be seek in specialized environments and

health units for adequate isolation of suspected cases and monitoring vital signs, such as blood oxygen saturation (SaO<sub>2</sub>). Approximately 20% of COVID-19 cases can get worse and part of these cases requires respiratory support through non-invasive mechanical ventilation or invasive mechanical ventilation, due to severe pulmonary inflammation. In addition, the drug therapies that are been used now, had been tried and tested in other diseases, such as MERS-CoV and SARS-CoV (Li et al. 2020a).

In Brazil, the first case of disease caused by the new coronavirus was confirmed on 26 February 2020, and it is also the first case in Latin America. By 10 November 2020, Brazil had registered more than 6,087,608 cases of COVID-19, with more than 169,485 deaths registered. The SARS-CoV-2 virus has a high rate of transmissibility and, in Brazil, the lethality rate is almost 3% (BRASIL 2020a).

Due to limitations in relation to the knowledge of the disease, the lack of a vaccine, the lack of medication, despite ongoing tests with various vaccines and drugs, there are still no specific treatments for COVID-19 (SARS-CoV-2). The WHO and the Ministry of Health in Brazil (MH) continue to provide updated information on clinical findings. Many of the symptoms can be treated based on the patient's clinical condition, this being, for now, the strategy of health professionals, that is, basically controlling the disease and treating the symptoms while the body itself heals the infection, with the help of supportive treatment (BRASIL 2020b).

Currently, several pharmacological treatments for COVID-19 are being proposed; these include antivirals previously used for other diseases (Liu et al. 2020), corticosteroids, besides the generic viral treatments such as vitamin C, zinc, and selenium (Juul et al. 2020; Singh et al. 2020). However, some non-pharmacological interventions are also being proposed in the world, mainly in order to prevent the contamination and spread of COVID-19. These measures include social distance, washing hands with soap and water, using masks, cleaning with 70% alcohol, closing schools and banning crowds, among others. In addition, non-pharmacological treatments, related to supportive therapies, such as oxygenation, have been used.

In addition to preventive interventions and supportive therapies for COVID-19, there are other types of non-pharmacological interventions being proposed worldwide. Thus, it is important to know the current status of non-pharmacological treatments; these treatments must be synthesized based on evidence, to guide health managers, mainly for the creation of recommendations for the population. Considering the presented data, this systematic review aims to present some of the non-pharmacological treatments used for therapy of patients with COVID-19, including supportive treatments, and through these studies, to show the current status, as well as the consensus among researchers and to disseminate knowledge of the techniques used as more

effective responses to the health emergency caused by the SARS-CoV-2 pandemic in Brazil.

## Methods

This systematic review was developed according to the Preferred Reporting Items Method for Systematic Reviews and Meta-Analysis (PRISMA-P) (Moher et al. 2016). Our team is compound by Doctors and Biomedical Engineers to ensure expertise in a number of areas.

### Study design

It is a protocol for the systematic review of retrospective and prospective studies, following the guidelines of PRISMA-P. The entire study selection process was carried out by six reviewers and summarized in a PRISMA flow diagram (Fig. 1).

### Inclusion/exclusion criteria

Eligible articles accounted for studies with respiratory diseases support treatments, including MERS and SARS, but focused on COVID-19. Due to the lack of randomized controlled trials, the authors also included epidemiological studies, cross-sectional studies, case studies, clinical observations, health organ reports, prospective cohort, case-control studies, systematic reviews, meta-analyzes and non-randomized studies associated with COVID-19. The research included Portuguese and English languages and was limited to articles published in 2020. A bibliographic review was conducted between March and November, 2020.

### Search sources

Three databases were consulted for evidence referring to the non-pharmacological treatments indicated for COVID-19 (Cochrane Central, MEDLINE and Embase) (Singh et al. 2020). For this systematic review, the following terms and combinations were used (Singh et al. 2020).

((“2019-nCoV” OR 2019nCoV OR nCoV2019 OR “nCoV-2019” OR “COVID-19” OR COVID19 OR “HCoV-19” OR HCoV19 OR CoV OR “2019 novel\*” OR Ncov OR “n-cov” OR “SARS-CoV-2” OR “SARSCoV-2” OR “SARSCoV2” OR “SARSCoV2” OR SARSCov19 OR “SARS-Cov19” OR “SARS-Cov-19”) OR “severe acute respiratory syndrome\*” OR ((corona\* OR corono\*) AND (virus\* OR viral\* OR virinae\*)) AND (“lung injury”) OR (“ventilation use”) OR (“respiratory injuries” OR prone)) AND (treatment) NOT Drugs NOT medicines NOT antivirals.

## Non-pharmacological treatments, interventions, and outcome included

Our criteria of inclusion of non-pharmacological treatments and outcomes were unrestricted, however, specific to treatments on COVID-19.

### Selection

Four authors (AAP, AOA, FPS, and STM) independently analyzed the titles and abstracts of the studies identified by the research strategy and confirmed the existing duplicates to remove them. Eligible studies were reassessed by reading the full text to compose this systematic review. In case of disagreement on the chosen articles, the opinion of a fifth examiner was requested. However, no study required consultation for a fifth reviewer.

The flowchart in Fig. 1 shows the study selection process.

### Data collection

Two authors (JFVG and VHFM) extracted data from the selected studies and two others (MRB and LCM) verified the accuracy and fidelity of the data presented and a fifth examiner resolved the existing disagreements. However, no study required consultation for a fifth reviewer.

### Assessment of bias quality and risk of included studies

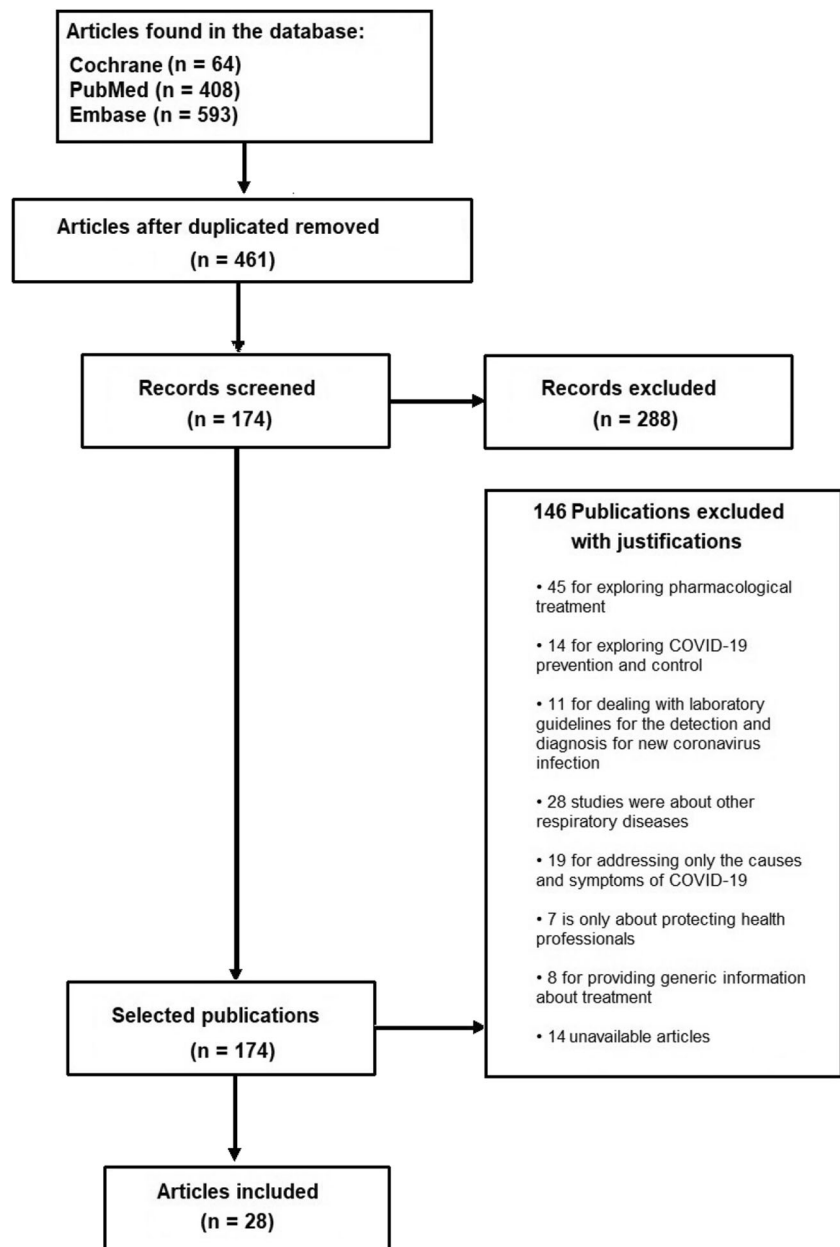
No methodological quality assessment tools have been used for this study, given that the results of studies on the effects of the SARS-CoV-2 pandemic are still preliminary, given the recent and abrupt global impact of this health emergency on public health services, it is currently not possible to assess the methodological quality of studies (Juil et al. 2020). Notwithstanding, the following items were analyzed:

- All articles that presented treatment non-pharmacological, but COVID-19 were not the main focus of the study were excluded.
- All articles that caused doubts about the inclusion in this systematic review were re-analyzed for relevance.
- Studies with failure to follow up above 10% were excluded.

## Results

The research in the databases resulted in a total of 1065 articles that had in their titles, or in the keywords, the search terms. Duplicates were disregarded and 461 articles remained.

**Fig. 1** Flowchart of the search process



After analyzing the titles and abstracts, 174 articles were selected.

After reading the full text of these 174 articles, a total of 146 were excluded, with 45 for exploring pharmacological treatment, 14 for exploring COVID-19 prevention and control, 11 for dealing with laboratory guidelines for the detection and diagnosis for new coronavirus infection, 28 studies were about other respiratory diseases, 19 for addressing only the causes and symptoms of COVID-19, 7 is about protecting health professionals, 8 for providing generic information about treatment and 14 unavailable articles.

Therefore, 28 articles were eligible to compose this systematic review, which present one or more supportive

treatment methods that are being used experimentally in other countries to fight the COVID-19 pandemic. The studies were grouped according to the used methods, as shown in Table 1.

## Discussion

Supportive treatment continues to be the main means used by health professionals to relieve the symptoms of people infected with SARS-CoV-2 and in need of care in health facilities, as there are no drugs or vaccines tested and approved for the treatment and prevention of COVID-19. Supportive treatments are the same as those applied

**Table 1** Studies included in the systematic review

Authors	Study design	Supporting treatment	Limitations
<b>Oxygen therapy</b>			
Arabi et al. (2020)	Narrative review	Nasal cannula, extracorporeal membrane oxygenation (ECMO), Prone position (PP), invasive ventilation, high-frequency oscillatory ventilation (HFOV), non-invasive ventilation	<ul style="list-style-type: none"> <li>• Study design</li> <li>• Indirect evidence</li> <li>• No blind</li> </ul>
Barrasa et al. (2020)	Cohort	Invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO), high-flow nasal cannula (HFNC)	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Guenancia et al. (2020)	Case series	High-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP)	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
De Carvalho et al. (2020)	Recommendations	Nasal prongs/reservoir mask, high-flow nasal cannula (HFNC), positive airway pressure (CPAP)/bilevel positive airway pressure (BiPAP), mechanical ventilation, prone position (PP), high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO)	<ul style="list-style-type: none"> <li>• Indirect evidence</li> <li>• Study design</li> <li>• Sample size</li> <li>• No blind</li> </ul>
Guo et al. (2020)	Systematic review	Nasal cannula, extracorporeal membrane oxygenation (ECMO)	<ul style="list-style-type: none"> <li>• Indirect evidence</li> <li>• No blind</li> </ul>
Rajdev et al. (2020)	Case report	Extracorporeal membrane oxygenation (ECMO)	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Riera et al. (2020)	Case series	Extracorporeal membrane oxygenation (ECMO)	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Robba et al. (2020)	Narrative review	Extracorporeal membrane oxygenation (ECMO), non-invasive ventilation (NIV), high-flow nasal oxygen (HFNO), mechanical ventilation	<ul style="list-style-type: none"> <li>• Study design</li> <li>• Indirect evidence</li> <li>• No blind</li> </ul>
Singhal (2020)	Narrative review	Nasal cannula, non-invasive ventilation (NIV)	<ul style="list-style-type: none"> <li>• Study design</li> <li>• Quality of primary studies</li> <li>• Indirect evidence</li> <li>• No blind</li> </ul>
<b>Prone position</b>			
Bastoni et al. (2020)	Case series	Prone position (PP)	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• Incomplete study</li> <li>• No blind</li> </ul>
Damarla et al. (2020)	Case series	Prone position (PP)	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Garcia et al. (2020)	Case series	Prone position (PP)	<ul style="list-style-type: none"> <li>• Study design</li> <li>• No blind</li> </ul>
Laverdure et al. (2020)	Cohort	Prone position (PP)	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Lee et al. (2020)	Case series	Prone position (PP)	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Makic (2020)	Narrative review	Prone position (PP)	<ul style="list-style-type: none"> <li>• Study design</li> <li>• Indirect evidence</li> <li>• No blind</li> </ul>

**Table 1** (continued)

Authors	Study design	Supporting treatment	Limitations
Shelhamer et al. (2020)	Cohort	Prone position (PP)	<ul style="list-style-type: none"> <li>• Not randomized</li> <li>• No blind</li> </ul>
Vibert et al. (2011)	Case report	Prone position (PP)	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Intravenous infusion			
Chen et al. (2020)	Case series	Intravenous infusion	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Li et al. (2020b)	Clinical observation	Intravenous infusion, extracorporeal membrane oxygenation (ECMO), invasive ventilation, non-invasive ventilation (NIV)	<ul style="list-style-type: none"> <li>• Study design</li> <li>• Number of primary studies</li> <li>• Indirect evidence</li> <li>• No blind</li> </ul>
Inhaled nitric oxide			
Ferrari et al. (2020)	Case report	Inhaled nitric oxide	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Longobardo et al. (2020)	Cohort	Inhaled nitric oxide	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Passive immunotherapy			
Alharthy et al. (2020)	Case series	Passive immunotherapy	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Islam et al. (2020)	Correspondence	Passive immunotherapy	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Joyner et al. (2020)	Case report	Passive immunotherapy	<ul style="list-style-type: none"> <li>• Study design</li> <li>• No blind</li> </ul>
Piechotta et al. (2020)	Systematic review	Passive immunotherapy	<ul style="list-style-type: none"> <li>• Quality of primary studies</li> <li>• No blind</li> </ul>
Shanmugaraj et al. (2020)	Systematic review	Passive immunotherapy.	<ul style="list-style-type: none"> <li>• Indirect evidence</li> <li>• No blind</li> </ul>
Olivares-Gazca et al. (2020)	Case series	Passive immunotherapy	<ul style="list-style-type: none"> <li>• Sample size</li> <li>• Study design</li> <li>• No blind</li> </ul>
Mesenchymal stem cells			
Al-Khawaga and Abdelalim (2020)	Systematic review	Mesenchymal stem cells	<ul style="list-style-type: none"> <li>• Quality of primary studies</li> <li>• Number of primary studies</li> <li>• No blind</li> </ul>

to people with acute respiratory distress syndrome (ARDS) in the absence of specific treatment for COVID-19. In the examined data sources, six supporting

treatments were found (oxygen therapy, prone position, inhaled nitric oxide, intravenous infusion, passive immunotherapy, mesenchymal stem cells (MSC)).



## Oxygen therapy

Oxygen therapy should be used for the treatment of hypoxemia. Hypoxemia is characterized as an  $O_2$  concentration below the normal range of 85 to 100 mmHg in arterial blood. Hypoxemia is defined by the British Thoracic Society as  $PaO_2 < 60$  mmHg or  $SaO_2 < 90\%$  (Al-Shaqsi and Brockway 2013).

Oxygen therapy is used as an alternative to relief of respiratory symptoms caused by COVID-19. It is recommended for respiratory and symptomatic support. Hypoxemic patients should receive oxygen therapy immediately and maintain a blood oxygen saturation level ( $SaO_2$ ) of at least 90% (in pregnant women, saturation should be between 92 and 95%) (Li et al. 2020b). The Ministry of Health recommends oxygen therapy in patients with severe acute respiratory syndrome and breathing difficulties, hypoxemia or shock (BRASIL 2020c).

## Invasive ventilation

Invasive ventilatory support is “positive pressure ventilation applied through an endotracheal or tracheostomy tube” (Buckley and Gillham 2007). According to current evidence, to improve symptoms caused by SARS-CoV-2, patients with ARDS due to respiratory viral infections (RVI) should be treated with invasive ventilation as a pulmonary protection strategy with low tidal volumes (6 mL/kg of predicted body weight) and plateau pressure  $< 30$  to 35 cmH<sub>2</sub>O (Arabi et al. 2020; BRASIL 2020c).

Evidence from meta-analysis studies shows that higher levels of positive end-expiratory pressure (PEEP) are associated with better survival among the subgroup of patients with ARDS (defined by  $PaO_2/FiO_2 \leq 200$  mmHg) (Xu et al. 2020). Titration of PEEP to obtain optimal oxygenation, possibly without aggressive recruitment maneuvers, remains a reasonable strategy for most patients (Arabi et al. 2020).

It is noteworthy that endotracheal intubation must be performed by an experienced physician, using personal protective equipment (PPE) (Li et al. 2020b).

## High-flow nasal cannula

Adequate tissue oxygenation must be maintained in patients with acute respiratory failure (ARF) and oxygen supplementation is essential for this. The high-flow nasal cannula is a new air supply device capable of delivering up to 100% oxygen. The nasal cannula improves the clinical condition of patients with ARF in intensive care units (ICUs) and emergency departments (Kang et al. 2015).

The high-flow nasal cannula has been indicated for patients with COVID-19 as a way to prevent intubation in patients who have respiratory arrest with acute hypoxemia (Arabi et al. 2020; Singhal 2020). Patients with mild hypoxemia

should be placed in a nasal cannula with a flow rate of 5 L/min. If the patient’s condition worsens, the high-flow nasal cannula should be considered, starting with 20 L/min and gradually increasing to 50–60 L/min. The oxygen fraction must be adjusted according to  $SaO_2$  (Guo et al. 2020).

The purpose of the article of Barrasa et al. (2020) was to report the epidemiology of the first patients with COVID-19 hospitalized in ICUs in the city of Vitoria in Spain. The study consisted of 48 patients, 3 received high-flow nasal therapy (HFNT) and 45 underwent intubation. The seven-day mortality of patients who required intubation was less than 15%. And after 15 days of admission to the ICU, half of the patients remained intubated and 33% died. The authors conclude that a properly implemented oxygenation strategy could save lives.

Robba et al. (2020) undertook a systematic review aimed at providing guidance on respiratory management for patients with COVID-19. The author’s hypothesis is that respiratory management should be customized according to the phenotype presented by the patient, which can be divided into three distinct types: (1) good compliance, but severe hypoxemia; (2) atelectasis and derecruitment are predominant; and (3) typical computed tomography (CT) pattern of moderate-to-severe ARDS, with alveolar edema and low compliance. The authors argue that high-flow nasal cannula (HFNC) should be used preferentially in relation to non-invasive oxygenation (NIO), as it reduces the risk of intubation. In addition, the risk of viral contamination by NIO is higher. Regarding ventilatory strategies, the authors consider that for the type phenotype moderate levels of PEEP should be used, for patients with type 2 phenotype the approach should be moderate to high levels of PEEP and for patients with type 3 phenotype should be applied the general principles used for ARDS.

## Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is characterized as a way of replacement cardiopulmonary support. Its operating mechanism consists of draining blood from the vascular system, using a mechanical pump, causing it to circulate outside the body. At this time, a membrane allows  $O_2$  to enter, hemoglobin becomes saturated with oxygen and  $CO_2$  is removed. Then, the blood is reinfused into the body’s circulation. The flow rate through the membrane determines oxygenation and  $CO_2$  elimination and can be controlled by adjusting the countercurrent gas through the oxygenator (Schmidt et al. 2013). The ECMO technique is indicated in three cases: respiratory support, cardiac support and cardiorespiratory support. This method has its application defined for adult, pediatric and neonatal patients (Extracorporeal Life Support Organization 2020).

Some authors claim that ECMO is associated with better results when used in patients with limited organic failure and good pre-morbid functional status. The use of ECMO can be

considered in patients who do not improve with the use of other strategies to support oxygenation, considering the individual characteristics of the patient as well as the risk-benefit ratio of the decision to use the intervention (Arabi et al. 2020). ECMO is recommended for patients who have the most severe acute respiratory distress syndrome (ARDS) (Li et al. 2020b). In addition, ECMO can also be used in patients with refractory hypoxemia, as long as it is performed in centers with experience in handling ECMO, these recommendations were reinforced by the WHO (Guo et al. 2020).

The use of ECMO is highly indicated in patients who are at high risk of death, if there is ARF and any of the following conditions are found, PaO<sub>2</sub>/FiO<sub>2</sub> below 80 mmHg for more than 6 h; PaO<sub>2</sub>/FiO<sub>2</sub> less than 50 mmHg for more than 3 h; and pH < 7.25 with PaCO<sub>2</sub> > 60 mmHg for more than 6 h (Extracorporeal Life Support Organization 2020).

Riera et al. (2020) conducted a case series study to assess the performance of the ECMO group. Nineteen patients diagnosed with COVID-19 were analyzed. The patients were transferred to the ICU of the University Vall d'Hebron Hospital, after cannulation in the hospitals of origin. The adverse effects presented were the following: 1 patient presented pulseless electrical activity (PEA) during transport; 9 patients had thrombotic events during extracorporeal membrane oxygenation and 13 patients had hemorrhagic events. The results showed that 12 patients were discharged from the hospital and 4 patients died. The authors concluded that recovery from extracorporeal membrane oxygenation can rescue healthy young patients with severe COVID-19 disease.

In a case study conducted by Rajdev et al. (2020), a 32-year-old man diagnosed with COVID-19, with a history of diabetes mellitus, was intubated due to SARS, but was not improving his hypoxemia. The patient was evaluated by a multidisciplinary team, which decided to start using the ECMO. The patient was decannulated after 17 days and was discharged after 47 days of hospitalization without supplemental oxygen. The authors suggest that using ECMO in the correct phenotype and in specialized centers can lead to positive results. In addition, young patients with less comorbidity have a better prognosis when using ECMO.

### High-frequency oscillatory ventilation

High-frequency oscillatory ventilation (HFOV) is characterized by being a form of respiratory therapy at very high rates. Higher frequencies result in lower tidal volumes and decrease the amplitude of alveolar pressure oscillations. The efficiency provided by HFOV is due to the change in the distribution dynamics of the gas flow in relation to conventional ventilation. This mechanical ventilation technique has alternative mechanisms for the gas exchange process, such as molecular diffusion, Taylor dispersion, turbulence, asymmetric velocity profiles, among others (Pillow 2005).

HFOV has been used as a rescue therapy for patients who do not respond to conventional ventilation. However, a meta-analysis with 1552 patients (55% with pneumonia) found that the effect of treatment with HFOV depended on the baseline severity of hypoxemia with damage among patients with mild to moderate ARDS, but possibly decreased mortality in patients with very severe ARDS (Arabi et al. 2020).

This treatment is possibly not used extensively for patients with COVID-19, because articles were searched in complementary databases and additional and specific articles about COVID-19 were not found.

### Non-invasive ventilation

Non-invasive ventilation (NIV) is a ventilatory support technique and, as its name indicates, does not use invasive methods, avoiding complications associated with orotracheal intubation. Thus, non-invasive pressure ventilation contributes to the preservation of airway defenses, speech and swallowing functions and prevention of airway trauma (Pamidi and Mokhlesi 2012).

The two main types of NIV are positive pressure and negative pressure. The use of positive pressure is aimed at directly inflating the lungs. Negative pressure is applied to the abdomen and chest in order to draw air into the lungs through the upper airways. The mode most used in intensive care units (ICU) is the positive pressure model (Pardo 2007). In this type of respiratory therapy, a mask, nasal or facial, is used as an interface between the patient and the mechanical ventilator (Pardo 2007). Face masks have a better seal, however, they are considered less comfortable than nasal masks. In addition, sealed helmets and tents have been widely used, as they create a positive pressure environment, making the patient more comfortable (Pardo 2007).

For patients with COVID-19, NIV has been recommended for patients in the early stages of the disease and for those who have milder forms of acute hypoxemic respiratory failure, present immunosuppression or cardiovascular problems (BRASIL 2020c; Singhal 2020), excluding cases in shock or multiple organ failure. Since, for patients who do not show signs of early recovery, NIV can delay, but not prevent invasive ventilation (Arabi et al. 2020). In addition, the use of NIV is recommended only for patients who can tolerate it (Li et al. 2020a, 2020b). If there is no response to NIV, the Ministry of Health recommends endotracheal intubation (BRASIL 2020c).

De Carvalho et al. (2020) provided ventilatory support guidance for children with COVID-19. They divided the disease into levels: mild respiratory diseases, severe hypoxemia and moderate cases. According to the levels, the suggested strategy is nasal prongs/reservoir mask, HFNC and continuous positive airway pressure (CPAP)/bilevel positive airway pressure (BiPAP) respectively. The authors conclude that



COVID-19 may behave similarly to ARDS, but the pathology is different and cannot be treated in the same way.

Guenancia et al. (2020) conducted a series case study, carried out in France, which describes the implementation of a non-invasive oxygenation support for 17 patients with COVID-19 in a unit called respiratory intermediate care (RICU) to implement non-invasive oxygenation (NIO). The NIO used were the HFNC and the continuous positive airway pressure (CPAP). This unit was created due to the lack of beds and fans in the ICUs. The results showed an average length of hospital stay of 7 days. And a mortality rate of 18%. The authors concluded that the use of NIO support techniques may be beneficial in the initial treatment of the acute respiratory distress syndrome associated with SARS-CoV-2.

### Prone position

Historically, the prone position has been proposed as unconventional therapy for life-threatening refractory hypoxemia. The prone position explores the severity and repositioning of the heart in the chest to recruit pulmonary alveoli, improving ventilation perfusion (Fanelli et al. 2013).

A multicentre randomized clinical trial ( $n = 474$ , 60% of patients with pneumonia) demonstrated that the early application of the prone position (at least 16 h per session) in patients with severe ARDS ( $\text{PaO}_2/\text{FiO}_2 < 150$  mmHg, with  $\text{FiO}_2 \geq 0.6$ ,  $\text{PEEP} \geq 5$  cmH<sub>2</sub>O, and tidal volume close to 6 mL/kg of predicted body weight) resulted in decreased mortality (Arabi et al. 2020). The prone position applied to patients with severe ARDS, related to avian disease A (H7N9), was associated with an improvement in oxygenation, sustained after returning to the supine position and with a reduction in carbon dioxide retention (Arabi et al. 2020).

Bastoni et al. (2020) reports a series case study with 10 patients diagnosed with COVID-19 who non-invasive oxygenation was administered with continuous positive airway pressure (CPAP) for acute respiratory failure, performed in Piacenza, Italy. These patients were referred to the emergency unit due to lack of places in the local ICU. The prone position was performed on 6 patients out of 10 candidates, the reasons related to the non-participation of the 4 patients was due to problems with the patients and not with the prone position technique. Subsequently, the 6 patients were transferred to the ICU, of which one died. Among the 4 patients in whom the prone position cannot be performed, 3 patients died. However, the results showed no difference in lung ultrasound after 1 h of the patient in the prone position. Despite the result, the authors suggest that the prone position is an option for patients who do not respond to non-invasive oxygenation in the absence of ICU beds.

Shelhamer et al. (2020) sought to verify whether patients on mechanical ventilation with moderate-to-severe ARDS undergoing standardized prone positioning had lower mortality

and improved intrapersonal physiological changes. The authors conducted a cohort study in New York City with 335 intubated and mechanically ventilated patients. Sixty-two patients were submitted to prone position and 199 served as a control, 74 patients were excluded. The effects were evaluated between days 1–3 and 4–7. The results showed that there was a decrease with significant difference in mortality related to prone positioning during days 1–3 ( $p < 0.01$ ) and physiological parameters during days 4–7.

Vibert et al. (2011) observed a 21-year-old pregnant woman diagnosed with COVID-19 on her admission to the hospital. The patient was hospitalized and on the tenth day of hospitalization, the administration of high-flow nasal oxygen (HFNO) was started due to decreased oxygen saturation. On the eleventh day, the patient's respiratory condition worsened and she was referred to the ICU where the patient underwent positional therapy, staying in the prone position, improving her respiratory status. After 5 days in the ICU, the patient returned to the obstetrics department, being discharged on the twenty-fourth day after admission.

Laverdure et al. (2020) conducted a cohort study with 36 patients diagnosed with COVID-19 and with ARDS requiring invasive mechanical ventilation. Patients were divided into two groups: low and high static compliance of the respiratory system. Positional therapy (prone position) was administered to 29 patients in which the  $\text{PaO}_2/\text{FiO}_2$  rate dropped below 150. In their conclusion, the authors suggest the use of established therapies for the treatment of ARDS to treat patients with COVID-19 and ARDS, including the prone position.

Garcia et al. (2020) performed a retrospective study among patients with ARDS due to SARS-CoV-2 submitted to prone position (PP) during veno-venous extracorporeal membrane oxygenation (VV-ECMO). The aim of the study was to describe the parameters of mechanical ventilation and gas exchange before and after the prone position. The study evaluated the safety of PP and compared patients with PP maintained with ECMO (prone ECMO group) to patients maintained in the supine position (supine ECMO group). A total of 208 patients with COVID-19 were part of the study, 125 patients with ARDS, of which 25 were submitted to VV-ECMO. Of these 25 patients under VV-ECMO, 14 were positioned at least once in the prone position, with a total of 24 procedures with an average duration of 16 h. The authors reported that patients in the prone ECMO group were less likely to be removed from ECMO, and the 28-day mortality rate was significantly higher (78.6%). In conclusion, the authors state that PP under VV-ECMO improves the oxygenation of patients with ARDS due to COVID-19 without compromising patient safety. The high mortality rate in patients placed in the prone position and with ECMO can be justified by the greater severity of the disease and the absence of immunomodulatory therapy, such as corticosteroids.

Makic (2020) carried out a systematic review on prone positioning (PP) in patients with COVID-19 and ARDS

showing in its conclusion implications for the practice of PP. As conclusion, it is stated that PP for hypoxemic respiratory failure and ARDS is part of an essential and standardized therapeutic intervention for the management of ARDS. The authors finish the study by reporting that the evidence of the use of PP in the beginning of ARDS care indicates improved patient survival, and that knowledge, skill and competence for critical care professionals are essential for implementing this intervention in patients with moderate-to-severe ARDS.

Damarla et al. (2020) performed a retrospective review (case series) of their experiences with the prone position in patients with COVID-19 and non-intubated. The study was carried out from March to April 2020 with nine adult patients at an academic medical center diagnosed with COVID-19, with a rapid increase in the need for oxygen and admission to the ICU, but still not requiring intubation, thus being suitable for prone positioning (PP). A patient, who was consulted at the ICU due to increased respiratory work, was also included. During the day, patients were asked to alternate between the prone and supine position every 2 h, and at night they were asked to sleep in the prone position, as long as it was bearable for the patient. All patients were followed up for 28 days until discharge status. As result, the authors describe that 1 h after PP, oxygenation improved rapidly, with median oxygen saturations going from 94 to 98%. After PP, work of breathing also improved and the average respiratory rate decreased from 31 breaths/min to 22 breaths/min. There were no adverse events in patients with PP and there was an improvement in dyspnea. Among the 10 patients who took part in the study, seven did not require escalation of respiratory care and eight did not need to be intubated. The two patients who required intubation were intubated after 24 h of PP. After 28 days, all patients were discharged from the hospital. As limitations to this series case study, the authors cite the possibility of bias in patient selection, absence of the control group, small sample, uncertainty that patients would have improved without PP. According to the article, despite the favorable change after 1 h of PP, after PP no dyspnea measurements were collected, data on patients' adherence to PP were collected only in the first episode of pronation to avoid overload of the nursing team.

In a number of cases, Lee et al. (2020) retrospectively reviewed 20 patients with ARDS COVID-19 from the National Center of Infectious Diseases (NCID) intensive care unit (ICU) from February 8 to March 29, 2020. All patients were diagnosed with moderate-to-severe ARDS and evidence of insufficiency ventilation, being placed on invasive mechanical ventilation. Among the 20 patients, seven were placed in pronation. Five patients were placed on PP with 72 h of endotracheal intubation and the remaining two patients on the seventh and eighth day. After 2 h of PP there was a significant improvement in oxygenation. An average of 3 sessions of PP per patient was used, with an average duration of 16.2 h. One of the patients had pre-existing asthma and the  $\text{PaO}_2/\text{FiO}_2$  ratio remained low despite PP and showed no improvement

even after undergoing two additional sessions of PP before being subjected to ECMO. Two patients died, one due to multiple organ failure and the second due to intracranial bleeding complications after ECMO. The authors emphasize the care with the team to minimize the fatigue of the professionals, as well as evidence that all professionals used personal protective equipment level 2. Pillows were used as support to protect the chest and pelvis and gel pads were used to prevent ulcers by pressure at the points with the highest pressure. The authors conclude that there was a strong improvement in patients with ARDS due to COVID-19 who were early and repeatedly placed on PP, in addition to minimal occurrence of adverse events. As a limitation of the study, they cite the small sample and suggest that further studies be carried out to validate proposed threshold and identify variations in response to treatment.

### Inhaled nitric oxide

Like HFOV, inhaled nitric oxide does not appear to be used extensively for patients with COVID-19, because articles were searched in complementary databases and additional and specific articles about COVID-19 were not found and, mainly, in some articles their use was not indicated.

Ferrari et al. (2020) describe in their study the response to inhaled nitric oxide (INO) in 10 critically ill patients due to COVID-19 exposed to mechanical ventilation. The effect of inhaled nitric oxide would be to dilate blood vessels in the region of ventilation. The authors concluded that the administration of inhaled nitric oxide did not show a significant improvement in relation to artery oxygenation.

Longobardo et al. (2020) conducted a cohort study with 99 patients diagnosed with COVID-19 and ARDS and with 91 patients admitted with ARDS not caused by COVID-19. A comparison was made between 27 patients diagnosed with COVID-19 and ARDS and 20 patients with ARDS not caused by COVID-19 and the two groups were administered inhaled nitric oxide (INO). The time between hospital admission and administration of INO, age, and  $\text{PaO}_2/\text{FiO}_2$  rate was similar between groups. The results showed that the increase in the  $\text{PaO}_2/\text{FiO}_2$  rate was lower in the group of patients diagnosed with COVID-19 and with ARDS. However, in patients in the group diagnosed with COVID-19 and ARDS, where thrombosis was limited, the  $\text{PaO}_2/\text{FiO}_2$  rate was increased after INO application. The authors conclude that the response in relation to the  $\text{PaO}_2/\text{FiO}_2$  rate was much lower in the group of patients diagnosed with COVID-19 and ARDS.

### Intravenous infusion

Currently, up to 80% of hospitalized patients receive intravenous therapy at some point during admission. This therapy allows the administration of medications, fluids, parenteral

nutrition and blood products via the peripheral or central intravenous route, through a catheter (Waitt and Waitt 2004).

The early intravenous infusion of immunoglobulin has been used as one of the supportive treatments for patients of COVID-19, being recommended for critically ill patients, as it increases the ability to fight infection (Li et al. 2020b).

Some studies have used immunoglobulin concomitantly with low molecular weight heparin anticoagulation therapy. However, this use was not recommended, as it presented some abnormalities (Chen et al. 2020).

Studies are still incipient for intravenous infusion, with some limitations, such as tests on a few confirmed patients with COVID-19 and reports based only on professional experiences (Li et al. 2020b).

### Passive immunotherapy

Treatment with intravenous immunoglobulin (IgIV) was introduced in the 1950s as a replacement therapy for patients with congenital antibody deficiency (Boros et al. 2005). The technique of IgIV therapy consists of extracting antibodies present in the blood of donors, already immunized, to be injected into another person's vein (Hughes et al. 2012), being immediately bioavailable in the circulation (Dhar 2009). They are sterile immunoglobulin G (IgG), purified and manufactured from human plasma, typically containing more than 95% unmodified IgG (Dhar 2009).

Passive immunotherapy based on monoclonal antibodies is considered an effective method for the clinical treatment of infectious diseases. Hence, it becomes an alternative in the treatment of COVID-19. SARS-CoV and SARS-CoV-2 use the same surface receptors as the host cell, so potential input blocking agents for SARSs can be evaluated as possible blockers for SARS-CoV-2 (Shanmugaraj et al. 2020). Monoclonal antibodies, directed to the spike protein in SARS-CoV and MERS-CoV, showed promising results *in vitro* and *in vivo*, which can be potentially effective against SARS-CoV-2. However, no monoclonal antibodies have been successfully marketed, due to the scale production of monoclonal antibodies being laborious, costly and time consuming.

A pilot study on the association of clinical improvement in patients with COVID-19 due to the infusion of convalescent plasma (CoPla) was carried out by Juan (Olivares-Gazca et al. 2020). The study was carried out at the Hematology and Internal Medicine Center, of the Ruiz Clinic in Puebla, Mexico, from April to May 2020. The eligibility criteria for patients confirmed with COVID-19 were severe pneumonia with rapid progression, PaO<sub>2</sub>/FiO<sub>2</sub> below 300, using mechanical ventilation or not, admitted to the intensive care unit (ICU), and over 18 years old. The study included nine patients who were treated with plasma from convalescent COVID-19 donors.

After 8 days, three of the five patients who were using mechanical ventilation were extubated, nine patients left the ICU and went to conventional hospital units, six patients were discharged to go home and two patients died. One of the patients who died had recovered from COVID-19 and on the day of his discharge he developed a fatal pulmonary embolism. This patient was not receiving anticoagulants. The second patient died after being transferred to the ICU from another hospital with few resources. The authors reported that there were no side effects due to CoPla administration and the 24-day survival was 77%. Limitations evidenced by the authors are small sample, inability to generalize the results, absence of a control group, existence of confounding factors, mainly due to the existence of other treatments concomitant with CoPla and a sample formed only by critically ill patients. However, they assess that the administration of CoPla to critically ill patients with COVID-19 can improve the clinical course of these patients as well as result in improved respiratory function, in addition to being accessible and safe.

Piechotta et al. (2020) conducted a systematic review to analyze whether transfusion of convalescent plasma or hyperimmune immunoglobulin is effective and safe in the treatment of people with COVID-19. The authors conclude that the current evidence is low on the safety and efficacy of convalescent plasma and hyperimmune immunoglobulin for the treatment of patients hospitalized with COVID-19.

Islam et al. (2020) reports 6 observational studies conducted in China and South Korea, using convalescent plasma in 33 patients, 28 of whom recovered from the disease and decreased their viral load and 5 died. The authors conclude that the role of convalescent plasma in combating COVID-19 is still uncertain and requires randomized clinical trials to confirm its effectiveness. However, the authors recommend the use.

Alharthy et al. (2020) presented a case study using therapeutic plasma exchange (TPE) with three patients with COVID-19 admitted to an intensive care unit (ICU). The patients were over 18 years old, they were being mechanically ventilated and they were classified as having acute respiratory distress associated with SARS-CoV-2. Therapeutic plasma exchange (TPE) started between 24 and 48 h after the admission of the patient to the ICU. Plasma was administered at a volume of 1.5 on the first day and 1 volume per day, totaling five doses, 4 h/day. No side effects, such as coagulopathy, infection, or allergies, were observed after the five TPE sessions. The authors report that the patients showed clinical improvement with gradual neurological recovery. The length of stay of patients in the ICU was between 27 and 32 days and, after 30 days of admission, the results of the RT-PCR test for COVID-19 were negative. Thus, they

conclude that in patients with COVID-19, the use of plasma can be an effective rescue therapy.

In a clinical trial, Joyner et al. (2020) analyzed, from April to May 2020, 14,288 adult patient patients in serious condition or at risk of death due to COVID-19. During this period 8932 patients were treated with convalescent plasma, among which, 5000 patients were part of the study. The hypothesis presented by the researchers is that the serious adverse events related to the transfusion would be low and that the mortality rate after 7 days would not be high in comparison with other experiments already carried out. At the beginning of the study, 4051 of the 5000 patients were diagnosed as being in serious condition or at risk of death and 949 were classified as being at high risk of progressing to severe or at risk of death. Before receiving plasma, 3316 patients were admitted to the ICU. After 4 h of transfusion there was an incidence of less than 1% of serious adverse events. Among the 36 serious adverse events reported, only 2 were considered to be related to the use of convalescent plasma. A total of 602 deaths occurred during 7 days of plasma treatment, with 456 deaths among patients who were admitted to the ICU and 146 among those who were not admitted to the ICU. The authors conclude considering that the mortality rate did not seem excessive and evaluate that the results, even if initial indicators, indicate that transfusion with convalescent plasma is safe in COVID-19.

## Mesenchymal stem cells

MSCs are multipotent cells that are easily accessible and culturally expandable and with genomic stability that can differentiate into a variety of cell types. Due to their regenerative and anti-inflammatory capabilities, MSCs are therapeutic cells that can be used in immunological diseases (Fan et al. 2019). However, as it is a recent technology, few studies exist in relation to COVID-19.

Al-Khawaga and Abdelalim (2020) conducted a systematic review of studies on acute lung injury and ARDS, explaining the mechanisms of the therapeutic role of MSC. According to

the authors, further studies are needed to define the right dosage, and the ideal source of MSCs. The authors believe that MSC has the potential to be used as therapy in the treatment of COVID-19 and that the treatment may reduce the progression of severe cases.

## Perspectives

It is important to highlight that, until the moment of this work, no systematic review addressing treatment therapies for COVID-19 that was focused on non-pharmacological treatments was found by the authors.

Figure 2 shows the limitations found in the studies that were included in this systematic review in relation to the total of the studies.

It can be seen in Fig. 2, that all studies had some limitations. No randomized or blinding study was found. Most studies also presented designs and sample sizes that indicate low level of evidence. Other problems encountered, but to a lesser extent, were indirect evidence, quality of primary studies, number of primary studies and incomplete study.

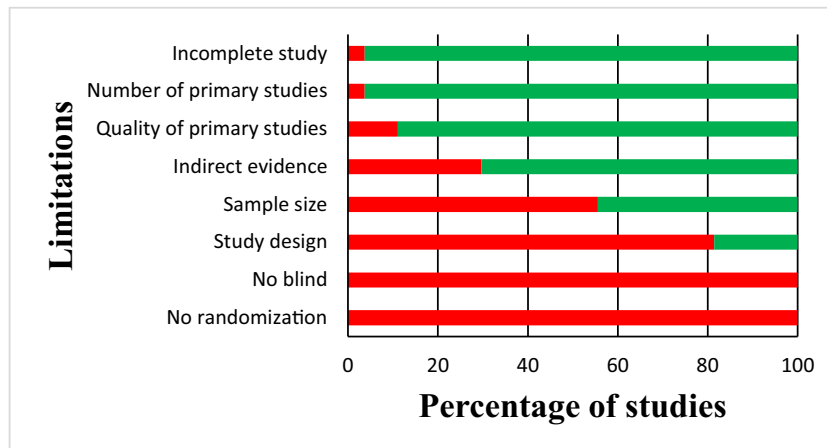
Table 2 shows some of the challenges and questions that must be faced and answered, for this and other pandemics that may arise.

The challenges and questions presented in Table 2 can only be answered by performing more studies, preferably randomized clinical trials, with a greater number of participants to increase the accuracy of the results, double-blind in studies which is possible and direct evidence. In addition, a multidisciplinary approach is necessary to cover the various specificities of treatment.

## Can we reach agreement on non-pharmacological treatments for COVID-19?

Our findings indicate that non-pharmacological treatments, with the exception of some related to oxygenation, do not yet have strong evidence in combating COVID-19. The

**Fig. 2** Limitations found in relation to the total number of studies included in this systematic review





**Table 2** Challenges and treatment issues to combat existing pandemics and diseases

Treatment	Challenges and issues
Oxygen therapy	<ul style="list-style-type: none"> <li>• What is the balance between using non-invasive oxygenation and the health of the health professional?</li> <li>• How to reduce tracheal hemorrhages and cardiac arrhythmia?</li> </ul>
Prone position	<ul style="list-style-type: none"> <li>• How to minimize events related to pressure ulcers?</li> </ul>
Inhaled nitric oxide	<ul style="list-style-type: none"> <li>• What is the optimal time for patient exposure to inhaled nitric oxide?</li> <li>• How to avoid acute renal failure due to patient's exposure to inhaled nitric oxide? (Ri et al. 2018).</li> </ul>
Intravenous infusion	<ul style="list-style-type: none"> <li>• The first major challenge of this treatment is to prove that it is really effective.</li> <li>• How to avoid allergies and, in rare cases, decreased lung function?</li> </ul>
Passive immunotherapy	<ul style="list-style-type: none"> <li>• How to minimize the risks related to transfusion?</li> <li>• When is the best time for the disease to apply passive immunotherapy?</li> <li>• How to minimize lung damage or irregular heartbeat caused by the transfusion?</li> </ul>
Mesenchymal stem cells (MSC)	<ul style="list-style-type: none"> <li>• What is the best source of MSCs?</li> <li>• What dosage to use?</li> <li>• How to resolve ethical issues?</li> </ul>

results are mostly based on inaccurate estimates due to the small number of participants, so the results are very heterogeneous. In addition, the evidence is indirect in most studies. However, several studies are being carried out to find some treatment for COVID-19 and some solutions have shown potential.

In this scenario, several studies using a randomized clinical trial should be carried out to provide evidence of safety and efficacy of the proposed treatments since most studies realized within the scope of COVID-19 still have a low level of evidence. Thus, although several treatments do not present significant differences with any treatment, the uncertainty of this result is very large due to the low methodological quality of the studies. The absence of studies with a higher level of evidence demonstrates the importance of this systematic review.

Some studies show that some treatments can play an important role in relation to COVID-19, but there are several challenges depending on the form of treatment, from the most recent treatments like MSCs to the most established ones like oxygen therapy. COVID-19 brought up several important and urgent issues, which were deemed to be overcome and established, such as the safety of the health professional during non-invasive ventilation.

Although the literature and statistical tools do not yet demonstrate the evidence of treatments, some authors indicate the use of the prone position. In addition, based on the initial results, there is much expectation regarding treatment with MSC.

Thus, in the current status of research regarding the non-pharmacological treatment of COVID-19, most authors agree that there is no evidence available to propose any specific therapy. So the authors also agree that research with greater methodological rigor, mainly randomized clinical trials,

should be carried out to generate more reliable evidence in relation to non-pharmacological treatments.

## Conclusion

In the current status of the research, there is still no specific non-pharmacological treatment approved for patients with COVID-19. Current clinical care is the same as that already used to treat patients with ARDS. So far, as an alternative to the treatment of COVID-19, is supportive therapy to control and mitigate symptoms. In the papers, it is common for the same author to defend various types of non-pharmacological treatments, which shows that there is still no specific treatment to fight COVID-19. In general, patients should be monitored closely, observing vital signs and oxygen saturation (Li et al. 2020b).

In this context, according to the studies selected for this review, different forms of non-pharmacological treatment have been used and tested to prevent adverse events and major health problems for patients, namely oxygen therapy, prone position, inhaled nitric oxide, intravenous infusion, passive immunotherapy, and MSC. It is worth mentioning that Brazil has a population that exceeds 209 million inhabitants, in which many of them (around 20%), according to data from the WHO (WHO 2020c), may need hospital care and treatment for COVID-19.

The available evidence is not able yet to indicate the benefits or harms of non-pharmacological treatments, including prone position, inhaled nitric oxide, intravenous infusion, passive immunotherapy, and MSC. Important information such as time of treatment, dosage, and application form are issues that still raise doubts. These questions directly impact knowledge of the safety and efficacy



of treatments, because the samples of most studies are small, leading to a high probability of error type I and at the same time it means a low power of statistical tests, increasing the probability of errors type II.

The limitation of this systematic review is in the primary studies, as most of them have serious methodological deficiencies. Thus, there is a consensus among researchers that it is still necessary to carry out randomized clinical trials, double-blind when possible and with a large number of patients.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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