REVIEW ARTICLE

A pragmatic approach and treatment of coronavirus disease 2019 (COVID-19) in intensive care unit

Sergio Henrique Loss[1]
Diego Leite Nunes[1]
Oellen Stuani Franzosi[2]
Cassiano Teixeira[1]

1. Médico Intensivista, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil.
2. Nutricionista, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.8.1157

SUMMARY

There is a new global pandemic that emerged in China in 2019 that is threatening different populations with severe acute respiratory failure. The disease has enormous potential for transmissibility and requires drastic governmental measures, guided by social distancing and the use of protective devices (gloves, masks, and facial shields). Once the need for admission to the ICU is characterized, a set of essentially supportive therapies are adopted in order to offer multi-organic support and allow time for healing. Typically, patients who require ventilatory support have bilateral infiltrates in the chest X-ray and chest computed tomography showing ground-glass pulmonary opacities and subsegmental consolidations. Invasive ventilatory support should not be postponed in a scenario of intense ventilatory distress. The treatment is, in essence, supportive.

KEYWORDS: *Coronavirus Infections. Betacoronavirus. Pandemics. Cuidados Críticos.*

INTRODUCTION

Infections of the new coronavirus (called COVID-19, i.e., coronavirus disease 2019) are caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and are a flu-like infection similar to the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) that occurred in 2002 and 2012, respectively[1,2]. The SARS-CoV-2's genome is a single-stranded positive-sense RNA[3] and it probably originated from bat-derived coronaviruses that directly infected humans or spread to an unknown intermediate host to humans in Wuhan, Hubei Province, China[4-6]. In addition to a similar flu presentation, COVID-19 can manifest itself as a neurological syndrome, heart failure, or acute myocardial infarction[7,8]. Most infections (80%) are mild. However, 6-10% will require transfer to the ICU[9]. Since much controversy involves the different types of therapy for this population we proceeded with a scoping review about therapies for critically ill patients infected with COVID-19 in order to offer intensivists the most consensual approach in an objective and simplified way.

DATE OF SUBMISSION: 25-May-2020
DATE OF ACCEPTANCE: 02-Jun-2020
CORRESPONDING AUTHOR: Sérgio Henrique Loss
Ramiro Barcelos, 2350, Porto Alegre, RS, Brasil – 90035-007
E-mail: sergio.loss@gmail.com

METHODS

This is a scoping review about critical care approaches to patients with COVID-19. A literature search of MEDLINE was conducted in PubMed throughout May 2020, using the terms coronavirus, COVID-19, SARS-CoV-2, pandemic, critical care, treatment. The retrieved papers were assessed and used in the review according to the quality and methodology used.

DISCUSSION

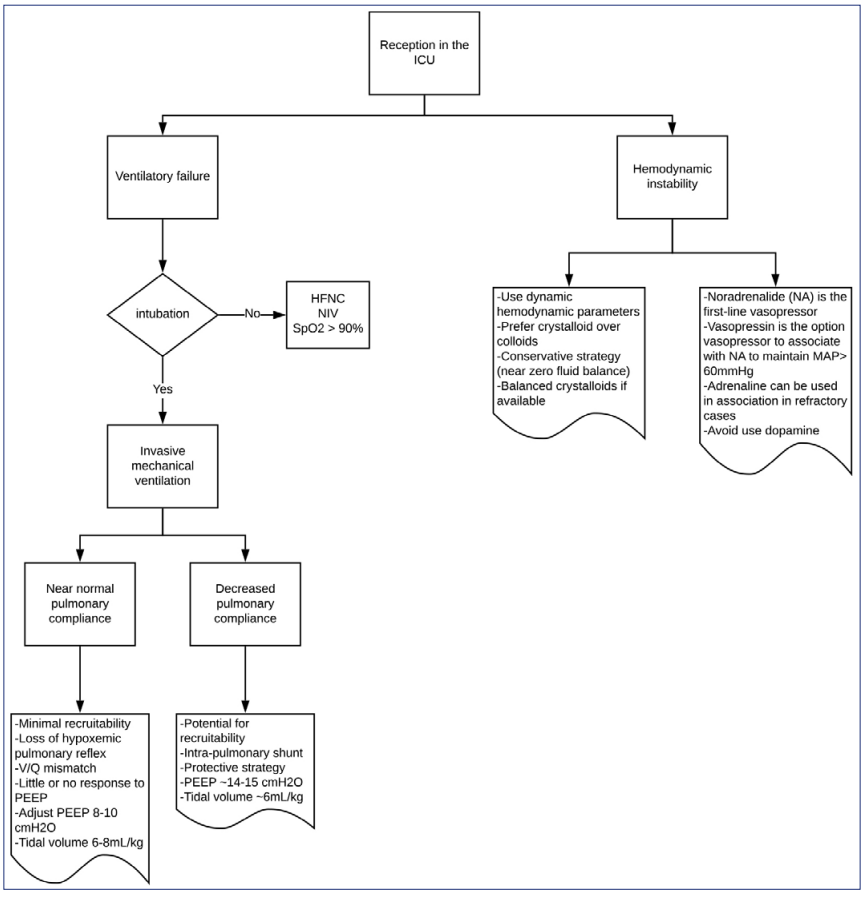
Admission to the unit

Patients with suspected or confirmed COVID-19 with progressive worsening of ventilatory failure or development of multiorgan dysfunction should be referred to the ICU, preferably in beds specifically dedicated to the treatment of this infection[1]. The entire security process for the assistance team must be clear. The institution must provide all necessary safety equipment (PPE – Personal Protective Equipment) [10], including suitable conditions for all staff[11]. Patients should be at least 2 meters apart[12].

Ventilatory support

Hypoxemic respiratory dysfunction is typical of a severe presentation in COVID-19[4]. Supplemental oxygen should be given when SO2 <90%[13]. Indications for ventilatory support, non-invasive or invasive, do not differ from routine indications for ICU. High-flow nasal oxygen supply does not significantly disperse bio-aerosol and is preferable over non-invasive ventilation (NIV). If the patient does not maintain SpO2 above 90%, especially in a context of significant suffering and excessive inspiratory effort, invasive mechanical ventilation is indicated. There are two different phenotypic presentations of ventilatory failure, one with normal or almost normal pulmonary compliance and severe hypoxemia (ventilation/perfusion mismatch), and the other with reduced compliance and intrapulmonary shunt[14-18]. Figure 1 summarizes the approach, types of ventilatory failure, and adjustments to the ventilator parameters.

FIGURE 1. VENTILATORY AND HEMODYNAMIC SUPPORT. HFNC: HIGH FLOW NASAL CANULA; NIV: NON-INVASIVE VENTILATION; V/Q: VENTILATION/PERFUSION; PEEP: POSITIVE END EXPIRATORY PRESSURE; MAP: MEDIUM ARTERIAL PRESSURE



Prone ventilation is indicated in patients with a PO2/FiO2 ratio <150 who were unable to maintain the ventilation strategy with a tidal volume of 4-6mL/Kg[19,20]. In refractory cases, extracorporeal membrane oxygenation (ECMO) with venous cannulation (ECMO V-V) may be attempted. Note that if this therapy is strongly considered, contact with a reference center should be made early in search of guidance and assessment of a window for clinical transfer conditions[21].

Hemodynamic

Hemodynamic instability is managed with crystalloid infusion, preferably using balanced solutions and vasopressors. The goal is to maintain an average blood pressure greater than 60mmHg[16,17]. The strategy is summarized in Figure 1.

Antiviral treatment

Hydroxychloroquine was the first drug proposed as an antiviral treatment due to its proven action in vitro against this virus class[22]. Subsequently, a non-randomized trial with a series of potential biases suggested that the association of hydroxychloroquine with azithromycin would decrease the time and severity of the disease[23]. Geleris et al.[24] included 1,376 patients with COVID-19 in a multivariable Cox model with inverse probability weighting according to the propensity score and they could not find an association with either a greatly lowered or an increased risk of the composite outcome of intubation or death. Rosenberg et al.[25] studied the association of treatment with hydroxychloroquine or azithromycin and hospital mortality in patients with COVID-19 and did not find any association between them. Despite the absence of evidence to support its use, some government protocols have recommended hydroxychloroquine at a dose of 400mg twice daily for 5 days in severe cases. When used, the QT interval must be monitored by electrocardiogram. The association of hydroxychloroquine and azithromycin should be avoided due to the potential cardiovascular effects[26].

The combination of two antiretrovirals (lopinavir-ritonavir) was tested on a randomized clinical trial enrolling 199 placebo-controlled patients. There was no evidence of improvement in mortality outcomes or reduction in the hospital stay. An important criticism of the study was that most participants were allocated 12 days after the onset of symptoms[27]. A recent review on the use of antiviral therapy against COVID-19 highlighted the importance of remdesivir, considering it a promising therapy (which could be confirmed in a randomized, double-blind, placebo-controlled clinical trial in patients with a severe presentation of the disease and expected to be published in May-June 2020)[28]. An excellent review of pharmacological treatments for COVID-19 has recently been published by Sanders et al.[29] and summarizes the current evidence on the main proposed, reused, or experimental treatments, providing a concise review of current clinical experience and treatment guidelines for this new coronavirus epidemic.

Other treatments

Steroids may be beneficial for a broad spectrum of critically ill patients, including those with cardiovascular, respiratory, and neurological conditions[30] and it seems to be associated with better outcomes in septic shock[31]. Since severe forms of COVID-19 have been linked to a cytokine storm, the use of corticosteroids has received special interest[32,33]. However, there is a wide divergence regarding corticosteroid use in patients with COVID-19 and its use should be evaluated on a case-by-case basis[34,35]. Published treatment protocols recommend methylprednisolone 0.5-1mg/kg/day for two weeks. However, until further data are available[36], the routine use of corticosteroid is not recommended[16,29]. However, patients with refractory shock should receive low-dose corticosteroid therapy[37].

Patients with COVID-19 can show a marked increase of D-dimer, meaning a coagulation disruption, which seems to be associated with increased mortality. Heparin use was shown to decrease mortality in this scenarium[38,39]. Thus, its utilization in this population seems to be reasonable. Prophylaxis of deep vein thrombosis/pulmonary thromboembolism is indicated in all patients (enoxaparin 40mg QD)[40,41].

Supportive treatment is often necessary and does not differ from routine practice in intensive care units. Fever is a complex, physiological, and adaptive response to infection that deserves additional assessment as to the need and safety of being medicated. The team must consider that fever can inhibit microbial reproduction, viral replication, and improve leukocyte function. Thus, perhaps fever should be treated only when it reaches values of 38.3-38.5C or higher[42,43].

Nutritional support

Perhaps, this area has the most fanciful proposal regarding immunity or outcomes of patients infected

with SARS-CoV-2 due to the miraculous effects of some micronutrients. In fact, the guidelines for nutritional therapy for critically ill patients published by respected societies, such as ASPEN, ESPEN, or BRASPEN, are perfectly applicable to critically ill patients with COVID-19[44-46]. Nutritional therapy and Intensive Care societies have recently published suggestions based on nutritional therapy guidelines and focused on clinical situations frequently identified in the course of SARS-CoV-2 disease[47-50]. The nutritional recommendations are summarized in Figure 2. Possibly, the COVID-19 pandemic is posing unpreceded challenges regarding nutritional assessment. Nevertheless, patients with SARS-CoV-2 disease should be treated individually, guided by the patient's conditions during intensive care support[47-50].

Regarding nutritional assessment, in the inability to obtain direct objective nutritional data, it may be necessary to evaluate secondary data for nutritional assessment when restrictions of ICU access exist, according to the institution's infection control division instructions. Secondary data can be obtained from the patient's records and by interviewing the family through various platforms. Nutritional risk assessment should be performed with validated tools (e.g. NRS-2002[51] and NUTRIC[52] scores). It is important to consider that ESPEN guidelines suggest that all patients with longer than 48 hours of ICU stay should be considered at nutritional risk[45]. The registered dietitian's findings should be registered on the patient's records and a coordinated nutritional therapy plan should be defined and shared with the medical team in order to provide safe and optimal nutritional therapy.

Objectively, nutritional therapy should be started early, that is, as soon as the patient demonstrates they are resuscitated (or about to be) and perfusion is established, preferably by a high density (> 1.2 kcal/mL) polymeric formula administered by gastric or post-pyloric feeding tubes (avoid endoscopy). Nutrition therapy should not be postponed solely by the use of neuromuscular agents, although deep sedation associated or not with neuromuscular agents may cause nutritional intolerance. Gastric residual monitoring is not recommended as standard care. Nutrition therapy should be given to patients undergoing prone positioning. If gastrointestinal intolerance persists after prokinetic therapy optimization, tropic nutrition may be considered (10-20 mL/h or 500 kcal/day).

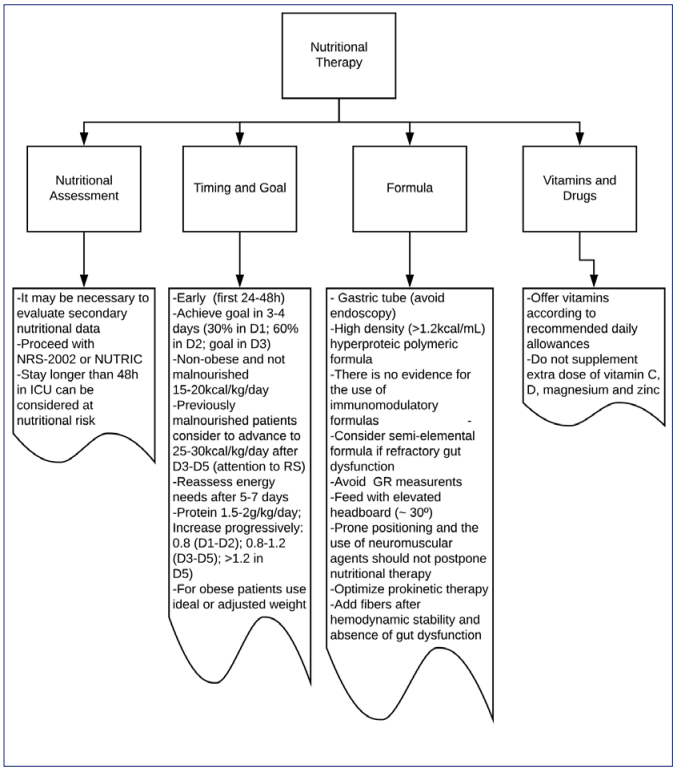
The calorie and protein doses are summarized in Figure 2. Trace elements and vitamins are offered according to the usual repletion practices. Currently, there is no evidence for immunomodulation. Fibers could be given according to the institution's practices as soon as the patient has hemodynamic stability and absence of digestive tract dysfunction (10-20g/day).

Prognosis

Recent cohorts showed rates of ICU admission or severe illness ranging from 4.9 to 26% of cases[53-58]. Most patients with COVID-19 appear to need mechanical ventilation (MV) due to acute respiratory distress syndrome (ARDS). Besides that, data about the duration of ventilation are limited but suggest prolonged MV for two weeks or more[53-55]. Common complications include acute kidney injury, mild transaminitis, cardiomyopathy, pericarditis, pericardial effusions, arrhythmias, sudden cardiac death, and superinfection (e.g., ventilator-associated pneumonia) [53-58].

Early data are emerging describing outcomes from COVID-19 in critically ill patients who develop ARDS[12,53,59,60]. Mortality appears lower than that in patients with severe acute respiratory syndrome (SARS-CoV) or Middle East respiratory syndrome

FIGURE 2. NUTRITIONAL THERAPY. NRS: NUTRITIONAL RISK SCREENING; NUTRIC: NUTRITION RISK IN CRITICALLY ILL; D: DAY; RS: REFEEDING SYNDROME; BMI: BODY MASS INDEX; GR: GASTRIC RESIDUAL VOLUME



(MERS). The mortality from COVID-19 appears driven by the presence of severe ARDS, and it is approximately 50% (range 16 to 78%). In a single-center retrospective cohort of 52 critically ill Chinese patients with COVID-19, 62% had died after 28 days, with a median duration of only seven days from intensive care unit (ICU) admission to death[53]. In another retrospective cohort of 201 Chinese patients with COVID-19, the mortality was 52% among those who developed ARDS[61]. Among those who received MV, 66% died, 21% were discharged, and 13% remained hospitalized. In an Italian cohort of 1591 patients, the ICU mortality was 26%, but a significant proportion remained in the ICU at the time of the publication, which may have underestimated the true mortality[57].

Across countries, the consistent major risk factor associated with death in critically ill patients with COVID-19 is older age[15,53,54]. In Chinese retrospective cohorts, death from ARDS was more likely to occur in those of older age, i.e., ≥64 years (hazard ratio [HR] 6.17; 95% 3.26-11.67)[53,61]. Preliminary reports from Italy and the United States are reporting similar outcomes[57,61,62]. Despite, the most reported predictors of severe prognosis in patients with COVID-19 included age, sex, features derived from computed tomography scans, C-reactive protein, lactic dehydrogenase, and lymphocyte count[63]. The speed of symptom progression does not appear to predict a worse outcome[53]. Other risk factors associated with death among critically ill patients include the following[38,55,57,62]:

- The development of ARDS, particularly severe ARDS, and the need for mechanical ventilation;
- Comorbidities (e.g., chronic heart and pulmonary conditions, hypertension, diabetes, chronic kidney disease);
- Markers of inflammation or coagulation (e.g., D-dimer level >1 microg/mL admission, elevated fibrin degradation products, prolonged activated partial thromboplastin and prothrombin times);
- Select laboratory studies (e.g., worsening lymphopenia, neutrophilia).

CONCLUSION

Patients with COVID-19 who need to be transferred to the ICU are complex and have a high mortality rate. Many studies are being conducted with the purpose of finding one or more treatments capable of eliminating the disease and providing a cure. Until then, treatment is multidisciplinary and essentially supportive.

RESUMO

Há uma nova pandemia global que surgiu na China em 2019 e está ameaçando diferentes populações com insuficiência respiratória aguda grave. A doença tem um enorme potencial de transmissibilidade e requer medidas governamentais drásticas, orientadas para o distanciamento social e pelo uso de dispositivos de proteção (luvas, máscaras e escudos faciais). Uma vez caracterizada a necessidade de admissão na UTI, um conjunto de terapias essencialmente de suporte é adotado para oferecer suporte multiorgânico e permitir tempo para a cura. Normalmente, os pacientes que necessitam de suporte ventilatório apresentam infiltrados bilaterais na radiografia de tórax e na tomografia computadorizada de tórax, mostrando opacidades pulmonares em vidro fosco e consolidações subsegmentares. O suporte ventilatório invasivo não deve ser adiado em um cenário de intenso sofrimento ventilatório. O tratamento é essencialmente de suporte orgânico.

PALAVRAS-CHAVES: *Infecções por Coronavirus. Betacoronavirus. Pandemia. Critical Care.*

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