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

Sergio Henrique Loss
Diego Leite Nunes
Oellen Stuani Franzosi
Cassiano Teixeira

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. The SARS-CoV-2’s genome is a single-stranded positive-sense RNA 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. In addition to a similar flu presentation, COVID-19 can manifest itself as a neurological syndrome, heart failure, or acute myocardial infarction. Most infections (80%) are mild. However, 6-10% will require transfer to the ICU. 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.
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. The entire security process for the assistance team must be clear. The institution must provide all necessary safety equipment (PPE – Personal Protective Equipment), including suitable conditions for all staff. Patients should be at least 2 meters apart.

Ventilatory support

Hypoxemic respiratory dysfunction is typical of a severe presentation in COVID-19. Supplemental oxygen should be given when SO2 <90%. 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. Figure 1 summarizes the approach, types of ventilatory failure, and adjustments to the ventilator parameters.

![Ventilatory and Hemodynamic Support Diagram](image-url)

**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/Kg15,20. 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 conditions21.

**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 60mmHg16,17. 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 class22. 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 disease23. 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 morality 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 effects26.

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 symptoms27. 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 conditions30 and it seems to be associated with better outcomes in septic shock31. Since severe forms of COVID-19 have been linked to a cytokine storm, the use of corticosteroids has received special interest32,33. 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 basis34,35. Published treatment protocols recommend methylprednisolone 0.5-1mg/kg/day for two weeks. However, until further data are available36, the routine use of corticosteroid is not recommended16,29. However, patients with refractory shock should receive low-dose corticosteroid therapy37.

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 scenario38,39. 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 higher42,43.

**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 BRASPIEN, are perfectly applicable to critically ill patients with COVID-19. 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. The nutritional recommendations are summarized in Figure 2. Possibly, the COVID-19 pandemic is posing unprecedented 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.

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 and NUTRIC 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. The registered dieter’s findings should be registered in 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. 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. Common complications include acute kidney injury, mild transaminitis, cardiomypathy, pericarditis, pericardial effusions, arrhythmias, sudden cardiac death, and superinfection (e.g., ventilator-associated pneumonia).

Early data are emerging describing outcomes from COVID-19 in critically ill patients who develop ARDS. Mortality appears lower than that in patients with severe acute respiratory syndrome (SARS-CoV) or Middle East respiratory syndrome...
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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 agudagrave.
A PRAGMATIC APPROACH AND TREATMENT OF CORONAVIRUS DISEASE 2019 (COVID-19) IN INTENSIVE CARE UNIT

10. Ferrioli M, Cistermino C, Leeov, Pisani L, Palange P, Nava S. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. Eur Respir Rev. 2020;29(155):200068.

11. Tyan K, Cohen PA. Investing in our first line of defense: environmental services workers. Ann Intern Med. 2020;172:223-7.

12. Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. JAMA. 2020; doi:10.1001/jama.2020.3633.

13. Barrot L, Asfar P, Mauny F, Winszewska H, Montini F, Badej J, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med. 2020;382(11):999-1008.

14. Tobin MJ. Basing respiratory management of COVID-19 on physiological principles. Am J Respir Crit Care Med. 2020;11(13):19-20.

15. Gattinoni L, Chiurriello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care. 2020;24(1):154.

16. Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med. 2020;8(6):506-17.

17. Poston JT, Patel BK, Davis AM. Management of critically ill adults with COVID-19. JAMA. 2020; doi:10.1001/jama.2020.4914.

18. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. Eur Respir J. 2020;55(5):2000892.

19. Guérin C, Reigner J, Richard JC, Beurlet P, Gacouin A, Bouland T, et al. PROS Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2199-68.

20. Gattinoni L, Taccone CF, Carlucci E, Marin J. Prone positioning in acute respiratory distress syndrome: rationale, indications, and limits. Am J Respir Crit Care Med. 2015;192(12):1266-83.

21. Barros L, Rivetti LA, Furlanetto BH, Fux GV, Cunha-Souza A, Silva MV, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19.19-general guidelines for surgeons (standard guidelines - subject to change). Braz J Cardiovasc Surg. 2020;35(2):1-11.

22. Liu C, Jiao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.

23. Gaumert P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment for COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;105949.

24. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hirpitsch G, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020;NEJMoa2012410.

25. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA. 2020;208630.

26. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCormy CM, Zimetbaum PJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine or azithromycin in the treatment of COVID-19 results of an open-label non-randomized clinical trial. J Electrocardiol. 2020;105949.

27. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.

28. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.

29. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatment of COVID-19: principles. Am J Respir Crit Care Med 2020;201(11):1319-20.

30. Ray JJ, Schumcl CI. Fever: suppress or let it ride? J Thorac Dis. 2015;7(12):E633-6.

31. McCabe SA, DiBaise JK, Mullin GE, Martindale RG. AGC Clinical Guideline: Nutrition therapy in the adult hospitalized patient. Am J Gastroenterol. 2016;111(3):315-34.

32. Singer P, Blaser AR, Berger MM, Alhazzani W, Carlson PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38(1):48-79.

33. Castro MG, Ribeiro PC, Souza IA, Gunha HFR, Silva MHN, Rech EEM, et al. Diretriz brasileira de terapia nutricional no paciente grave. BRASFOR. 2020;8(5):475-81.

34. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCormy CM, Zimetbaum PJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine or azithromycin in the treatment of COVID-19 results of an open-label non-randomized clinical trial. J Electrocardiol. 2020;105949.

35. Villar J, Confalonieri M, Pastores SM, Meduri GU. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by coronavirus disease 2019. Crit Care Explor. 2020;2(4):e00111.

36. ClinicalTrials.gov. Efficacy and safety of corticosteroids in COVID-19. [cited 2020 May 19]. Available from: https://clinicaltrials.gov/ct2/show/NCT04273351.

37. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. [cited 2020 May 19]. Available from: https://www.covid19treatmentguidelines.nih.gov/.

38. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thorac Haemost. 2020;18(4):844-7.

39. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thorac Haemost. 2020;18(5):1094-9.

40. Klok FA, Kruip MJA, van der Meer NJM, Arbous MS, Gommers DAMP, Kant KM, et al. Incidence of thrombotic complications in critically ill COVID-19 patients with COVID-19. Thromb Res. 2020;191:145-7.

41. Cattaneo M, Bertinato EM, Brocchi S, Brizco C, Malavolta D, Manzoni M, et al. Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified? Thromb Haemost. 2020; doi:10.1055/s-0040-1712097.

42. Dai YT, Lu SH, Chen YC, Ko W. Correlation between body temperature and survival rate in patients with hospital-acquired bacteremia: a prospective observational study. Biol Res Nurs. 2015;17(5):469-77.

43. Ray JJ, Schumcl CI. Fever: suppress or let it ride? J Thorac Dis. 2015;7(12):E633-6.

44. McCabe SA, Dibaise JK, Mullin GE, Martindale RG. AGC Clinical Guideline: Nutrition therapy in the adult hospitalized patient. Am J Gastroenterol. 2016;111(3):315-34.

45. Singer P, Blaser AR, Berger MM, Alhazzani W, Carlson PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38(1):48-79.

46. Castro MG, Ribeiro PC, Souza IA, Gunha HFR, Silva MHN, Rech EEM, et al. Diretriz brasileira de terapia nutricional no paciente grave. BRASFOR. 2020;8(5):475-81.

47. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCormy CM, Zimetbaum PJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine or azithromycin in the treatment of COVID-19 results of an open-label non-randomized clinical trial. J Electrocardiol. 2020;105949.

48. Ray JJ, Schumcl CI. Fever: suppress or let it ride? J Thorac Dis. 2015;7(12):E633-6.
56. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al; China Medical Treatment Expert. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.

57. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. JAMA. 2020. doi: 10.1001/jama.2020.4031.

58. Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. JAMA. 2020. doi: 10.1001/jama.2020.4344.

59. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

60. Bhatraju PK, Ghassemi EJ, Nichols M, Kim R, Jerome KR, Nallam AK, et al. COVID-19 in critically ill patients in the Seattle region: case series. N Engl J Med. 2020;382(21):2012-22.

61. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;200994.

62. Richardson S, Hirsch JS, Narasimhan M, Crawford J, 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(20):2052-9.

63. Wynants L, Van Calster B, Bonten MMJ, Collins GS, Debray TPA, Vos M, et al. Prediction models for diagnosis and prognosis of COVID-19 infection: systematic review and critical appraisal. BMJ. 2020;369:m326.