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MAJOR ACTIONS FOR RESEARCH, MANAGEMENT, AND ADOPTION OF PREVENTIVE MEASURES ON SARS-COV-2 IN SEVERE ACUTE RESPIRATORY SYNDROME: A SYSTEMATIC REVIEW

Maria Luiza Raduan Meinberg², João Marcelo Raduan Meinberg⁴, João Pedro Raduan Meinberg², Isabela Daher Anbar², João Pedro Daher Anbar², Thiago Melo Ignácio dos Santos³, Antonio Carlos Meinberg¹, Toufic Anbar Neto², Denise Daher Anbar², Idiberto José Zotarelli Filho^{2,5}

¹School of Medicine of São José do Rio Preto, Famerp - Discipline of Anesthesiology, São José do Rio Preto/SP, Brazil

²Faceres - Medical School of São José do Rio Preto/SP, Brazil

³União Das Faculdades Dos Grandes Lagos (Unilago) Medical School, São José do Rio Preto/SP, Brazil.

⁴Faculty of Health Sciences of Barretos-FACISB, Barretos/SP, Brazil

⁵Zotarelli-Filho Scientific Work, São José do Rio Preto/SP, Brazil

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*Corresponding author:

Dan Călugăru, MD, PhD

ABSTRACT

In March 2020, the new coronavirus (COVID-19) spread throughout the world, causing respiratory disease and deaths, especially in risk groups such as the elderly, pregnant women, immunocompromised people, and others. The World Health Organization (WHO; WHO, English) declared, on January 30, 2020, that the outbreak of the disease caused by COVID-19 constitutes a Public Health Emergency of international importance. 6,287,771 cases of COVID-19 (93,246 new compared to the previous day) and 379,941 deaths (3,621 new compared to the previous day) were confirmed worldwide by June 3, 2020. In the Region of the Americas, 1,036,155 people who were infected with the new coronavirus recovered, according to data from June 3, 2020. In Brazil, on January 22, 2020, the Center for Emergency Operations in Public Health for COVID-19 was activated, a strategy provided for in the National Response Plan to Public Health Emergencies of the Ministry of Health (MS). **Objective:** To present, using a systematic review, the main considerations about the existing actions for notification, registration, investigation, management, and adoption of preventive measures on SARS-CoV-2 in Severe Acute Respiratory Syndrome (SARS). **Methods:** The present study followed a systematic review model. After literary search criteria using the MeSH terms, a total of 58 clinical studies were compared and submitted to eligibility analysis and, after that, 26 studies were selected, following the rules of PRISMA. The search strategy was carried out in the databases PubMed, Embase, Ovid and Cochrane Library, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile. **Main findings and Conclusion:** It is recommended that patients diagnosed with SARS be hospitalized and that the cases identified with the symptoms of severity are admitted to an intensive care bed. These symptoms are persistent hemodynamic instability (blood pressure that did not respond to volume replacement (30 mL/kg in the first 3 hours), indicating the use of vasoactive amine, signs, and symptoms of respiratory failure, including hypoxemia (PaO₂ below 60 mmHg) in need supplementation of oxygen to maintain arterial oxygen saturation above 90%, evolution to other organic disorders, such as acute renal failure and neurological dysfunction. It was defined that the clinical criteria for hospital discharge should take into account the improvement of the clinical picture, the absence of tachypnea and hypoxia, the absence of O₂ supplementation for at least 24 hours, hemodynamic stability, good oral acceptance and absence of fever. Prophylactic use of antibiotics has not recommended, but use should be considered suspect of associated bacterial infection.

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INTRODUCTION

In the context of epidemics and pandemics, in November 2019, an outbreak of respiratory disease caused by the new coronavirus (SARS-CoV-2), was detected in the city of Wuhan, China (World Health Organization, 2020). In March 2020, the new coronavirus (COVID-19) spread throughout the world causing respiratory disease and deaths especially in risk groups such as the elderly pregnant women, immunocompromised people, and others (World Health Organization, 2020). The World Health Organization (WHO) declared, on January 30, 2020, that the disease outbreak caused by COVID-19 constitutes a Public Health Emergency of International Importance - the highest level of alert in the Organization, as provided for in the Regulations International Health. On March 11, 2020, COVID-19 has characterized by WHO as a pandemic (World Health Organization, 2019). About 6,287,771 cases of COVID-19 (93,246 new about the previous day) and 379,941 deaths (3,621 new concerning the previous day) were confirmed worldwide by June 3, 2020 (World Health Organization, 2020). In the Region of the Americas, 1,036,155 people who were infected with the new coronavirus recovered, according to data from June 3, 2020. The Pan American Health Organization (PAHO) and WHO is providing technical support to Brazil and other countries, in the preparation and response to the COVID-19 outbreak (World Health Organization, 2020).

In Brazil, on January 22, 2020, the Public Health Emergency Operations Center for COVID-19 was activated, a strategy provided for in the National Public Health Emergency Response Plan of the Ministry of Health (MS). Thus, the Ministry of Health established a structured document based on existing actions for notification, registration, investigation, management, and adoption of preventive measures, in analogy to the accumulated knowledge about SARS-CoV-2 and the Influenza Treatment Protocol: 2017 of the MS (Agência Nacional De Vigilância Sanitária, 2020). The recommendations are also guided by the Covid-19 Expert Consensus for Clinical Management, held on March 10 and 11, 2020, at the headquarters of the Pan American Health Organization / World Health Organization (PAHO / WHO) in Brasilia, when national and international experts were gathered for discussion and deepening on the subject (Brasil, 2017; Brasil, 2020; Brasil, 2017).

In this context, Severe Acute Respiratory Syndrome (SARS) (Severe Acute Respiratory Syndrome - SARS) is a severe acute respiratory disease caused by SARS-CoV. SARS is much more drastic than other coronavirus infections (Centers For Disease Control And Prevention, 2019). SARS is an influenza-like illness that occasionally causes severe progressive respiratory failure. SARS-CoV was first detected in Guangdong, China, in November 2002 and subsequently spread to more than 30 countries (Guan, 2020). SARS-CoV is transmitted from person to person by close personal contact. It believed to transmitted more readily by respiratory droplets produced when an infected person coughs or sneezes. The diagnosis of SARS is clinical, and treatment is supportive (Huang, 2020). Therefore, this study presented through a systematic review the considerations about the actions for notification, registration, investigation, management, and adoption of preventive measures on SARS-CoV-2 in Severe Acute Respiratory Syndrome (SARS).

MATERIALS AND METHODS

Study Design: The present study followed a systematic review model. After literary search criteria using the MeSH Terms that were cited in the item below on "Search strategies", a total of 58 clinical studies were compared that were submitted to the eligibility analysis and, after that, 26 studies were selected (official documents do Brazil, WHO and scientific articles), following the rules of systematic review - PRISMA (Transparent reporting of systematic reviews and meta-analyzes-<https://www.prisma-statement.org/>).

Search Strategy and Information Sources: The search strategy was carried out in the databases PubMed, Embase, Ovid and Cochrane Library, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: - search by MeSH Terms: *COVID -19. SARS-CoV-2. Severe Acute Respiratory Syndrome. Acute Respiratory Distress Syndrome. Prevention*, and use of "and" Booleans between mesh terms and "or" among historical findings.

DEVELOPMENT AND DISCUSSION

Supportive early therapy and monitoring – SARS: In the context of SARS, it is necessary to administer supplemental oxygen therapy immediately to patients with SARS and difficulty breathing, hypoxemia, or shock with a SpO₂ target > 94% (Instituto Latino Americano De Sepse, 2018). In adults with signs of emergency (obstruction or shortness of breath, severe respiratory distress, central cyanosis, shock, coma, or seizures), they must receive airway management and oxygen therapy during resuscitation to achieve SpO₂ ≥ 94% (. It is necessary to start oxygen therapy at 5 L/min and assess flow rates to reach the SpO₂ target ≥ 93% during resuscitation, or use a face mask with a reservoir bag (10-15 L/min) if the patient is in a healthy state critical (Instituto Latino Americano De Sepse, 2018). After patient stabilization, the target is SpO₂ > 90% in adults (without pregnancy) and ≥ 92% -95% in pregnant patients.

In children with emergency signs (obstruction or shortness of breath, severe respiratory distress, central cyanosis, shock, coma, or seizures) they must receive airway management and oxygen therapy during resuscitation to achieve SpO₂ ≥ 94%, otherwise, the goal is SpO₂ ≥ 90%. The use of a nasal cannula is preferable in young children, as they can be better tolerated (Weiss, 2020). Still, it has indicated to use a conservative treatment of fluids in patients with SARS when there is no evidence of shock (Wu, 2019). Patients with SARS should be treated cautiously with intravenous fluids, as aggressive fluid resuscitation can worsen oxygenation, especially in environments where the availability of mechanical ventilation is limited. This applies to the care of children and adults. It has also indicated to administer antibiotics within an hour of the initial assessment of patients with sepsis, to collect cultures within an hour ideally before starting the antibiotic and descale based on the microbiological result or clinical judgment (Tian,; Wang, 2019). Also, it was indicated not to routinely administer systemic corticosteroids for the treatment of viral pneumonia or SARS outside clinical trials, except for other reasons. It is necessary to closely monitor patients with SARS for signs of clinical complications such as respiratory failure and rapidly progressing sepsis and apply supportive interventions immediately (Zhang).

Table 1. Clinical syndromes associated with SARS-CoV-2 infection [1].

<i>Mild disease</i>	<ul style="list-style-type: none"> ✓ Picture compatible with upper airway infection, without signs of dehydration, dyspnea, sepsis, or organ dysfunction. ✓ The most common signs and symptoms are fever, cough, difficulty breathing, sore throat, nasal congestion, headache, malaise, and myalgia. Immunosuppressed, the elderly and children may have atypical conditions and show no signs of dehydration, fever, or difficulty breathing. ✓ In pregnant women, due to physiological adaptations or adverse events in pregnancy, dyspnoea, fever, gastrointestinal symptoms or fatigue may overlap with Covid-19 symptoms.
<i>Pneumonia without complications</i>	<ul style="list-style-type: none"> ✓ Adult infection of the lower respiratory tract without signs of severity. ✓ A child without signs of severe pneumonia with cough or difficulty breathing and rapid breathing. ✓ Observation: Follow the respiratory rate reference values according to the age range for evaluation: *respiratory incursions per minute (ripm). ✓ 1 to 12 months: 30 to 53 ripm ✓ 1 to 2 years: 22 to 37 ripm ✓ 3 to 5 years: 20 to 28 ripm ✓ School: 18 to 25 ripm ✓ Adolescent: 12 to 20 ripm
<i>Severe pneumonia</i>	<ul style="list-style-type: none"> ✓ Adolescent or adult: lower respiratory tract infection with any of the following signs of severity described below: respiratory rate > 30 incursions per minute; severe respiratory effort; SpO₂ < 93% in room air; cyanosis; organic dysfunction. ✓ Children with a cough or difficulty breathing more than at least one of the following criteria: <ul style="list-style-type: none"> ✓ central cyanosis or spO₂ < 90%; ✓ severe respiratory effort; ✓ signs of PNM with aspects of severity (use of accessory muscles for breathing; inability or refusal to breastfeed or drink fluids; wheezing or stridor at rest; unavoidable vomiting; altered sensory: irritability or drowsiness; convulsions). ✓ The respiratory rate that denotes severity in children will depend on age, namely: <ul style="list-style-type: none"> ✓ < 2 months: ≥ 60 ripm ✓ 2 to 11 months: ≥ 50 ripm ✓ 1 to 5 years: ≥ 40 ripm ✓ The diagnosis is clinical. Chest images can identify or exclude complications.
<i>Acute respiratory distress syndrome (ARDS)</i>	<ul style="list-style-type: none"> ✓ Onset or worsening of respiratory symptoms, up to one week after the onset of the disease. It may also present: radiological changes (infiltrates, bilateral opacities, lobar/pulmonary atelectasis, or nodules); pulmonary edema not explained by heart failure or hyperhydration. ✓ Oxygenation impairment in adults and children: <ul style="list-style-type: none"> • ADULTS: <ul style="list-style-type: none"> • Lightweight: 200 mmHg < PaO₂ / FiO₂ ≤ 300 mmHg (with PEEP or C_{cap} ≥ 5 cm H₂O, or not ventilated). • Moderate Sara: 100 mmHg < PaO₂ / FiO₂ ≤ 200 mmHg (with PEEP ≥ 5 cm H₂O, or not ventilated). • Severe Sara: PaO₂ / FiO₂ ≤ 100 mmHg (with PEEP ≥ 5 cm H₂O, or not ventilated). • When PaO₂ is not available, SpO₂ / FiO₂ ≤ 315 suggests Sara (including in unventilated patients). • CHILDREN: <ul style="list-style-type: none"> • OI = Oxygenation Index and OIU = Oxygenation Index using SpO₂. Use the PaO₂ based metric, when available. If PaO₂ is not available, wean FiO₂ to maintain SpO₂ ≤ 97% to calculate OSI or SpO₂ / FiO₂ ratio: <ul style="list-style-type: none"> • Non-invasive ventilation or C_{cap} bi-level ≥ 5 cm H₂O through a full face mask: PaO₂ / FiO₂ ≤ 300 mmHg or SpO₂ / FiO₂ ≤ 264. • Light Sara (with invasive ventilation): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5. • Moderate Sara (with invasive ventilation): 8 ≤ OI < 16 or 7.5 ≤ OIU < 12.3. • Severe condition (with invasive ventilation): OI ≥ 16 or OIU ≥ 12.3.
<i>Sepsis</i>	<ul style="list-style-type: none"> ✓ Systemic inflammatory response syndrome with organ dysfunction in the presence of presumed or confirmed infection. Frequent signs of organ dysfunction are altered level of consciousness, oliguria, tachy and/or dyspnoea, low oxygen saturation, tachycardia, weak pulse, cold extremities, coagulopathy, thrombocytopenia, acidosis, elevated serum lactate or bilirubin.
<i>Septic shock</i>	<ul style="list-style-type: none"> ✓ Sepsis accompanied by hypotension [mean arterial pressure (MAP) < 65 mmHg] despite adequate volume resuscitation and requiring the use of vasopressors to maintain MAP > 65 mmHg. ✓ Children: any type of hypotension (SBP < 5th percentile or > 2 SD below normal for age) or two or three of the following: altered mental status; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in children under 12 months and HR < 70 bpm or > 150 bpm in children); prolonged capillary filling (> 2 sec) or weak pulse; tachypnea; stained or cold skin or petechial or purple rash; increased lactate; oliguria; hyperthermia or hypothermia.

Table 2. Interventions to avoid patient complications [World Health Organization, 2020]

<i>EARLY INTERVENTIONS</i>	<i>MANAGEMENT</i>
<i>Reduce Days Of Invasive Mechanical Ventilation</i>	<ul style="list-style-type: none"> ✓ Use weaning protocols that include daily assessment of spontaneous respiratory capacity. ✓ Minimize the sedation, continuous or intermittent, aiming at specific final titration points or with daily interruptions of continuous sedative infusions.
<i>Reduce The Incidence Of Pneumonia Associated With Ventilation</i>	<ul style="list-style-type: none"> ✓ Prefer oral intubation to the nasal and perform oral hygiene regularly. ✓ Keep the patient in a semi reclined position (head rise between 30 ° and 45 °). ✓ Use closed suction system; drain periodically and dispose of the condensate in pipe. ✓ Use a new ventilation circuit for each patient; perform the exchange whenever it is dirty or damaged, but not routine. ✓ Replace the humidifier as malfunctions, dirtiness or every 5-7 days, following the manufacturer's recommendations and according to the protocols defined by the health service ccih. ✓ Reduce the invasive mechanical ventilation time.
<i>Reduce incidence of venous thromboembolism</i>	<ul style="list-style-type: none"> ✓ Use pharmacological prophylaxis in patients without contraindication. If contraindications are used, use mechanical prophylaxis.
<i>Reduce incidence of blood infection by catheter</i>	<ul style="list-style-type: none"> ✓ Adopt a simple checklist to remind the date of inserting the catheter and removing it when no more needed.
<i>Minimize occurrence of decubal ulcers</i>	<ul style="list-style-type: none"> ✓ Promote change of decubus every two hours.

Source: World Health Organization, June 2020, adapted.

Laboratory tests of hematology and biochemistry and ECG should be performed on admission and as clinically indicated to monitor complications, such as acute liver injury, acute kidney injury, acute cardiac injury, or shock. The application of timely, effective, and safe supportive therapies is the mainstay of therapy for patients who develop severe manifestations of COVID-19 (20). In pregnant patients, after their resuscitation and stabilization, it is necessary to analyze the fetus. It is a differential to understand the patient's comorbidities for individualized care and prognosis. Thus, Table 1 below presents the major clinical syndromes associated with SARS-CoV-2 infection (World Health Organization, 2020).

Treatment of hypoxemic respiratory failure and SARS: Recognition of severe hypoxemic respiratory failure occurs when a patient with respiratory distress has failed standard oxygen therapy, requiring advanced oxygen/ventilation support. If these patients need O₂ via a nasal catheter greater than 5 liters/minute to sustain SpO₂ > 93% and/or have a respiratory rate > 28 rpm or CO₂ retention (PaCO₂ > 50 mmHg and/or pH < 7.25) they should be intubated and mechanically ventilated immediately. Thus, mechanical ventilation should be instituted early in patients with persistent hypoxemic respiratory failure (despite oxygen therapy), respecting appropriate precautionary measures (21). However, the National Health Surveillance Agency (Anvisa), through Technical Note 4/2020, contraindicates the use of non-invasive mechanical ventilation (NIV) and high-flow nasal catheter (HFNC) (Agência Nacional De Vigilância Sanitária, 2020).

The procedure with endotracheal intubation is necessary if the patient does not respond to oxygen therapy. Patients with SARS, especially young children or people who are obese or pregnant, can quickly desaturate during intubation, requiring pre-oxygenation with an inspired fraction of oxygen (FiO₂) at 100% for 5 minutes, using a facial mask with reservoir bag. Fast-sequence intubation is appropriate after an airway assessment that shows no signs of difficult intubation (LiK). The patient submitted to protective invasive mechanical ventilation may be ventilated in volume or controlled pressure mode (VCV or PCV) with a tidal volume equal to 6 mL/kg of predicted weight and plateau pressure less than 30 cmH₂O, with distention pressure or driving pressure (= Plateau pressure minus PEEP) less than 15 cmH₂O (Associação De MedicinaIntensiva Brasileira, 2020). It is also necessary to adjust the smallest enough PEEP to maintain SpO₂ between 90-95%, with FiO₂ < 60% (use ARDSNet's PEEP/FiO₂ table for low PEEP (LIGHT SARS)). It was found that the use of higher PEEP proved to be causing pulmonary hyperinflation and worsening of the evolution of part of the patients with COVID-19 (Associação De MedicinaIntensiva Brasileira, 2020). In this context, placing patients with SARS in a prone position can improve oxygenation, but patient safety must be guaranteed. In cases of PaO₂ / FIO₂ less than 150, with adequate PEEP according to the PEEP/FiO₂ table, it is suggested to use protective ventilation by placing the patient in a prone position for at least 16 hours. To perform the rotation and to maintain the patient in a prone position, adequate sedoanalgesia should be provided and, if necessary, curarization. The patient can remain supine if, after being "unresponsive", he remains with PaO₂ / FIO₂ > 150. Otherwise, one can consider putting the patient back in a prone position (Associação De MedicinaIntensiva Brasileira, 2020).

In addition, it is necessary to adopt a conservative fluid management strategy for patients with SARS without tissue hypoperfusion. Prevent the patient from disconnecting from the ventilator, which can result in loss of PEEP and atelectasis. It is also necessary to use in-line catheters for suctioning the airways and clamping the endotracheal tube when it is necessary to disconnect (for example, transferring to a transport ventilator or changing the HME filter) (Associação De MedicinaIntensiva Brasileira, 2020).

Complication Prevention, Airway Management, and Non-Invasive Ventilation: In critically ill patients who require care at the ICU level, non-invasive ventilation (NIV), mechanical ventilation, or extracorporeal life support is considered if necessary (Liu, 2019). The development of SARS and respiratory decompensation plays a central role in the pathogenesis of COVID-19. In this sense, the principles of treatment are listed as hemodynamic management, with vasopressor support, nutritional support, blood glucose control, prompt assessment and treatment of nosocomial or concomitant bacterial pneumonia, prophylaxis against deep vein thrombosis and gastrointestinal bleeding and proper positioning of the patient to assist in oxygenation and ventilation, as shown in Table 2 below (World Health Organization, 2020).

In this sense, data from China and Italy suggest that patients with hypoxemic COVID-19 respond well to PEEP, indicating a crucial role of NIV as a therapeutic and palliative measure to prevent intubation. Statistics from retrospective analyzes in China indicate that up to 30% of admitted patients required NIV, 84 while the first reports from Italy indicate values close to 31%. Given current epidemiological trends, these requirements are likely to exceed the current capacity of most hospitals, if not all, if aggressive preparatory measures are not taken (Liu, 2019). In this effort, it is important to characterize patients with COVID-19 who need treatment in an ICU. In this context, a retrospective study was carried out with 1,591 consecutive patients with COVID-19 confirmed in the laboratory and referred for admission to the ICU at the center of the Fondazione IRCCS coordinator Ca 'Granda Ospedale Maggiore Policlinico, Milan, Italy, of the 72 hospitals in this network among February 20 and March 18, 2020. The date of the final follow-up was March 25, 2020. Therefore, in this series of cases of critically ill patients with laboratory-confirmed COVID-19, admitted to ICUs in Lombardy, Italy, the majority were older men, a large proportion required mechanical ventilation and high levels of PEEP, and ICU mortality was 26% (Grasselli *et al.*, 2020). Another study looked at the relationship between obesity and SARS by SARS-CoV-2. In this retrospective cohort study, the relationship between clinical characteristics, including body mass index (BMI) and the need for invasive mechanical ventilation (IMV) in 124 consecutive patients admitted to intensive care by SARS-CoV-2, was analyzed, in a single French center. Obesity (BMI > 30 kg/m²) and severe obesity (BMI > 35 kg/m²) were present in 47.6% and 28.2% of cases, respectively. Overall, 85 patients (68.6%) required IMV. The proportion of patients who needed IMV increased with the BMI categories (p < 0.01, chi-square test for trend), and was higher in patients with a BMI > 35 kg/m² (85.7%). In multivariate logistic regression, the need for IMV was significantly associated with male gender (p < 0.05) and BMI (p < 0.05), regardless of age, diabetes, and hypertension.

The proportion ratio for IMV in patients with a BMI > 35 kg/m² versus patients with a BMI <25 kg/m² was 7.36. Therefore, there was a high frequency of obesity among patients admitted to intensive care with COVID-19. The severity of the disease worsened as the BMI increased. Thus, obesity is a risk factor for the severity of SARS-CoV-2, requiring greater attention to preventive measures in susceptible individuals (Simonnet, 2020). Based on current data from China and Italy, it is recommended to expand the storage of NIV devices and ventilators in hospitals in general. To combat hospital spread and aerosolization of the SARS-CoV-2 virus, priority was given to double-limbed NIV devices with expiratory filters, such as the PB840 ventilator Viral filter proximal to the leak port on single-limb devices, single-member NIV devices use CPAP with viral filters before PEEP valves. It is strongly recommended to provide part of the emergency and inpatient units for patients with COVID-19, with patient bays and rooms equipped to administer NIV (Giwa, 2019).

Conclusion

Through official documents of the Ministry of Health of Brazil, based on the regulations of the World Health Organization, it is recommended that hospitalized patients diagnosed with SARS and that the cases identified with the symptoms of severity have admitted to an intensive care bed. These symptoms are persistent hemodynamic instability (blood pressure that did not respond to volume replacement (30 mL/kg in the first 3 hours), indicating the use of vasoactive amine (example: norepinephrine, dopamine, adrenaline), signs and symptoms of respiratory failure, including hypoxemia (PaO₂ below 60 mmHg) requiring oxygen supplementation to maintain arterial oxygen saturation above 90%, progressing to other organic disorders, such as acute renal failure and neurological dysfunction. It was defined that the clinical criteria for hospital discharge should take into account the improvement of the clinical picture, the absence of tachydyspnea and hypoxia, the absence of O₂ supplementation for at least 24 hours, the hemodynamic stability, the good acceptance of the oral route and the absence of fever. The reappearance of tachycardia, recurrence of fever, worsening of the general condition, or respiratory symptoms indicate the need for an immediate return of the child who has already has discharged from health services. Prophylactic use of antibiotics was not recommended, but use should be considered based on the suspicion of associated bacterial infection. It is recommended that critically ill patients, without Covid-19 etiological confirmation, be managed according to the SARS protocol and that supportive treatment should focus on reversing hypoxemia. Mechanical ventilation indication should follow pediatric protective ventilation protocols in patients with SARS.

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