

Beyond ventilatory support: challenges in general practice and in the treatment of critically ill children and adolescents with SARS-CoV-2 infection

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<http://dx.doi.org/10.1590/1806-9282.66.4.521>

SUMMARY

Severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2 infection) is a new challenge for all countries, and children are predisposed to acquire this disease. Some studies have demonstrated more severe diseases in adults, but critically ill pediatric patients have been described in all ages. Pulmonary involvement is the major feature, and ventilatory support is common in critical cases. Nevertheless, other very important therapeutic approaches must be considered. In this article, we reviewed extensively all recent medical literature to point out the main clinical attitudes to support these pediatric patients during their period in respiratory support. Radiologic findings, fluid therapy, hemodynamic support, use of inotropic/vasopressors, nutritional therapy, antiviral therapy, corticosteroids, antithrombotic therapy, and immunoglobulins are analyzed to guide all professionals during hospitalization. We emphasize the importance of a multi-professional approach for adequate recovery.

KEYWORDS: Child. Coronavirus. Sars-CoV-2. COVID-19.

INTRODUCTION

A pneumonia case of unknown cause detected in Wuhan, China, was first reported to the WHO Country Office in China on 31 December 2019, but current case data in China reveal that children < 18 years of age accounted for only 2.4% of all reported cases (WHO data, 2020). However, there have been multiple reports, to date, of children with asymptomatic

Sars-CoV-2 infection (Severe acute respiratory syndrome coronavirus 2). The main sources of the infection are patients infected by novel coronavirus disease (COVID-19) with or without clinical symptoms. In addition, patients in the incubation period may also be able to transmit the virus based on case evidence¹. Since then, however, more regions around the world

DATE OF SUBMISSION: 11-Apr-2020

DATE OF ACCEPTANCE: 13-Apr-2020

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have launched pathogen detection campaigns and, since younger children cannot wear masks and no other special preventive and control measures have been taken, the number of child infection cases has increased significantly. Therefore, higher attention to this part of the population should be given. At the same time, children with other diseases (such as congenital heart, lung, and airway diseases, malnutrition, renal dysfunction, liver dysfunction, immunodeficiency, tumors, etc.) are vulnerable to infections by Sars-CoV-2 and, more specifically, predisposed to a severe clinical condition^{1,2}.

Sars-CoV-2 originated from bats and is confirmed to be similar to Sars-CoV (Severe acute respiratory syndrome caused by Coronavirus in 2003), entering cells by binding to the angiotensin-converting enzyme 2 (ACE-2) cell receptor. According to the current data, the main routes of transmission are respiratory droplet transmission and contact transmission. It has also been reported that Sars-CoV-2 can be transmitted through aerosols, the fecal-oral route, and suspected mother-to-infant transmission, but some pediatric cases may progress to lower respiratory tract infection. Severe COVID-19 in children is rare. To date, the largest review of children with COVID-19 included 2143 children in China. Only 112 (5.6%) of 2143 children had severe disease (defined as hypoxemia), and 13 (0.6%) developed respiratory or multiorgan failure or pediatric acute respiratory distress syndrome (PARDS)^{1,3}.

In adults, certain findings are associated with severe illness, such as high serum ferritin and bilateral abnormalities on chest CT. It is very difficult to determine common clinical characteristics in children with severe disease, and it is unclear whether there is a common biomarker due to the small number of cases^{1,4}.

Radiologic Findings

The chest x-ray may be normal in early or mild disease. Of all adult patients with COVID-19 requiring hospitalization, 69% had an abnormal chest radiograph at admission, and 80% had radiographic abnormalities sometime during hospitalization. Findings are more significant around 10-12 days after symptom onset. The most frequent findings are airspace opacities, whether described as consolidation or, less commonly, ground-glass opacification (GGO). The distribution is most often bilateral, peripheral, and lower-zone predominant, and pleural effusion is rare (3%)^{5,6}.

Growing evidence shows the usefulness of lung ultrasound in patients with COVID-19 and pneumonia from diagnosis, to monitoring, and follow-up. In the setting of COVID-19, wireless probe and tablets represent the most appropriate ultrasound equipment. The following patterns have been observed, with a tendency to bilateral and posterobasal predominance: multiple B-lines (ranging from focal to diffuse with spared areas, representing thickened subpleural interlobular septa); irregular, thickened pleural line with scattered discontinuities; subpleural consolidations, alveolar consolidation, restitution of aeration during recovery (reappearance of bilateral A-lines)⁵⁻⁷.

Unlike adult patients, only a small number of pediatric patients had multilobes affected, so we assume that children and adolescents generally have milder CT findings than adults. In adults, the findings in CT scan can be very diverse depending on high or low compliance⁸: most appeared as pure GGO, GGO with consolidation, interlobular septal thickening, bronchiolar wall thickening, and asymmetric paving pattern, whereas rare manifestations included halo sign, pleural effusion, pericardial effusion, and lymphadenopathy. In a pediatric study that analyzed 6 patients, only GGO and consolidative GGO were found^{5,6,9}.

Fluid Therapy

For the acute resuscitation of children and adolescents with COVID-19 and shock, we suggest using a conservative over a liberal fluid strategy. Buffered/balanced crystalloids over unbalanced crystalloids can be useful with adequate metabolic and electrolyte monitoring. For the acute resuscitation of children and adolescents with COVID-19 and shock, we recommend using crystalloids over colloids. All colloids are more costly than crystalloids, and the availability of colloids is limited in some settings (e.g. some low- and middle-income countries)¹⁰⁻¹².

One study performed by Maitland et al demonstrated that fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in resource-limited settings in Africa. The results of this study challenge the importance of bolus resuscitation as a lifesaving intervention in resource-limited settings for children with shock who do not have hypotension and raise questions regarding fluid-resuscitation guidelines in other settings as well. Another study conducted the Surviving Sepsis Campaign Guidelines and did not demonstrate

any advantages in more aggressive fluid therapy treatment in children with septic shock¹⁰⁻¹⁵.

One dynamic analysis during fluid therapy seems to be related to a better evolution.

Hemodynamic Monitoring and Inotropic/Vasopressor Support

Shock can be a presentation in children with COVID-19, but the prevalence is low even in patients with severe respiratory dysfunction. Cardiac injury may correlate with the prevalence of shock and impact in the prognosis. In a study of 150 adult patients from 2 hospitals in Wuhan, China, shock was a major reason for death in 40% of the cases, which may, at least in part, be due to fulminant myocarditis. Monitoring some clinical hemodynamic non-invasive and invasive parameters is very important: skin temperature, capillary refilling time, cardiac rate, invasive arterial pressure, oximetry, capnography, pulse pressure variation, mental status, diuresis, sequential central venous pressure, central venous oxygen saturation, lactate, and cardiac index^{10,11,15}.

Accumulating clinical data, in addition to the common clinical presentation of respiratory failure caused by COVID-19, the cardiovascular manifestations induced by this viral infection have generated considerable concern. In adults, for example, NT-proBNP elevation and arrhythmias were significantly more common in patients with elevated troponin levels, and NT-proBNP was significantly correlated with troponin levels. Special attention is necessary for patients with congenital cardiac malformation because viral illness can further damage myocardial cells through several mechanisms including direct damage by the virus and systemic inflammatory response¹⁴⁻¹⁶.

For children and adolescents with COVID-19 and shock, we prefer epinephrine or norepinephrine (depending on the manifestation of hypo- or hyperdynamic shock), instead of dopamine. In the case of COVID-19 and shock with strong evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and epinephrine or norepinephrine, we suggest adding dobutamine or another inotropic agent^{15,16}.

Nutritional Therapy

It's very important to avoid overfeeding patients with SARS-CoV-2 due to the risk of hypercapnia. In adults, 50.5% of patients reported a digestive symptom, including: lack of appetite (81 [78.6%] cases),

diarrhea (35 [34%] cases), vomiting (4 [3.9%] cases), and abdominal pain (2 [1.9%] cases). Altered digestive process and malabsorption can occur, and special diets (oligomeric without lactose) may be necessary. We also need to bear in mind that viruses can persist in feces long after they are absent from nasopharyngeal secretions. It has been found that ACE2 is not only expressed in lung Alveolar type 2 progenitor cells (AT2 cells), but also in upper esophageal and stratified epithelial cells, as well as intestinal epithelial cells in the ileum and colon. Therefore, intestinal symptoms of SARS-CoV-2 may be associated with the invasion of intestinal epithelial cells. Another study in adult patients with SARS-CoV-2 infection who were transferred to the intensive care unit found a higher frequency of abdominal pain in these patients than in those with SARS-CoV-2 infection who did not require intensive care, and 10% of patients with COVID-19 experienced diarrhea and nausea symptoms^{17,18}.

In critically ill patients with SARS-CoV-2 infection and severe pulmonary injury, avoiding gastroesophageal reflux in consequence of excessive gastric distention is a major attitude. The gastric administration of the diet is preferred to optimize digestive activity but in the case of failure, we suggest the postpyloric via (jejunal preferably)^{17,18}.

Nutritional treatment recommendations to date are based on observations, rather than evidence from clinical trials.

Drug Therapy

Since the COVID-19 outbreak in December 2019, doctors around the world have faced several challenges in the management of COVID-19 patients. One of them is the choice of adequate therapy^{1,19-21}. A wide range of medications is being studied for the management of these patients; however, none of them has been established as the gold standard yet. Supportive therapy, like the ones cited previously in this article, are still the mainstay in the management of COVID-19 patients^{1,20}. Since there are no specific antiviral agents against Sars-CoV-2, multiple pharmacologic agents are being tested, some of them such as anti-viral agents, antimalarial drugs, corticosteroids, intravenous immunoglobulin, and selective cytokine blockers, such as anakinra or tocilizumab^{1,22-25}. Among these options, one available choice is using a broad-spectrum antiviral drug like nucleoside analogs and HIV-protease inhibitors that could attenuate virus infection²⁶. Besides antiviral agents, antimalarial

drugs have also been tested with apparently positive results²⁷. In children, until now, no antiviral therapeutic agent is recommended and the only treatment recommendation described suggests the use of nebulized interferon-alpha-2b^{20,28}.

Given the multiple treatment options, we chose to unravel the drugs that seem more promising and the various studies that have been conducted. Most of these studies have been carried out in adult populations since children seem to have a milder clinical course, with multiple, but still unknown, possible reasons^{1,20,29-32}. One suggested reason is that children may be less susceptible to the infection as a result of possible differences in the expression of the angiotensin-converting enzyme 2 (ACE2)^{24,25,32}. Despite that, the importance of children in virus transmission remains uncertain. If bacterial coinfection is suspected, antibiotic therapy must be timely initiated^{1,20}.

Antimalarial agents, such as chloroquine and its derivative, hydroxychloroquine, potential antiviral drugs, have shown positive results during in vitro testing against SARS-CoV-2 and in some clinical studies with COVID 19 adult patients^{27,33,34}. Chloroquine blocks viral entry to endosomes by increasing their pH, inhibiting the replication and spread of SARS-CoV-2^{33,34}. The immunomodulant effect of chloroquine may enhance the antiviral effect in vivo^{23,26,27,33}. The low cost and safety profile of chloroquine are major benefits for its use in the healthcare system; however, this is still a topic for debate.

The use of lopinavir and ritonavir, both antiviral drugs, is being discussed as a treatment option against Sars-CoV-2^{26,33,35}. One study conducted in Hong Kong showed benefits in SARS patients treated with lopinavir/ritonavir and ribavirin when compared with only ribavirin^{36,37}. However, a recent open-label trial with 199 patients conducted in China found no benefits in the lopinavir/ritonavir group and had more adverse events with the use of the medication³⁸. Another retrospective study did not observe the shortening of viral shedding duration after lopinavir/ritonavir treatment³⁹. Further studies are necessary to establish the real role of this medication in the Sars-CoV-2 treatment, especially in the pediatric population.

Corticosteroids

Infection by Sars-CoV-2 can induce an important inflammatory response and provoke the release of cytokines, therefore corticosteroid use for the treatment of patients with severe illness was an option

since they can reduce the inflammatory-induced lung injury²³. Despite that, posterior evidence suggested that corticosteroids did not affect mortality. Instead of this desired result, corticosteroids delayed viral clearance. So, in the meantime, the use of corticosteroids should not be routine⁴⁰.

Notwithstanding the evidence against the use of corticosteroid, in some clinical situations, they are beneficial, such as PARDS, encephalitis, hemophagocytic syndrome, or septic shock and asthma patients^{1,10,22,32}.

Coagulopathy and Antithrombotic Therapy

To date, there is no literature regarding anticoagulation in COVID-19 patients in the pediatric population. All information comes from adult studies⁴¹⁻⁴³.

In adult patients with COVID-19, two recent retrospective studies have shown that the existence of disseminated intravascular coagulation is common in nonsurvivors, with abnormal coagulation results, in particular elevated D-dimer and fibrin degradation product^{42,44,45}. This information may help guide therapy and evaluate prognosis. Besides these results, a recent article reported that occlusion and microthrombosis formation in pulmonary small vessels occurred in one critical patient with COVID-19 after lung organ dissection⁴⁶. A recently published study demonstrated that anticoagulant therapy seems to be associated with better prognosis in severe COVID-19 patients, especially those with markedly elevated D-dimer⁴⁷.

Considering the risk for venous thromboembolism in patients with severe COVID-19, expert consensus in China and by the International Society of Thrombosis and Haemostasis recommend a prophylactic dose of low molecular weight heparin to all COVID-19 patients who require hospital admission, in the absence of any contraindications⁴⁷⁻⁴⁹. It is also recommended the therapeutic administration of heparin in cases of pro-thrombotic conditions. Unfortunately, until the time of this publication, there are no data that support its use in children.

Plasma / Immunoglobulins

No specific treatment has been proven to be effective for Sars-CoV-2, and specific drugs have been researched. Convalescent plasma or immunoglobulins have been used as an empirical treatment during the Ebola virus outbreak in 2014 and in the Middle East respiratory syndrome coronavirus in 2015. In patients with pandemic 2009 influenza A H1N1 virus infection (H1N1pmd09), there was a reduction in the relative

risk of mortality and no adverse events were observed. Therefore, the use of convalescent plasma transfusion could be beneficial in patients with SARS-CoV-2. The plasma is donated from recovered SARS-CoV-2 patients that may have a high level of antibodies⁴⁷⁻⁵⁰. Recently, Shen et al.⁴⁷ described a case series of 5 patients with severe disease, rapid progression, and refractory hypoxemia. They were treated with plasma and their clinical condition improved, as did their body temperature, PaO₂/FiO₂ ratio, and chest imaging⁵¹. A study performed by Zhang et al.⁵⁰ showed no serious adverse reactions associated with the transfusion of convalescent plasma in four critically ill patients infected with SARS-CoV-2. The risks of convalescent plasma administration are associated with the transfer of blood substances, which include infections and immunological reactions to serum constituents. The

Surviving Sepsis Campaign guideline of COVID-19 suggests against the routine use of standard intravenous immunoglobulin (IVIG) and the routine use of convalescent plasma because poor efficacy data are available and more evidence is necessary¹⁰. The FDA (US Food and Drug Administration) has approved the use of plasma from recovered patients to treat people who are critically ill with COVID-19⁵¹. Therefore, therapy with convalescent plasma may be considered within the context of a well-designed clinical trial.

Physiotherapy during COVID-19

It's very important to have adequate management of the physiotherapy team considering the following aspects: avoid or minimize movement of professionals during work shifts; encourage psychological assistance programs to the entire team in consequence of

TABLE 1. INTERVENTIONS INVOLVING THE PARTICIPATION OF A PHYSICAL THERAPIST

INTERVENTIONS INVOLVING THE PARTICIPATION OF A PHYSICAL THERAPIST	MODERATE INFECTION	SEVERE INFECTION	CRITICAL INFECTION
Removal of airway secretion (upper and/or lower)	If secretion present in airway	YES	YES
Pulmonary Reexpansion	If atelectasis	If atelectasis	YES
Prone Position	Not applicable	YES	YES
Early mobilization	If comorbidities and/or immobilization syndrome	YES	NO
Mobilization/Exercises (passive and/or active-assisted)	If comorbidities and/or immobilization syndrome	YES	YES
Low flow oxygen (uo to 6 L/min)	YES	NO	Not applicable
High Flow Nasal Oxegen therapy (HFNO)	If in negative pressure ward (or ventilated isolation ward) + indicated PPEs	NO	Not applicable
Non-Invasive Ventilation (NIV)	If in negative pressure ward (or ventilated isolation ward) + indicated PPEs	If in negative pressure ward (or ventilated isolation ward) + indicated PPEs	Not applicable
Cuff-pressure monitoring	YES, if patitent with tracheostomy	YES, if tracheostomy or intubated patient	YES
Bag-mask ventilation	NO	NO	YES, if bacterial filter use in a bag and/or acrylic box
Manual Hiperinsufflation	NO	NO	YES, if bacterial filter use in a bag and/or acrylic box
Respiratory mechanic monitoring	If in NIV or chronic ventilated patient	YES	YES
Inhaled nitric oxide (Noi)	Not applicable	NO	YES
HFOV / HFV	Not applicable	Not applicable	Not applicable
Endotracheal intubation	NO	May be necessary	YES
Extubation	NO	May be necessary	YES, when clinically stable
Unplanned extubation	Not applicable	May occur	May occur
Airway aspiration	May be necessary	YES	YES

OBS: in asymptomatic cases or cases with mild COVID-19 infection there is no need for a physical therapist in the hospital environment; it is understood as "not applicable" when there is no scientific evidence and/or clinical report of the benefits of the conduct; it is understood as YES when the conduct can be applied in pediatrics and includes the performance of a Physiotherapist; it is understood as NO when the conduct is not applied in pediatrics and/or does not require the participation of a Physiotherapist. LEGEND: NIV = non-invasive ventilation; HFOV = high frequency oscillatory ventilation; HFV = high frequency ventilation due to flow interruption; Noi = inhaled nitric oxide; PPE = personal protective equipment.

the high risk of Burnout (state of emotional, physical, and mental exhaustion caused by excessive and prolonged stress)⁵².

We recommend guiding and instructing all awake patients to cough correctly during physiotherapy procedures: when coughing or sneezing, cover the mouth and nose with the forearm or a handkerchief, which should be immediately discarded. Then wash hands with soap and water or 70% gel alcohol⁵².

The interventions that include the participation of a physical therapist are listed in table 1 and must consider the severity of the disease infection for the indication or not of the procedures.

CONCLUSIONS

The Sars-CoV-2 infection is a new challenge for all healthcare professionals. In children and adolescents, frequently, the disease is milder in clinical and radiologic aspects if compared to adults, but critically ill pediatric patients have been described in all ages.

Several approaches as important as respiratory support must be considered. The analysis of radiologic findings, adequate fluid therapy, hemodynamic support, early nutritional therapy, and physiotherapy are essential during treatment. Other therapeutics (corticosteroids, antiviral therapy, antithrombotic therapy, and use of immunoglobulins) are controversial but can be useful after solid investigation. We emphasize the importance of a multi-professional approach for adequate recovery.

Acknowledgments

We would like to thank Dr. Jorge David Aivazoglou Carneiro

Authors Contribution

Juliana Ferreira Ferranti; Isadora Souza Rodriguez; Emiliana Motta; Cíntia Johnston; Werther Brunow de B Carvalho; Artur Figueiredo Delgado - Contribution: bibliographic survey, design, critical analysis, writing and agreement on the conclusions.

RESUMO

A síndrome respiratória aguda grave (SRAG) pelo novo coronavírus (SARS-CoV-2) é um novo desafio para todos os países e crianças estão predispostas a adquirir a doença. Alguns estudos demonstraram quadros mais graves em adultos, mas crianças criticamente doentes foram descritas em todas as idades. O envolvimento pulmonar é a principal característica e a necessidade de suporte ventilatório é comum nos casos mais graves. Entretanto, outras abordagens terapêuticas importantes devem ser consideradas. Nesse artigo revisamos extensamente a literatura médica até o momento a fim de citar os principais recursos terapêuticos para o manejo dos pacientes pediátricos durante o período de suporte ventilatório. Achados radiológicos, terapia fluidica, terapia antiviral, o uso de corticosteroides, terapia antitrombótica e o uso de imunoglobulinas foram analisados a fim de guiar os profissionais durante o período de hospitalização desses pacientes. Nós reforçamos a importância de uma abordagem multiprofissional para recuperação adequada.

PALAVRAS-CHAVE: Criança. Coronavírus. SARS-CoV-2. COVID-19.

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