

# What if COVID-19 affects the child: which weapons and how to use them

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**Abstract.** – Since the reports in Wuhan (China), in December 2019, of the first cluster of cases of pneumonia caused by the new Coronavirus called 2019-nCoV or SARS-CoV-2, there has been a pandemic spread of the infection. By now, we have no specific therapy to counteract this emergency. The latest epidemiological data suggest that children are just as likely as adults to get infected by the virus. Most of them show mild clinical pictures or are completely asymptomatic, but there is an increased risk for severe disease in infancy (<12 months of age) and in children with underlying medical conditions. In this article, research achievements on the treatment of pediatric SARS-CoV-2 infection are examined.

*Key Words:*

COVID-19, 2019-nCoV, SARS-CoV-2, Treatment, Pediatrics, Review.

## Introduction

In December 2019, the first cluster of pneumonia cases was reported in Wuhan (China), which have been attributed to the new Coronavirus identified as 2019-nCoV or SARS-CoV-2: the term COVID-19 is instead used to define the pathology that it causes<sup>1</sup>.

Since then, there has been a progressive spread of the infection globally. Thus, the World Health Organization declared COVID-19 pandemic, on March 11, 2020<sup>2</sup>. We cannot currently rely on a specific therapy for SARS-CoV-2 infection. Therefore, clinical management is usually based on supportive therapy and treatment of complications<sup>3</sup>.

Epidemiologically, although literature showed a lower susceptibility to the virus above children, further data have indicated that transmission events may occur in children as in adults. However, pediatric patients are less likely to be symptomatic or to develop severe disease<sup>4</sup>. In addition, recorded deaths are rare<sup>5</sup>.

This article aims to examine the results so far achieved in terms of treatment of COVID-19, with particular attention for the pediatric population.

## Epidemiology

As per the WHO estimates of March 28, 2021, there have been 126,372,442 confirmed cases and 2,769,696 deaths reported worldwide<sup>6</sup>. In Italy, as of April 4, 2021, the confirmed cases are 3,616,960 with 108,637 deaths<sup>7</sup>.

Initially, scientific papers reported that children only accounted for 1-5% of diagnosed COVID-19 cases, but more recent data<sup>8</sup> show that 9%-12% of patients in the United States are pediatric. In addition, the prevalence of infected children might be underestimate due to the high number of asymptomatic children who have not been tested<sup>4</sup>.

In fact, they often develop milder disease and death less commonly occurs among them than in adults<sup>9</sup>. Nevertheless, it has been reported that children younger than 1 year of age or affected by pre-existing comorbidities (such as congenital heart disease, bilateral hydronephrosis, renal calculus, obesity) have a higher risk to show severe manifestations<sup>4</sup>.

### **General Treatment**

Initial assessment should make the determination if the patient has a mild, moderate or severe illness. Indeed, patients with mild symptoms can be managed at home with supportive care, appropriate isolation, and education of caregivers regarding emergency warning signs<sup>8</sup>. First of all, it is necessary that the child rests in bed and that sufficient caloric intake and the maintenance of the hydro electrolytic balance are guaranteed. Suppose body temperature exceeds 38.5°C or is associated with significant general discomfort, in that case, it is recommended to apply physical cooling techniques and possibly administer antipyretics (ibuprofen orally 5-10 mg/kg or paracetamol orally 10-15 mg/kg)<sup>10-12</sup>.

On the other hand, patients with moderate to severe symptoms should be hospitalized for specialized care<sup>8</sup>.

### **Pharmacological Therapy**

SARS-CoV-2 is a single-stranded RNA virus capable of entering the cells through the link between its surface S glycoprotein and the angiotensin 2 converting enzyme (ACE2). Given the lack of a specific antiviral agent to treat the infection, decrease viral shedding and subsequent transmission, several molecules have been proposed<sup>13</sup> for the treatment of the infection, taking into account the structural characteristics of the virus and the mechanisms of the viral cycle.

In detail, the different therapies are reported in Table I.

### **Antiviral Therapy**

According to the current guidelines for the management of COVID-19, the main antiviral drugs are the following:

- Interferon- $\alpha$  (IFN- $\alpha$ )
- Lopinavir/ritonavir (LPVr)
- Ribavirin
- Arbidol (Umifenovir)<sup>14</sup>

### **Interferon- $\alpha$**

Interferon- $\alpha$  is a broad-spectrum antiviral that can induce the release of intracellular enzymes, which cause alterations in the viral messenger RNA and inhibit protein synthesis<sup>15</sup>. Clinically, the first use can help to alleviate symptoms and shorten the course of the disease by reducing viral load.

In children, the following use is recommended:

**1. Interferon- $\alpha$  nebulization:** 100,000-200,000 IU/kg for mild forms or 200,000-400,000 IU/kg for more severe cases, twice a day for 5-7 days.

**2. Interferon- $\alpha$ 2b spray:** 1-2 administrations on each side of the nasal cavity, 8-10 to the oropharynx for a treatment course of 5-7 days, indicated in the initial phase of the disease or following close contact with a suspected case. The daily dosage should not be less than 800,000 IU<sup>12</sup>. IFN- $\alpha$  overdose could cause liver enzyme abnormalities, renal failure, and clotting disorders. For this reason, it is contraindicated in patients with hepatic impairment or creatinine clearance (CrCl) <50 mL/min, as well as with a history of mental illness, heart disease, or aplastic anemia.

Adverse reactions to IFN- $\alpha$  mainly include fever and flu-like symptoms, growth retardation (especially when combined with ribavirin), and suicidal ideation (more common in adolescents)<sup>16</sup>.

### **Lopinavir/ritonavir (LPVr)**

Lopinavir is a known antiretroviral approved for the treatment of HIV infection, which has shown efficacy in inhibiting the chymotrypsin-like protease 3 of new Coronaviruses (MERS-CoV, SARS-CoV, and HCoV-229E)<sup>17</sup> and recently *in vitro* also against SARS-CoV-2<sup>18</sup>.

It is administered in combination with ritonavir, with less antiviral power but it is able to increase the bioavailability of lopinavir through the block of cytochrome p450<sup>19</sup>. LPVr has the advantage to be widely available and has an established toxicity and drug-drug interactions profile<sup>20</sup>. It is available orally in tablets and in solution (formulation most suitable for children with body surface area less than 0.6 m<sup>2</sup> or unable to swallow the tablets). In the USA, it is contraindicated under the age of 14 days, in China under 6 months of age<sup>16</sup>, whereas in Italy and other European countries it is suitable for children aged 2 years and over<sup>21</sup>. The use of lopinavir/ritonavir (200 mg/50 mg) is recommended at the following doses:

- weight 7-15 kg: 12 mg/3 mg/kg
- weight 15-40 kg: 10 mg/2.5 mg/kg
- weight > 40 kg: 400 mg/100 mg.

Therapy should be administered twice a day for 1-2 weeks.

The use should be monitored when liver function is impaired and administered in association with drugs that may affect cytochrome CYP3A

**Table I.** Main drugs for COVID-19 in pediatric age.

Drug	Age	Dosage	Warnings
IFN- $\alpha$	Nebulization: use with caution if age < 2 months	Nebulization: 100.000-200.000 IU/kg or 200.000-400.000 IU/kg twice/day for 5-7 days. Spray: 1-2 spray in each nostril and 8-10 spray in oropharynx for 5-7 days.	AE: fever, suicidal ideation, growth retardation Overdosage: Liver enzyme alteration, renal failure, coagulation disturbances Contraindications: altered liver function, CrCl < 50 mL/min, history of mental diseases, cardiopathy, aplastic anemia
LPVr	USA > 14 days China > 6 months Italy and Europe > 2 years	<ul style="list-style-type: none"> <li>• 7-15 kg: 12 mg/3 mg/kg twice/day</li> <li>• 15-40 kg: 10 mg/2,5 mg/kg twice/day</li> <li>• &gt; 40 kg: 400 mg/100 mg twice/ day for 1-2 weeks.</li> </ul>	AE: diarrhea, vomiting, skin rash, prolonged PR interval, second or third grade block Contraindications: altered liver function
Ribavirin	China > 6 year USA and Europe > 3 years	Infusion i.v.: 10 mg/kg (max 500 mg) 2-3 times/day.	AE: fever, headache, neutropenia, fatigue. Overdosage: hemolytic anemia, cardiac injuries Contraindications: altered liver function, CrCl < 50 mL/min, and SCr > 2 mg/dL.
Arbidol	Russia and China > 2 years (prophylaxis and treatment of influenza)	0,2 g twice a day, no more than 10 days	AE: nausea, diarrhea, vertigo
Oseltamivir		<ul style="list-style-type: none"> <li>• &lt; 12 months: 3.5 mg/kg twice/day</li> <li>• <math>\geq</math> 12 months: – <math>\leq</math> 5 kg: 30 mg twice/day; – 15-23 kg: 45 mg twice/day; – 23-40 kg: 60 mg twice/day; – &gt; 40 kg: 75 mg twice/day.</li> </ul>	AE: vomiting, diarrhea, abdominal pain, insomnia, and neuropsychiatric disorders
Remdesivir		<ul style="list-style-type: none"> <li>• Weight &gt; 40 kg: a single 200 mg dose on day one, followed by a daily 100-mg dose from day 2 up to 10 days.</li> <li>• Weight &lt; 40 kg: a single dose of 5 mg/kg on day one, followed by a daily dose of 2.5 mg/kg from day 2 up to 10 days.</li> </ul>	For pediatric age only for compassionate use
Corticosteroids		Methylprednisolone i.v.: 1-2 mg/kg/day for 3-5 days dexamethasone: 6 mg/day for 10 days	Use if: <ul style="list-style-type: none"> <li>• Rapid worsening of imaging during ARDS;</li> <li>• Eencephalitis and encephalopathy; septic shock;</li> <li>• Wheezing and respiratory difficulty</li> </ul>
Immunoglobulins		1 g/kg/day for 2 days or 400 mg/kg/day for 5 days	Use only in severe cases.
Tocilizumab		8 mg/kg (max 800 mg), infusion time of 1 hour.	During the treatment monitor: leucocytes count, liver function, CRP. Caution in TBC and chemotherapy

Adapted from Wang Y, Zhu LQ. Pharmaceutical care recommendations for antiviral treatments in children with coronavirus disease in 2019. *World J Pediatr* 2020; 16: 271-274. doi:10.1007/s12519-020-00353-5.

activity. LPVr may cause an increase in the PR interval or a second/third-degree block: it should, therefore, be used with caution in children with

congenital QT-elongation syndrome. The most common adverse reactions include diarrhea, vomiting, skin rash<sup>16</sup>.

In case of unavailability of LPVr, the darunavir/ritonavir combination, which guarantees similar activity and proven safety, can be used as an alternative at a dosage of 600 mg twice a day<sup>22</sup>.

According to a randomized controlled trial conducted in hospitalized adults with SARS-CoV-2 infection and respiratory failure, LPVr appears to have little to no role in the treatment of the disease since no significant difference in terms of clinical improvement was detected<sup>23</sup>.

Moreover, a retrospective multicenter analysis showed that LPR treatment was associated with a longer hospitalization duration, a longer nasopharyngeal swab negative time and it caused more adverse reaction than conventional treatment with interferon- $\alpha$ 2b inhalation therapy<sup>24</sup>.

### **Ribavirin**

Ribavirin is a nucleotide analogue that inhibits viral RNA polymerase, thereby inducing a mutagenic effect on the genome<sup>25</sup>. This drug is authorized for the treatment of respiratory syncytial virus (VRS) infections in children and, in combination with interferon- $\alpha$ 2b, of hepatitis C. It has also been used against SARS-CoV<sup>26</sup>, because it seems to play an important role in the therapy of COVID-19<sup>27</sup>. The oral formulation is not recommended in China for children under 6 years of age, in Europe and the USA under 3 years. In a pediatric patient with COVID-19, an intravenous infusion at the dose of 10 mg/kg (maximum 500 mg) 2-3 times a day is indicated.

This drug should be used with caution in case of hepatic impairment, while it should be avoided in all patients who have a CrCl <50 mL/min or serum creatinine (SCr) > 2 mg/dL.

The most common adverse reactions are fever (80%), headache (62%), neutropenia (33%), fatigue (30%)<sup>16</sup>. In addition, an overdose of ribavirin could cause hemolytic anemia and severe cardiac damage<sup>28</sup>. Given the limited benefits and the significant toxicity that emerged from the use of ribavirin against other Coronaviruses, its use in the treatment of COVID-19 seems unpromising, apart from as a combined therapy at low doses<sup>13</sup>.

### **Arbidol (Umifenovir)**

Arbidol (umifenovir) is an antiviral approved in Russia and China for the prophylaxis and treatment of influenza, able to block the fusion of the virus with the cell membrane, targeting hemagglutinin (HA)<sup>29</sup>. It appears that arbidol can

act in a similar way against SARS-CoV-2, also interfering with the formation of the complex glycoprotein S-ACE2<sup>13</sup>. Currently, the compound is not indicated in children with COVID-19. It is available as an oral formulation: the recommended dosage is 200 mg twice a day (no more than 10 days). The most frequent adverse reactions include nausea, diarrhea, and dizziness<sup>16</sup>.

### **Antibiotic Therapy**

The use of antibiotics must be avoided indiscriminately, but it cannot be ignored in case of bacterial superinfections responsible for a clinical worsening of the child<sup>11,12</sup>. Some authors suggest, indeed, the routine administration of an antibacterial treatment based on the finding of co-infection in a substantial percentage of pediatric patients in their case series<sup>30</sup>. In general, it is indicated to start an empirical therapy with broad-spectrum antibiotics (such as second or third generation cephalosporins)<sup>31</sup>, at the usual dosage<sup>32</sup>, and then, after having obtained the result of the antibiogram, a targeted therapy must be set up.

### **Antithrombotic Prophylaxis**

COVID-19 is often associated with the hypercoagulable state which can lead to venous thromboembolism (VTE) or microthrombosis. The mechanisms that activate coagulation are complex and they are part of organism defense against pathogens, in this case against SARS-CoV-2. During the infection, dysregulation of coagulation, platelet activation and leukocyte recruitment in the microvasculature take place and play an important role in the context of COVID-19-associated complications. Patients with mild COVID-19 should not receive pharmacological thromboprophylaxis but an appropriate hydration, above all in presence of fever, should be encouraged. Patients with moderate COVID-19 who need hospitalization should receive anticoagulation therapy with low-molecular-weight heparin (LMWH) prophylactic dose. In patients with severe COVID-19, it is recommended to intensify anticoagulation therapy. In critically ill COVID-19 patients, it is recommended to introduce an anticoagulation therapeutic dose. During treatment, anti-factor Xa levels and APTT ratios are good ways to determine the efficacy of therapy. Moreover, it is recommended a regular monitoring of D-dimer, fibrinogen, platelet count, PT, PTT, PCR and ferritin.



**Prophylactic dose:** (target anti-Xa: 0.2-0.4 units/mL)

- < 2 months: 0.75 mg/kg/dose
- > 2 months to < 18 years old: < 40 kg: 0.5 mg/kg/dose; > 40 kg: 40 mg

**Prophylactic intensified dose:** (target anti-Xa: 0.4-0.8 units/mL)

- < 2 months: 1 mg/kg/dose
- > 2 months to < 18 years old: < 40 kg: 0.75 mg/kg/dose; > 40 kg: 40-60 mg

**Therapeutic dose:** (target anti-Xa: 0.6-1.1 units/mL)

- < 2 months: 1.5 mg/kg/dose
- > 2 months to < 18 years old: < 40 kg: 1 mg/kg/dose; > 40 kg: 40 mg

On discharge, it is recommended at least two weeks of anticoagulation therapy and imaging studies to evaluate thrombosis. In literature, data on moderate and severe COVID-19 in children are limited but are growing. For this reason, other studies are required to better evaluate the safety and efficacy of anticoagulation therapy<sup>33</sup>.

### ***Convalescent Plasma Therapy (CPT)***

A systematic literature review, conducted by an Italian group, showed that CPT in children with COVID-19 may be a valuable therapeutic option and it can be administered in children with severe and critical disease. However, the main limitations and biases of this review are that it includes only clinical case reports. In literature, only cases with a positive outcome have been reported so they cannot represent the entire pediatric population. In spite of that, this review can stimulate future researches based on more powerful and more reliable studies<sup>34</sup>.

## **Immunomodulating Therapy**

### ***Chloroquine and Hydroxychloroquine***

Chloroquine and hydroxychloroquine are two drugs initially used in the treatment of malaria, and then, in rheumatological diseases. They share a broad spectrum of potentially effective mechanisms of action against SARS-CoV-2: purely antiviral (obstacle to the entry of the virus into the cell through the inhibition of glycosylation of the ACE-2 receptor; block of the fusion process due to the rise of endosomal and lysosomal pH) and immunomodulating (suppression of the cytokine storm through interference with the antigen pre-

sentation process; only in case of hydroxychloroquine: pro-inflammatory gene transcription block mediated by TLR signaling)<sup>35</sup>.

Chloroquine should be used with caution in case of heart disease, liver or kidney dysfunction, porphyria, and mental illness. Adverse reactions include dizziness, headache, loss of appetite, at higher doses ocular toxicity, arrhythmias, psychosis, and leukopenia. As regards drug interactions, chloroquine has an inhibitory effect on the neuromuscular junction, which could be enhanced by the combined treatment with clindamycin, streptomycin, gentamicin. Furthermore, the association with heparin could increase the risk of bleeding, while the simultaneous use of digitalis could cause a heart block<sup>16</sup>. It is also fundamental to verify the activity of the G6PD enzyme in the patient before administering the drug<sup>20</sup>.

Ali et al<sup>36</sup>, through the analysis of the drug's pharmacokinetics and toxicity, analyzed the possible efficacy of treatment with hydroxychloroquine. They suggest using hydroxychloroquine as soon as possible, when the infection is suspected or confirmed, and to continue treatment until complete remission, dividing the dose into 3 or 4 daily administrations to minimize the incidence of side effects.

Hernandez et al<sup>37</sup> carried out a systematic review with the aim of weighing the risks and benefits of treatment with hydroxychloroquine but the studies involved in the review were few, and the results that they reached were contradictory.

Maharaj et al<sup>38</sup> performed a simulation in which an exposure to the drug for 5 days was studied (400 mg every 12 hours × 2 doses followed by 200 mg every 12 hours × 8 doses). Simulated unbound hydroxychloroquine in plasma was found to be much lower than *in vitro* concentrations needed to mediate antiviral activity.

Finally, Boulware et al<sup>39</sup> performed a randomized controlled trial to analyze the use of prophylactic hydroxychloroquine in SARS-CoV-2 post-exposure. 821 participants were enrolled and divided into two groups: one group received the drug, and the other group received a placebo. There were no significant differences in the two groups regarding the incidence of a disease compatible with COVID-19, and the group treated with hydroxychloroquine showed a greater number of side effects.

A systematic review of seven different clinical trials evaluating hydroxychloroquine or chloroquine as therapy for COVID-19 in adults patients concluded that there was insufficient evidence to

support routine use of these drugs to treat the infection<sup>40</sup>. In addition, Maharaj et al<sup>38</sup> assessing the pediatric specific dosing regimens for remdesivir and hydroxychloroquine raised concerns about the use of hydroxychloroquine for COVID-19 treatment, because unbound plasma exposures were less than those needed to mediate an antiviral effect.

In conclusion, chloroquine and hydroxychloroquine are two molecules on which research has recently concentrated its energies, and several trials are still underway. However, the results appear discordant and contradictory. The most recent studies seem to suggest the ineffectiveness of treatment with hydroxychloroquine or chloroquine alone or in combination with azithromycin, but further studies are needed to have a definitive answer above the efficacy of these drugs.

### **Tocilizumab**

Tocilizumab is a monoclonal antibody that acts against the interleukin-6 receptor (IL-6R), available for rheumatoid arthritis from several years. The rationale for its use lies in counteracting inflammatory dysregulation, characteristic of the most critical forms of infection, and supported in particular by Th1 lymphocytes and monocytes, through the release of large quantities of IL-6<sup>41</sup>. In the literature, several works<sup>42,43</sup> report that tocilizumab can produce significant benefits in a short time, in terms of improvement of the respiratory picture, defervescence, reduction of inflammation indexes and discharge in patients severely affected by SARS-CoV-2.

The guidelines suggest using tocilizumab at a dose of 8 mg/kg (maximum 800 mg), with an infusion time of at least 1 hour. Subsequent administrations should be evaluated based on clinical response.

During treatment, it is necessary to monitor leukocyte count, AST/ALT, and PCR values since tocilizumab could be responsible for severe infections and hepatitis. It should also be administered with caution in case of tuberculosis or chemotherapy<sup>22</sup>.

### **Corticosteroids**

The use of glucocorticoids in patients with ARDS (associated or not with 2019-nCoV infection) is much debated in the literature. On the one hand, they can suppress the inflammatory lung picture, on the other hand, they induce inhibition of the immune response and patho-

gen elimination. In addition, the adverse effects typically associated with corticosteroid therapy are known<sup>44</sup>.

In a retrospective study conducted in 201 COVID-19 patients in China, treatment with methylprednisolone in the presence of ARDS was associated with a reduced risk of death<sup>45</sup>. In addition, the multicenter Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, a large controlled, open-label trial, comparing a range of possible treatments in patients who were hospitalized with COVID-19, shows a reduction in 28-day mortality among patients treated with dexamethasone who were receiving either invasive mechanical ventilation or oxygen alone<sup>46</sup>.

Chen et al<sup>11</sup> suggest evaluating the use of corticosteroids in pediatric patients in the following situations:

- rapid deterioration of the picture to imaging and in the presence of ARDS;
- appearance of encephalitis and encephalopathy;
- appearance of septic shock;
- clear signs of wheezing and difficulty in breathing.

In all these cases, it is recommended to use intravenous methylprednisolone at a dosage not exceeding 1-2 mg/kg/day for 3-5 days<sup>11</sup>.

A randomized controlled trial<sup>47</sup> was conducted in the UK whose goal was to study the effect of another corticosteroid, dexamethasone. 2100 patients were enrolled in the treated arm and received a dose of 6 mg per day for 10 days, while in the control arm, patients received standard care for coronavirus infection. In the trial, dexamethasone reduced deaths by one-third in patients who were on ventilators and decreased the risk of dying by 20% in patients undergoing oxygen therapy. In patients with a mild clinical picture, however, it had no effect. On the one hand, the result of this trial is extraordinary, on the other hand, further large-scale studies are needed to confirm the effectiveness of this therapy<sup>47,48</sup>.

### **Immunoglobulins**

Intravenous immunoglobulins (IV Ig) have been used for over 30 years in the treatment of pathologies on an inflammatory or autoimmune basis, as well as for the treatment and prophylaxis of serious infections, especially in immunocompromised patients<sup>49</sup>.

Despite this, the mechanisms underlying their efficacy have not yet been clearly defined. It

seems that they could interfere with the activation of numerous innate immunity cells, neutralize activated complement components and modulate the activity of B lymphocytes and plasma cells, acting also on T cells function and cytokine production<sup>50</sup>.

Xie et al<sup>51</sup> highlighted how the administration of IV Ig in critical forms of COVID-19 could give promising results, especially in terms of a reduction of hospitalization and mortality at 28-day.

The current pediatric indication is for severe cases, at a dose of 1 g/kg/day for 2 days or 400 mg/kg/day for 5 days<sup>11</sup>.

## Other Drugs

### ***Oseltamivir***

Oseltamivir is a neuraminidase inhibitor used against the flu virus. Although it does not have *in vitro* activity against 2019-nCoV, it was initially used in the treatment of COVID-19<sup>13</sup>, as reported in pediatric patients<sup>52</sup>.

This drug is also present in the diagnostic-therapeutic algorithm developed by the Consensus of Iranian experts for the management of the child with COVID-19. In particular, it is recommended for administration in combination with other antivirals and immunomodulators, at the following dosage:

- < 12 months: 3.5 mg/kg bid
- ≥ 12 months:
- ≤ 5 kg: 30 mg bid;
- 15-23 kg: 45 mg bid;
- 23-40 kg: 60 mg bid;
- > 40 kg: 75 mg bid<sup>53</sup>.

The main side effects of this drug include vomiting, diarrhea, abdominal pain, insomnia, and neuropsychiatric disorders. Dalvi et al<sup>54</sup> did not observe any difference in the occurrence of adverse effects in patients less than or older than 1 year.

### ***Remdesivir***

Remdesivir (RDV) is a nucleotide analogue that is incorporated into the viral RNA chain and, through this mechanism, has proven to be effective against the Ebola virus and respiratory Coronaviruses<sup>55</sup>. Based on *in vitro* studies conducted both on MERS-CoV<sup>56</sup> and 2019-nCoV<sup>57</sup>, this drug seems a very promising molecule for the treatment of COVID-19. By now, remdesivir is the only antiviral therapy with FDA approval for the treatment of adults

and pediatric patients older than 12 years of age and weighing more than 40 kg requiring hospitalization for COVID-19<sup>4</sup>. A Spanish nationwide multicenter observational study<sup>58</sup> of children under 16 years of age who received compassionate treatment with RDV showed that it was associated with a successful clinical outcome and adverse reactions were not observed. RDV is a promising treatment but few data regarding safety and efficacy in children are available. Several clinical trials are underway to evaluate its effectiveness, particularly in a double-blind, randomized controlled trial that compares the administration of remdesivir with the use of supportive therapy alone. It should be remembered that this drug is available for pediatric age only for compassionate use<sup>13</sup> and the recommended doses is:

- weight > 40 kg: a single 200 mg dose on day one, followed by a daily 100 mg dose from day 2 up to 10 days.
- weight < 40 kg: a single dose of 5 mg/kg on day one, followed by a daily dose of 2.5 mg/kg from day 2 up to 10 days<sup>59</sup>.

### ***Favipiravir***

Favipiravir is an RNA-dependent RNA polymerase inhibitor that is being assessed as a potential therapy for COVID-19. It was approved for the treatment of novel influenza in 2009 and Ebola in 2014-2016. This drug seems to be promising for pediatric use, due to its high tolerability in adults and to the possibility of the tablets to be ground up and taken with food or liquids.

Although specific dosing recommendation is still lacking, the dose scheme created for the treatment of the Ebola virus or the influenza virus can be considered suitable<sup>60</sup>.

## Treatment of Critical Cases

### ***Organ Function Support***

In the case of circulatory dysfunction, the use of vasoactive drugs is recommended. Patients with acute renal impairment and renal failure should undergo dialysis, either CVVH (Continuous Venovenous Hemodialysis) or CVVHDF (Continuous Venovenous Hemodiafiltration) type. If liver failure develops in conjunction with renal failure, plasmapheresis is indicated. At the same time, it is essential to monitor brain function and act promptly if intracranial hypertension or seizures appear<sup>11</sup>.

### **Respiratory Support**

When respiratory distress occurs, and it is not possible to maintain a good saturation through the administration of oxygen with a mask or nasal cannula, it is necessary to evaluate the use of positive pressure non-invasive ventilation (CPAP). Despite this, if the picture does not improve, mechanical ventilation with endotracheal intubation must be applied<sup>11</sup>. The Pediatric Difficult Intubation Collaborative (PeDI-C) group of the Pediatric Anesthesia Society recommends using second-generation supraglottic devices to discourage the use of low or high flow nasal cannulas or ventilation with bag-mask, given the risk of viral dispersion by aerosol. If this is not possible, the application of a pure oxygen mask is recommended above the cannulas<sup>61</sup>.

### **Bronchoalveolar Lavage (BAL)**

Bronchoalveolar lavage (BAL) is not indicated in most patients, as it can increase the risk of cross-infection. You can consider it in case of:

- evident symptoms of airway obstruction,
- massive refractory atelectasis,
- significant increase in inspiratory pressure peak (PIP) during ventilator therapy,
- tidal volume reduction,
- poor blood oxygenation that cannot be resolved by conservative treatments<sup>11</sup>.

### **Extracorporeal Membrane Oxygenation (ECMO)**

ECMO is a system based on a complex cardiopulmonary bypass circuit which, through an artificial membrane, provides oxygenation of the blood in those patients in whom the functionality of the heart and lungs is compromised. There are two types of ECMO: venovenous (VV) and veno-arterial (VA). The first mainly provides respiratory support and is the most used in acute lung injury of ARDS. This method must be taken into consideration when mechanical ventilation, blood purification, and other available tools are ineffective in controlling the evolution of the respiratory picture. On the other hand, ECMO is a complicated and expensive high-risk system that requires highly qualified personnel<sup>62</sup>.

In addition, ECMO is contraindicated or should be used with extreme caution in cases where mechanical ventilation lasts for more than 2 weeks or if the young patient has severe brain damage or coagulation disorders<sup>11</sup>.

### **Case Reports in Children**

In the literature, data available referred to children treated for COVID-19 are scarce but provide a picture of the most used therapies in the pediatric field.

In a group of 10 patients aged 1 to 18 years examined by Zhu et al<sup>52</sup>, 50% received antiviral treatment, in particular interferon- $\alpha$ 2b (40%), lopinavir/ritonavir (40%), and oseltamivir (10%); only one case (10%) required oxygen therapy and another 10% required an empirical antibiotic therapy.

Qiu et al<sup>63</sup> report data on a cohort of 36 children (0-16 years), all treated with interferon- $\alpha$  for aerosol, and 14 (39%) with lopinavir/ritonavir, while oxygen was administered to 6 patients (17%).

In the retrospective analysis undertaken by Song et al<sup>64</sup> on 10 children aged between 1 month and 14 years, all of them received symptomatic antipyretic treatment, whereas only 4 (40%) were given lopinavir/ritonavir.

A report of 4 pediatric cases (20 months-11 years) in Malaysia confirms the tendency of the infection to have a milder clinical course in children: none of them required treatment with antivirals, but 2 (50%) received paracetamol, in one case (25%) associated with oral penicillin V and loratadine, while another child (25%) was treated with MDI salbutamol<sup>65</sup>.

Xu et al<sup>66</sup> reported 10 children with ages ranging from 2 months to 15 years: all were treated with the interferon- $\alpha$  oral spray, one of them (10%) also received azithromycin.

COVID-19 in children received growing attention after UK pediatricians alerted about a particular disease presentation, involving overlapping features of Kawasaki's disease, toxic shock syndrome, acute abdominal conditions and encephalopathy. This emerging disorder was at first named "pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2" (PIMS-TS), and then reclassified as "multisystem inflammatory syndrome in children" (MIS-C)<sup>67</sup>. As of July 29, 2020, 570 cases have been reported to the US CDC that met the definition of this new syndrome. Among all patients, 527 (92.5%) were treated, including 424 (80.5%) who received intravenous immunoglobulin, 331 (62.8%) who received steroids, 309 (58.6%) who received antiplatelet medication, 233 (44.2%) who received anticoagulation medication and 221 (41.9%) who were treated with vasoactive medication. Most



patients (n=364; 63.9%) required to be admitted to an intensive care unit (ICU) and 10 of them (1.8%) died<sup>68</sup>.

Saraiva et al<sup>69</sup> an interesting report from Portugal describe the experience in a level III pediatric referral hospital on the therapeutic management of hospitalized children with COVID-19. A total of 200 cases of SARS-CoV-2 infection were followed in the period from March 7, 2020 to June 14, 2020: among these, 80 were hospitalized (only 37 of them due to the virus) and 4 children (11%) were admitted to the ICU. Considering the cohort of COVID-19 hospitalized children, those affected by mild illness without risk factors (n=10; 27%) did not receive therapy. Antiviral drugs were proposed for 20 (59%) children, with a clinical or laboratory improvement observed usually 24 to 72 hours after the beginning of the treatment. In detail, hydroxychloroquine was administered in 13 (35%) patients, 8 (22%) received LPV/r and 3 (8%) were treated with remdesivir. IV Ig associated with methylprednisolone were used in children with MIS-C (n=2; 5%) and ARDS (n=1; 3%), with a favorable evolution after 24 to 48 hours of treatment. Antibiotics were administered in

16 (43%) patients, due to suspected respiratory bacterial infection. Oseltamivir was used in a patient with *influenza* B coinfection. Among more severe cases, oxygen therapy was required in 7 (19%) patients and other 3 (8%) underwent invasive mechanical ventilation. Inhaled therapy with bronchodilators and corticosteroids was used in 16 (43%) patients. Prophylactic enoxaparin was administered in 2 adolescents (one with sickle-cell disease and severe COVID-19 pneumonia and the other with MIS-C with multi-organ dysfunction). Inotropic support was needed in patients with myocarditis (n=1; 3%), MIS-C (n=1; 3%) and ARDS (n=1; 3%)<sup>70</sup>.

### Conclusions

On a global scale, the rapid spread of 2019-nCoV has placed the scientific community in front of a unique challenge in recent history. Although the virus seems to attack children less aggressively, the pediatrician's task is to identify the best management strategies among those gradually developed to deal with this emergency. Currently,

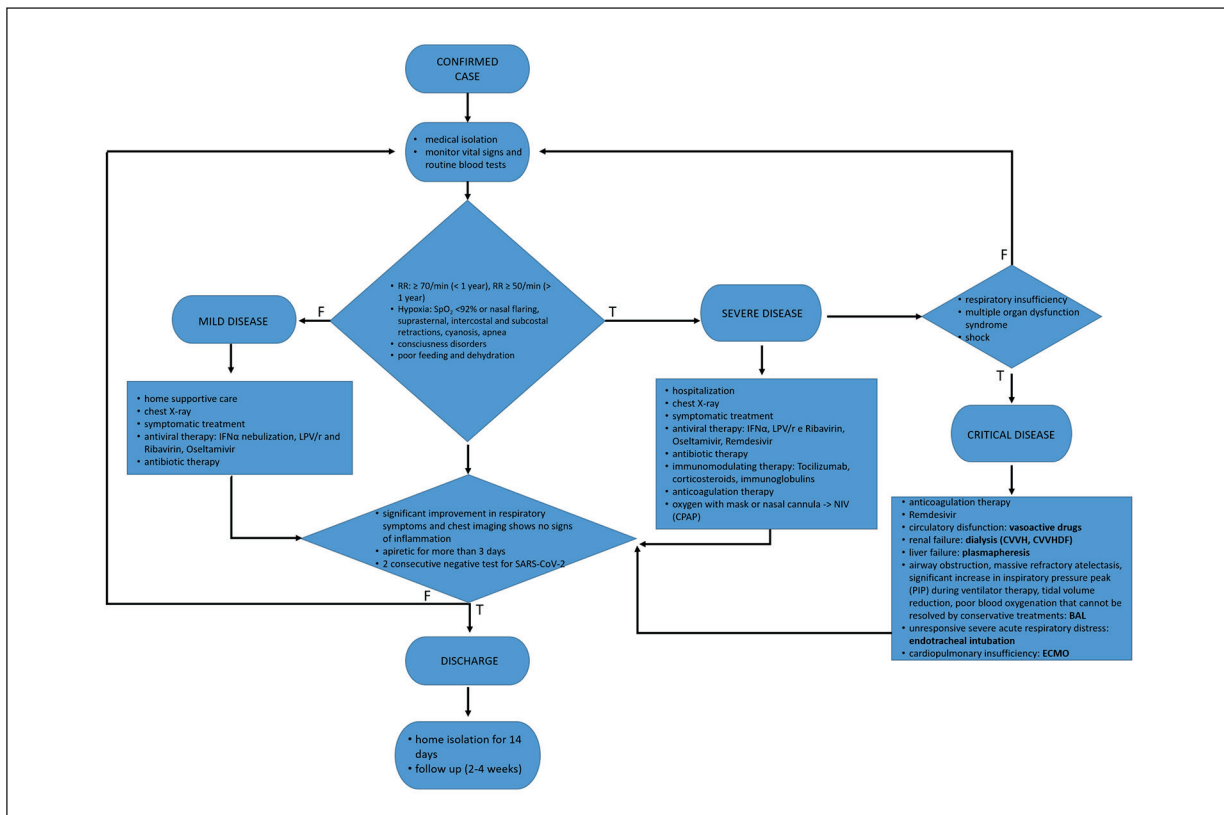


Figure 1. Management and treatment of children affected by COVID-19. Flow chart proposed by Anedda L and Bianchini L.

we have no specific therapy against COVID-19. Therefore, the therapeutic approach is based on supportive measures and the experimental use of drugs that other pathologists usually administer.

In particular, the administration of antiviral therapy (interferon- $\alpha$  or a combination of lopinavir-ritonavir and low-dose ribavirin, if possible) is indicated in the pediatric patient. In the required cases, it is indicated to resort to oxygen therapy and, in the event of a bacterial overlap, to antibiotic treatment on an empirical basis.

Rarely, clinical conditions in children require the use of more aggressive drug therapies (such as corticosteroids or immunoglobulins) and support techniques for lung (CPAP or mechanical ventilation) or other organ functions (hemodialysis, ECMO) (Figure 1). The hope is that the unceasing work of researchers all over the world will soon lead to the identification of safe and effective molecules to counteract SARS-CoV-2 infection. This will allow the definition of unique protocols of proven validity for the pediatric patient.

#### Conflict of Interest

The Authors declare that they have no conflict of interests.

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