Treatment of children with COVID-19: position paper of the Italian Society of Pediatric Infectious Disease

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Abstract

A statement of consensus was formulated after reviewing available literature on pediatric treatment strategies for COVID-19 by the Steering and Scientific Committee of the Italian Society of Infectious Pediatric Diseases in connection with the Italian Society of Paediatrics.

Keyword

COVID-19, SARS CoV-2, Children, Treatment

Background

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been reported in Hubei province, China, and from there the virus spread worldwide. Starting from the end of February 2020, the number of cases of coronavirus disease 2019 (COVID-19) outside China rapidly increased, moving the World Health Organization (WHO) in declaring COVID-19 as a pandemic on 11 March [1].

Most children with SARS-CoV-2 infection develop none or mild symptoms, needing only supportive treatment [2]. However, few cases of severe COVID-19 in children have been reported [3].

No good quality evidence are available regarding therapy of COVID-19, hence treatment regimens of COVID-19 has not been standardized. Moreover, at present there are no clinical trials for COVID-19 treatment involving children and the only published paper regarding pediatric treatment is a Chinese experts' consensus published in early February [4]. Moreover, the evidence is rapidly evolving and the therapeutic indications can be changed very quickly. However, doctors need patient management guidance from scientific societies and expert groups. In Italy, the Italian Society for Infectious and

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Tropical Diseases provided updated guidance for treatment of adults COVID-19 cases [5]. The Italian Society of Pediatric Infectious Diseases steering and scientific committee developed a position paper on treatment of children with COVID-19, reviewing the current literature on this topic and providing indications based on the available evidences.

Since new evidences will be available in the next weeks/months, the Italian Society of Pediatric Infectious Diseases will guarantee to maintain treatment indication updated on the website www.sitip.org (updated English and Italian versions of the present document).

Methods

The consensus statement was formulated by the steering and scientific committee of the Italian Society of Pediatric Infectious Diseases in connection with the Italian Society of Pediatrics.

Decision was made after reviewing available literature on pediatric treatment strategies for COVID-19 at 29th March on Pubmed with the following search strategies: (SARS-CoV-19 OR COVID-19 OR Coronavirus) AND treatment. Moreover, national and international recommendations of WHO and scientific societies available online were evaluated. Ongoing clinical trials were searched on https://clinicaltrials.gov/ and https://www.aifa.gov.it/sperimentazioni-cliniche-covid-19.

Definitions

Clinical syndromes associated with COVID-19 in children were defined adapting the WHO classification as follows [6].

***Asymptomatic case*:** infection identified during screening or contact tracing, with no symptoms.

***Mild case*:** fever and/or fatigue and/or upper airways symptoms without radiological/ultrasound findings (if performed).

Moderate case: fever and/or fatigue and/or upper airways symptoms (cough or mild respiratory distress) and/or poor feeding and/or pneumonia identified with chest X-ray or ultrasound.

Severe case:

- Fever and cough, plus at least one of the following:
  - Oxygen saturation on finger pulse (SpO2) < 92% on room air
  - Severe respiratory distress (grunting, severe chest indrawing), cyanosis, intermittent apnea
  - Fast breathing (regardless of fever and crying): respiratory rate (RR) in breaths/minute >60 <3 months; >50 3-12 months; >40 1-5 years; >30 >5 years)
- Systemic symptoms: drowsiness, lethargy, seizures, dehydration

***Critical case*:**

- Pediatric acute respiratory distress syndrome (PARDS)
- Sepsis-associated organ dysfunction
- Septic shock
- Coma

PARDS was defined according to Pediatric Acute Lung Injury Consensus Conference Group definition [7].

Sepsis-associated organ dysfunction and septic shock were defined according to Surviving Sepsis Campaign definition [8].

Regardless of the early stage of the disease, the following indicators should be assessed as related to an increased risk of rapid progression to the severe/critical stage.

***Clinical early warning indicators*:**

- Increased tachypnoea, despite 2 hours of intravenous rehydration and low flow nasal cannula oxygen therapy
- Impaired consciousness
- Progressive increasing of lactate values
- Bilateral lung infiltration or multiple lobes involvement, pleural effusion or rapid progression of the lesions in a short period of time
- Age < 3 months
- Underlying diseases (congenital heart disease, bronchopulmonary dysplasia, anomalies of respiratory tract, abnormal hemoglobin, anemia, severe malnutrition, congenital or acquired immunodeficiency)

<u>Treatment approach based on the different scenarios:</u>

***Asymptomatic or mild cases*:** only antipyretic therapy

Moderate illness with alarm symptoms *(excepting for age <3 months),* ***severe and critical cases****:*

Hydroxychloroquine

+/-

Azithromycin or **Lopinavir/ritonavir ***

in case of unavailability or intolerance of lopinavir/ritonavir:

Darunavir/ritonavir - Darunavir/cobicistat

* to be considered only in the first 10 days from symptoms onset

The combination of hydroxychloroquine with either azithromycin or lopinavir/ritonavir should be carefully evaluated for each patient on the basis of risk/benefit ratio.

Warning: Hydroxychloroquine and azithromycin can cause QTc prolongation. Perform electrocardiogram (ECG) and QTc assessment for QTc prolongation increased risk.
For hydroxychloroquine, carry out glucose 6 phosphate dehydrogenase (G6PDH) dosage in case of risk factors for deficiency.

Duration of therapy: 5-7 days, extendable according to clinical course.

In critical cases, a request for compassionate use of Remdesivir can be made in the absence of a therapeutic response.

Immunomodulating therapy:

This therapy must be considered in case of simultaneous presence of:
- ARDS or progressive deterioration of respiratory function
- Marked alteration or increasing trend of IL-6 and/or D-dimer and/or ferritin and/or C-reactive protein
- Interval of at least 7 days from the beginning of the symptoms

Methylprednisolone
in alternative
Tocilizumab or **Anakinra**

The available dosages and formulations of the various drugs are indicated in the text.

Clinical picture	Supportive care	Antiviral treatment
Asymptomatic infection	None	None
Mild case: fever and/or asthenia with upper respiratory signs	None In case of fever >38°C: paracetamol	None
Moderate case: fever and/or asthenia and/or respiratory signs/symptoms, such as cough, mild distress with	• Airway suction in case of obstruction • Oxygen therapy using nasal cannulas or facial mask with Venturi system (if oxygen saturation in air <95%)	If you experience alarm symptoms (except for age <3 months only): Hydroxychloroquine +/-

polypnea and/or difficulty in feeding, signs of dehydration	• Intravenous access, adequate fluid and caloric intake based on hydration status • Give paracetamol in case of fever >38°C • Monitor vital signs (Bedside-PEWS)[9] every 8 hours (or before in case of changes in the clinical picture)	Azithromycin in alternative, only if in the first 10 days of the onset of symptoms Hydroxychloroquine +/- Lopinavir / ritonavir (Darunavir / ritonavir-Darunavir / Cobicistat in case of unavailability / intolerance)
Severe illness: - SpO2 <92% on finger pulse oximeter taken at rest - Labored breathing (moaning, nasal flattering, sternal, clavicular and internal recesses ribs), cyanosis, intermittent apnea - Tachypnea, in apyrexia and absence of crying (respiratory rate >60 breaths/minute <3 months; >50 breaths /minute 3-12 months; >40 breaths /minute 1-5 years; >30 breaths/ minute >5 years) - Systemic signs of worsening: lethargy, inability to feed/drink, convulsions - Suspected sepsis - Shock or other organ failure requiring care	• Airway suction in case of obstruction • Oxygen therapy using nasal cannulas or facial mask with Venturi system or High Flow Nasal Cannula or Non-Invasive ventilation (target oxygen saturation >95%), refer to WHO Interim guidance • Intravenous access, adequate fluid and caloric intake based on hydration status. Monitor urinary output. • Give paracetamol in case of fever >38°C • Monitor vital signs (Bedside-PEWS) [9] every 8 hours (or before in case of changes in the clinical picture) • Avoid empiric antibiotic treatment if no evidence of bacterial infection (consult an infectious disease specialist or refer to hospital guidelines) • Consider immunomodulation: methylprednisolone or interleukin inhibitors if available (Tocilizumab, Anakinra) • Consider venous thromboembolism prevention: low molecular-weight heparin	Hydroxychloroquine +/- Azithromycin in alternative, only in the first 10 days from symptoms onset Hydroxychloroquine +/- Lopinavir / ritonavir (Darunavir / ritonavir-Darunavir / Cobicistat in case of unavailability / intolerance) Possible request for Remdesivir for compassionate use to be added to hydroxychloroquine +/- azithromycin therapy in case of non-response
Critical illness ARDS Sepsis-associated organ dysfunction Septic shock Coma	• Airway suction in case of obstruction • Oxygen therapy using nasal cannulas or facial mask with Venturi system or High Flow Nasal Cannula or Non-Invasive Ventilation (target oxygen saturation >95%). In case of mechanical ventilation refer to WHO Interim guidance • Intravenous access, adequate fluid and caloric intake based on hydration status. Monitor urinary output. • Give paracetamol in case of fever >38°C • Monitor vital signs (Bedside-PEWS) [9] every 8 hours (or before in case of changes in the clinical picture) • Avoid empiric antibiotic treatment if no evidence of bacterial infection (consult an	Hydroxychloroquine +/- Azithromycin Or, only in the first 10 days of symptoms onset Hydroxychloroquine +/- Lopinavir / ritonavir (Darunavir / ritonavir-Darunavir / Cobicistat in case of unavailability / intolerance) Possible request for Remdesivir for compassionate use to be added to Hydroxychloroquine +/- azithromycin therapy

	infectious disease specialist or refer to hospital guidelines) • Add immunomodulation: methylprednisolone or interleukin inhibitors if available (Tocilizumab, Anakinra) • Add venous thromboembolism prevention: low molecular-weight heparin	

Supportive care

Antipyretic therapy: prefer Paracetamol (10-15 mg/kg every 4-6 hours) in case of fever >38.5°C. Avoid ibuprofen in case of dehydration, vomiting and diarrhea, as it is associated with an increased risk of kidney failure. Some authors have suggested a correlation between the use of ibuprofen and an unfavorable course of SARS-Cov-2 infection [10]. However, these data are not currently confirmed and the European Medicines Agency does not contraindicate the use of non-steroidal anti-inflammatory drugs [11].

Inhalation therapy: in case of need for inhalation treatment with topic steroids and/or bronchodilators (e.g. patient with recurrent wheezing undergoing exacerbation and suggestive symptoms or confirmed SARS-Cov-2 infection), it is suggested the use of pressurized suspensions with spacer chamber. The use of nebulisers is not recommended to avoid particles aerosolization and increased contagiousness.

Ongoing steroid treatment should not be stopped [12].

Venous thromboembolism prophylaxis: severe COVID-19 seems to be associated in adults with an increased risk of disseminated intravascular coagulation and venous thromboembolism. A study on 449 adult patients with severe infection showed a lower mortality rate in those receiving anticoagulant therapy [13]. Therefore, recently adults protocols suggest strategies for prevention and management of coagulative disorders secondary to COVID19 infection with low molecular-weight heparin especially in case of ARDS [6, 14]. However, children have a much lower incidence of thrombotic complications than adults, even under higher risk conditions such as major surgery or polytrauma [15]. Therefore, this prophylaxis is not currently suggested in children.

An exception can be made for neonatal age and adolescents, where constitutionally the incidence of thrombotic complications is higher [16]. Preventive anticoagulant therapy can therefore be considered for these age groups, in cases where severe inflammatory conditions occur and therefore hyperactivation of the clotting process could lead to the appearance of important thrombotic complications.

The suggested treatment is with subcutaneous enoxaparin 100-200 U/Kg/die, that can be increased to 150-300 U/Kg/die in neonates.

Antiviral treatment

Lopinavir/ritonavir

Lopinavir/ritonavir is a boosted protease inhibitor, used, in association with other drugs, in the therapy of *Human Immunodeficiency Virus* (HIV) infection, starting from the age of 14 days of live [17].

Its security profile is well known, as it has been largely used in HIV infections in the pediatric age,

It is available both in oral suspension and tablets.

On the base of some clinical trials, the Chinese guideline on SARS-Cov-2 pneumoniae recommend the early use of lopinavir/ritonavir [18].

On 18 March 2020, the results of a double blinded, randomized, open-label trial, which compared lopinavir/ritonavir associated to standard of care and standard of care alone, on 199 SARS-Cov-2 pneumonia hospitalized patients, have been published on *New England Journal of Medicine* [19]. The study did not evidence any statistically significant differences in the clinical improvement. Mortality at 28 days showed a 5.8% difference in favor of lopinavir/ritonavir use, although not statistically significant (95% Confidence Interval, CI95%: −17.3-5.7). Patients in which lopinavir/ritonavir therapy has been started before the 12 days of symptoms had a significantly reduction of symptoms duration (hazard ratio: 1.25; CI95%: 1.77-2.05). Data about mortality, stay in Intensive Care Unit and duration of hospitalization were not stratified for the start of therapy before and after 12 days. The results of this study cannot be transferred to pediatric population, to patients with mild-moderate symptoms, and to patients who underwent an early therapy.

Lopinavir/ritonavir **is not** indicated in premature neonates before the 42 weeks of corrected age and in all cases before 14 days of live [20].

Available formulations:

Lopinavir/ritonavir tablets (200 mg+ 50 mg)
Lopinavir/ritonavir oral suspension (80 mg + 20 mg/mL), which must be conserved in the fridge

Dosage:

- Adults: 400/100 mg (2 tablets) twice a day
- 14 days -12 months: 300 mg/75 mg/m^2 (corresponding to a 3.75 mL/Kg) twice a day OR 16/4 mg/Kg (corresponding to 0.2 mL/Kg) twice a day
- > 12 months - 18 years: if < 15 Kg: 12/3 mg/Kg (corresponding to 0.15 mL/Kg) twice a day; if >15 Kg: 10/2.5 mg/Kg (corresponding to 0.125 mL/Kg) twice a day

Simplify dosage

- if > 15 Kg and able to swallow tablets:

15-25 Kg: 1 tablet twice a day

>25 Kg-35 Kg: 1 + ½ tablet twice a day

> 35 Kg: 2 tablets twice a day

- if < 15 Kg or unable to swallow tablets:

7-10 Kg: 1.25 mL twice a day

10-15 Kg: 1.75 mL twice a day

15-20 Kg: 2.25 mL twice a day

20-25 Kg; 2.75 mL twice a day

25-30 Kg: 3.5 mL twice a day

30-35 Kg: 4 mL twice a day

35-40 Kg: 4.75 mL twice a day

>40 Kg: 5 mL twice a day

Darunavir/ritonavir

Darunavir is a protease inhibitor, that needs a booster (ritonavir or cobicistat), indicates, in association to other drugs, for HIV infection therapy, starting from the age of 3 years old [17].

Data regarding its efficacy in the management of SARS-Cov-2 infection are currently not available; there is an ongoing trial in China [21].

Darunavir has demonstrated a tolerability profile better than lopinavir/ritonavir in the treatment of HIV infection .

Darunavir is **not** recommended in patients under 3 years of age and weighting less than 15 Kg [22]. Starting from 12 years old and 40 Kg of weight, formulation associated with cobicistat can be used [23].

Available formulations:

Darunavir oral suspension 100 mg/mL

Darunavir 75, 150, 300, 400, 600 and 800 mg tablets

Ritonavir oral suspension 80 mg/mL

Ritonavir 100 mg tablets

Ritonavir 100 mg bags

Darunavir/Cobicistat 800/150 mg tablets

Dosage:

- 15-30 Kg: 600 mg (6 ml) Darunavir /100 mg (1.25 ml) ritonavir once a day with food
- >30 – 40 Kg: 675 mg (6.8 ml) Darunavir /100 mg (1.25 ml) ritonavir once a day with food
- > 40 Kg: 800 mg (8 ml) Darunavir /100 mg (1.25 ml) ritonavir once a day with food OR Darunavir/Cobicistat 1 tablet once a day with food

Remdesivir

Remdesivir is a nucleotide analogue, which is incorporated in the viral RNA chain, determining its premature termination. It has been developed from Gilead in 2017 for Ebola therapy. *In vitro* studies, it has been demonstrated its high spectrum efficacy against different coronavirus [24-25].

Another interesting characteristic of this drug is that it seems to have a high genetic barrier to the resistance development (demonstrated in SARS studies). Remdesivir has a short plasmatic half-life, but it is rapidly converted into its active form (in 2 hours from the infusion) and it has a 14 hours intracellular half-life [26].

At the moment, there are 9 ongoing trials evaluating clinical efficacy of this drug in the therapy of moderate and severe SARS-Cov-2 infections [21].

Two studies (GS-US-540-5774 Study and GS-US-540-5773 Study) are currently ongoing in Italy; both studies are sponsored by Gilead and involve only adult patients [27].

Dosage:

- Adults: 1st day 200 mg IV in 30 minutes, followed by 100 mg IV /day for other 9 days
- Children (<40 Kg): 1st day 5 mg/Kg IV (in 30 minutes), followed by 2.5 mg/Kg IV (in 30 minutes)/day for other 9 days.

For request to Gilead for compassionate use of Remdesivir, an online form must be filled in (*https://rdvcu.gilead.com/*).

Hydroxychloroquine

Hydroxychloroquine (and chloroquine) could have an antiviral activity [28]. The mechanism is currently not fully clarified. However, *in vitro* studies suggest that they could act by increasing the endosomal pH required for virus / host cell fusion and interfering with the glycosylation of the SARS-Cov-2 cell receptor

[29]. In particular, hydroxychloroquine appears to have better *in vitro* activity towards SARS-CoV-2. The anti-inflammatory activity of these molecules, through the inhibition of the production of Interleukin (IL) -6 and Tumor Necrosis Factor (TNF) -α, could contribute to their effectiveness. In addition, these molecules have been in use for decades, showing a good safety profile. Compared to chloroquine, hydroxychloroquine is a drug more readily available and with a higher safety profile [30].

In February 2020, a panel of experts in China summarized the results of the use of chloroquine (500 mg every 12 hours for 10 days) in adults with COVID-19, suggesting that its use would be associated with an improvement in the clinical success rate, reducing the hospitalization and improving the outcome [31]. In a non-randomized trial on 36 adult patients, including 20 treated with hydroxychloroquine (200 mg 3 times a day for 10 days) and 16 controls, the efficacy in reducing the viral load in the respiratory tract was assessed [32]. In 6 patients, hydroxychloroquine had been associated with azithromycin. After 6 days from the start of therapy, 100% of the patients taking hydroxychloroquine and azithromycin had negative effects on the nasopharyngeal level, compared to 57.1% of the hydroxychloroquine alone and 12.5% of the control group.

Hydroxychloroquine is currently under investigation in clinical trials for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection, and treatment of patients with mild, moderate, and severe COVID-19 [33]. Currently, more than 20 trials are underway to evaluate the efficacy of these drugs in patients with COVID-19 [21].

Available formulations:

Hydroxychloroquine tablets 200 mg

Dosage:

Adults: 400 mg twice a day the first day, followed by 200 mg twice a day for overall 5-7 days
Children: 2.5-3 mg/kg twice a day

Precautions for use:

Perform ECG before administering the drug to rule out long QT
In case of risk factors, dose G6PDH before use

Other antiviral therapy

Favipiravir is an antiviral drug authorized in Japan for the treatment of flu. It works by inhibiting RNA polymerase-RNA-dependent. The medicine is not authorized in Europe or in the USA.

On February 14, a clinical trial was started in China to evaluate the efficacy of Favipiravir in SARS-Cov-2 pneumonia. Preliminary results on 80 patients with non-serious SARS-Cov-2 infection, published only in Chinese, seems to show a better efficacy of this drug compared to lopinavir/ritonavir [28].

Many clinical trials are currently undergoing to evaluate the efficacy of Favipiravir in SARS-Cov-2 infection and the AIFA Scientific Technical Commission is evaluating a clinical trial program for this drug [27, 34].

Ivermectin, an FDA-approved anti-parasitic, seems to have broad-spectrum anti-viral activity *in vitro*, is an inhibitor of the causative virus (SARS-CoV-2), 2 hours post infection with SARS-CoV-2 able to effect 5000-fold reduction in viral RNA at 48 h [35].

Immunomodulant treatment

Steroids

At present, there are no clear evidences to support the use of systemic steroids during SARS-Cov-2 infection unless specific needs (e.g. asthmatic patient who does not respond to 3 doses of bronchodilator, severe allergic reaction). In particular, in patients on chronic systemic or inhaled steroid therapy, treatment stopping is not necessary. Some data suggest that methylprednisolone could have an immunomodulating activity in case of ARDS, decreasing the risk of death [36]. Its use is also indicated in case of a worsening of pulmonary function after at least 7 days from the beginning of symptoms, in association with marked alteration or tendency to increasing of IL- 6 and/or D-dimer and/or ferritin and/or C-reactive protein.

In these cases, can be used:

- Methylprednisolone 1-2 mg / Kg (max 80 mg) once a day

A short course is indicated (2-5 days).

Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody belonging to the G1 immunoglobulin subclass and directed against both soluble and membrane IL-6 receptors [37].

This drug is indicated for the treatment of moderate and severe rheumatoid arthritis, systemic juvenile idiopathic arthritis (from the age of 1 year), juvenile idiopathic polyarthritis (from the age of 2 years) and severe release of cytokines induced by CAR-T lymphocytes (chimeric antigen receptor t cell) (from the age of 2 years).

Some studies suggested that the alveolar damage in COVID-19 is caused by a cytokine storm (including IL-6) and this would be the prerequisite for the use of Tocilizumab [38].

Xu et al. published the results of its use on 21 patients with severe or critical SARS-Cov-2 infection, reporting an improvement in fever, need for oxygen therapy, pulmonary x-ray images and blood tests (lymphocyte count and C-reactive protein) [39].

Based on these results, different clinical trials have been started. The Italian multicenter study TOCIVID-19 has been promoted by the National Cancer Institute, IRCCS, G. Pascale Foundation, Naples. The recruitment of the prospective phase has been completed, while the observational study continues. The protocol includes the enrollment of patients of any age.

Other two studies started at the end of March in Italy, but not enrolling pediatric patients [27].

For the supply of Tocilizumab, a request can be sent to Roche.

Therapeutic scheme:

- Tocilizumab vial 20 mg/mL
- First infusion at a dosage of 10-12 mg/kg <30 kg and 8 mg/kg >30 kg, (maximum dosage 800 mg, duration of infusion at least 60 minutes)
- Second infusion 12 hours after the first (at the discretion of the doctor, in case of no response)
- A possible third infusion after 24 hours may be considered.

After 24 hours from the last administration, repeat the plasma dosage of IL-6 and / or D-dimer.

When to use it:

• Serious or critical cases

• End of the initial phase of high viral load of COVID-19 (afebrile> 72h and/or at least 7 days after the onset of symptoms)

• High levels of IL-6 (>40 pg/ml); alternatively, high levels of d-dimer and/or PCR and/or ferritin and/or fibrinogen increasing progressively.

When not to use it:

• AST / ALT value above 5 times normal levels

• Neutrophils value lower than 500 cells/mL

• Platelets value lower than 50,000 cells /mL

• Documented sepsis from other pathogens other than COVID-19

• Presence of comorbidities related, according to clinical judgment, to an unfavorable outcome

• Complicated diverticulitis or intestinal perforation

- Immunomodulating and anti-rejection therapy
- Known hypersensitivity to the drug

It is also recommended to avoid administration of Tocilizumab if anti-MRPV vaccination has been carried out in the past 30 days.

If possible, before starting therapy:

- Quantiferon test
- HBV and HCV markers

Other immunomodulant therapies

Assuming that the alveolar damage of severe forms of SARS-Cov-2 infection is caused by a cytokine storm [40], two other clinical trials have been started in Italy on the use of emapalumab (anti-interferon gamma monoclonal antibody) and associated anakinra (IL-1 receptor antagonist) and the use of sarilumab (monoclonal antibody that binds to the IL-6 receptor). A Belgian study comparing tocilizumab, anakinra and siltuximab is going to start soon.

Information and forms relating to the studies are available on AIFA website, but there is no prevision for enrollment of pediatric patients [27].

Among the new therapies planned for the future is the infusion of hyperimmune plasma from cured patients. This approach, already used in China and previously for Ebola and SARS, seems to give good results at least in the most serious cases. In the USA 3 studies have been launched that will evaluate this approach [41].

Antibiotic therapy

The choice to add empirical antibiotic therapy should only be made if there is reasonable evidence of bacterial superinfection. Laboratory parameters suggestive of bacterial infection are represented by an increased procalcitonin, C-reactive protein and the presence of neutrophilic leukocytosis. From a clinical point of view, the persistence of fever for more than 3 days can be suggestive of bacterial infection [4, 42]. The start of an empirical antibiotic therapy is also recommended in the presence of comorbidities, such as immunodeficiency, cystic fibrosis, other chronic diseases of the respiratory tract, severe neuromotor disability.

In case of productive cough, the collection of a sputum sample for culture examination before the start of antibiotic therapy would be indicated.

In patients without risk factors, we recommend:

- Amoxicillin 90 mg /Kg/day in 3 doses, in case of possible oral intake
- Ceftriaxone 80-100 mg/Kg/day, in case of impossibility of oral intake. This drug is also recommended for the possibility of administering once a day and therefore reducing the risks for healthcare professionals.

Azithromycin:

Recent French data have suggested a possible efficacy of azithromycin in combination with hydroxychloroquine as a background therapy for SARS-Cov-2 infection. The exact role of this drug in COVID-19 is unknown, as no *in vitro* data are available at present. It has been supposed a dual role, antiviral and anti-inflammatory. The anti-inflammatory action of azithromycin has been already demonstrated in many conditions. Regarding the theoretical antiviral activity, the only published study is on a small sample size (36 patients, of whom only 6 receiving the combination of azithromycin/hydroxychloroquine) [32]. In this study, by Gautret and colleagues, 100% of the patients taking hydroxychloroquine and azithromycin had negative nasopharyngeal swab 6 days from the start of therapy, compared to 57.1% of the hydroxychloroquine alone and 12.5% of the control group. However, a more recent study on virological and clinical results of 11 adult patients with a serious disease raises doubts about the antiviral efficacy of this combination, as it reports results in contrast to those of Gautret et al [43]. Considering the lack of a strong rationale and the absence of evidence of certain effectiveness in the treatment of COVID-19 patients, the use of azithromycin should be considered carefully and the QTc interval strongly monitored.

Dosage:

- Adults: 500 mg the first day, then 250 mg/day for other 4 days
- Children: 15 mg/Kg the first day, then 7.5 mg/Kg once a day for other 4 days

Drug interactions

The drugs used for the therapy of SARS-Cov-2 infection, especially lopinavir/ritonavir, can have interactions with other drugs.

Before administering those treatment, evaluate possible interactions on drugs [44].

Informed consent

For all drugs, consent for off-label use must be requested and the procedures provided by the reference Healthcare Company must be followed.
As for Remdesivir, since it is an experimental drug, the procedures for compassionate use must be followed.

Conclusion

In conclusion this position paper summarizes the suggested treatments in COVID-19 infected children based on a review of the current literature carried out by the Scientific Committee of the Italian Society of Infectious Pediatric Diseases. Since most children infections have a benign course, pharmacological treatment should be reserved to those with more severe cases.

New evidences will be available in the next weeks/months, therefore the Italian Society of Pediatric Infectious Diseases will guarantee to maintain treatment indication updated on the website www.sitip.org

Abbreviation

AIFA	Agenzia Italiana del Farmaco
AST / ALT	Aspartate & Alkaline transaminase
COVID-19	Coronavirus 2019
ECG	electrocardiogram
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
PARDS	Pediatric acute respiratory distress syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SpO2	Oxygen saturation
TNF	Tumor Necrosis Factor
WHO	World Health Organization

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All authors have agreed to the publication

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