Critically-ill pediatric patients with COVID-19. An update

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ABSTRACT

The COVID-19 pandemic has grabbed worldwide attention. The different national governments are making an effort to optimize resources and provide effective treatments inasmuch as they are supported by the evidence, at a rate of production in line with the pressing needs. In the field of pediatrics, COVID-19 has a low severity rate compared to the adult population. Approximately 6 % of cases present with a severe course, accounting for patients younger than 1 year and/or with underlying conditions. The therapeutic approach to pediatric patients with COVID-19 is unclear. The small number of pediatric cases hinders the possibility of making evidence-based recommendations for critically-ill patients. The objective of this review is to summarize the different current publications about the clinical course of COVID-19 and its management in critically-ill pediatric patients.

Key words: *COVID-19, critical disease, pediatrics, SARS-CoV-2, severe acute respiratory syndrome.*

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INTRODUCTION

As in the case of any pandemic, the pediatric population may become infected with coronavirus type 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2); however, in their case, the disease appears to be less severe compared to the adult population.[1] The incidence of SARS-CoV-2 ranges between 1.3 % and 12 %, depending on the analyzed country or region, and severity, defined based on respiratory distress and hypoxemia, was 5.2 % in the largest published series (N = 2143), where 0.6 % of patients developed acute respiratory distress syndrome (ARDS) and multiple organ failure.[2]

Mortality in the different pediatric series that had been reported to the date of this article was between 0.1 % and 5.9 % among hospitalized cases.[3-9] In Argentina, symptoms were mild in 75 % of patients and moderate in 22.1 % (including tachypnea, intercostal retraction, pneumonia, malaise, chest pain, dyspnea, food refusal). Only 3 patients reported severe symptoms; none required mechanical ventilation (MV) and no deaths were registered.[10] Viral co-infections were also observed in up to two-thirds of cases.[11]

The scarce number of pediatric cases hinders the possibility of making solid, evidence-based recommendations for critically-ill patients; therefore, they are the result of a combination of different bibliographic sources corresponding mostly to adult patients or institutional guidelines/protocols. For example, the recommendations made by the Pediatric Acute Lung Injury Consensus Conference – Paediatric Mechanical Ventilation Consensus Conference (PALICC-PEMVECC).[12,13] The immediate need to respond to the current pandemic calls for behaviors that take into consideration resource availability, the advent of seasonal epidemics, the risk of staff exposure, adequate treatments, etc.

Clinical presentation and classification of severity

It is unknown why children are less susceptible to COVID-19 compared to adults. An explanation would be the lower angiotensin-converting enzyme-2 (ACE2) gene expression in the nasal epithelium, which works as a receptor and entry door for SARS-CoV-2.[14] It has also been suggested that there is an early polyclonal B cell response and a production of substantial amounts

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of plasmablasts, mostly of the IgM isotype. This response has not been observed in adults with a severe course (whose B-cell compartment is depleted). Therefore, a child's immune response may play a double role: to protect and to reduce immune-mediated tissue damage, particularly, in the lung parenchyma.[15]

Dong et al.[4] defined COVID-19 severity based on clinical characteristics, lab tests, and chest X-ray, and established the following diagnostic criteria:

Asymptomatic disease: no symptom or clinical sign and normal chest X-ray.

Mild disease: symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing, in association or not with gastrointestinal symptoms. The physical examination shows pharyngeal congestion.

Moderate disease: pneumonia, fever, and frequent cough (ineffective cough, followed by productive cough), sometimes wheezing, but no clear hypoxemia (peripheral oxygen saturation [SpO_2] > 92 %), and auscultatory abnormalities. Some cases may be asymptomatic, but the chest computed tomography (CT) is pathological.

Severe disease: early respiratory symptoms (fever and cough) may be accompanied by gastrointestinal symptoms (diarrhea). The disease progresses over approximately 1 week with dyspnea and central cyanosis. SpO_2 is below 92 %.

Critical disease: rapid progression to ARDS; patients may also develop shock, encephalopathy, myocardial injury or heart failure, coagulation disorder, and acute kidney injury.

In the past weeks, pediatric patients have presented with a condition similar to toxic shock or Kawasaki disease and a serology that evidenced a potential prior SARS-CoV-2 infection. Tests have shown high white blood cells, platelets, C-reactive protein, and liver enzymes, with no alterations in ferritin, troponin, and D-dimer.[16,17] A torpid clinical course occurs occasionally with a low fatality rate, as described by the different pediatric series analyzed (*Table 1*).

When considering only patients admitted to the pediatric intensive care unit (PICU), the mortality rate increases to 5.5 %, as observed in the online registers of Virtual PICU Systems, where approximately 30 % of cases are older than 18 years.[18] Two publications described pediatric patients admitted to the PICU. The patients in the series described by Shekerdemian (N = 48) had a high incidence of preexisting comorbidities (83 %), with a 4.2 % mortality. In relation to the treatment provided, 38 % of patients required invasive MV, with extracorporeal membrane oxygenation (ECMO) in 1 case; 61 % received targeted therapies, alone or in combination, including hydroxychloroquine (alone or with azithromycin), remdesivir, tocilizumab, and convalescent plasma.[8] The other series, by González-Dambrauska[9] (N = 17), showed that 71 % of cases had a comorbidity, 82 % required ventilatory support, and mortality was 5.9 %.

TABLE 1. *Seriously-ill patients with COVID-19. Pediatric series*

Author	Number of patients	Serious/critical	Ventilatory support			Death
		% (N)	HFNC	NIV	IMV	% (N)
Parri et al.[3]	67 (hospitalized out of 100 in total)	4.7 (3)	3	1	1	1.5 (1)
Dong et al.[4]	731 (confirmed out of 2143 suspected cases)	2.8 (21)	NS	NS	NS	0.1 (1)
Lu et al.[5]	171	1.7 (3)	NS	NS	3	0.6 (1)
Castagnoli et al.[6]	1065 (from 18 studies)	0.2 (2)	NS	NS	1	0.1 (1)
CDC COVID-19 Response Team[7]	147 (hospitalized out of 2572 in total)	10 (15)	NS	NS	NS	0.1 (3)
Shekerdemian et al.[8]	48 (across 46 PICUs from the USA)	100 (48)	11	4	18	4.2 (2)
González-Dambrauskas et al.[9]	17 (across 10 PICUs from Chile, Colombia, Italy, Spain, and USA)	100 (17)	7	4	8	5.9 (1)
Total	2246					0.45 (10)

NS: not specified; HFNC: high-flow nasal cannula; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation; PICUs: pediatric intensive care units.

Indications for admission to the pediatric intensive care unit

Patients with severe acute lower respiratory tract infection (ALRTI) or extrapulmonary manifestations associated with severe conditions and/or progressive worsening (*Table 2*).

Pathophysiological considerations and ventilatory support

The respiratory condition caused by COVID-19 in the adult population is characterized by marked hypoxemia and relatively adequate respiratory mechanics, with two clinical presentations:

L phenotype: in this presentation, the respiratory system shows a good pulmonary compliance, where lung volume is high, recruitability is minimal, and hypoxemia is the result of the loss of vasomotor tone and reflex vasoconstriction (vasoplegia), with the subsequent alteration of the ventilation/perfusion ratio (V/Q).

H phenotype: it is possibly a progression of the L type in patients exposed to induced damage (excessive respiratory effort) and behaves more like typical ARDS and shows low pulmonary compliance.[19,20]

According to this interpretation, different recommendations were made based on pathophysiology:

Since invasive MV is not a treatment itself, it should not be started due to hypoxemia alone; an impaired sensorium is the guiding parameter.[21]

TABLE 2. *Clinical conditions of critically-ill pediatric patients with COVID-19*

Severe pneumonia	Cough or respiratory distress, plus at least 1 of the following: • Central cyanosis or $SatO_2 < 92\ \%$. • Severe respiratory distress: grunting, nasal flaring, suprasternal retractions, severe chest retraction or thoracoabdominal dissociation. • Inability or difficulty feeding. • Altered mental status, lethargy or loss of consciousness or seizures. • Severe tachypnea (breaths/min) -< 2 months: ≥ 60; 2-11 months: ≥ 50; 1-5 years: ≥ 40-. • Blood gases: $PaO_2 < 60$ mmHg, $PaCO_2 > 50$ mmHg. Diagnosis is made clinically; chest X-rays may rule out complications (atelectasis, infiltrates, effusion).
Other manifestations associated with severe conditions	Coagulation disorders, myocardial damage, gastrointestinal dysfunction, high liver enzymes, and rhabdomyolysis.
ARDS[12]	• Onset time: new or worsening condition in the 10 previous days. • Chest X-ray, CT or ultrasound: new single/bilateral infiltrate(s) compatible with acute involvement of lung parenchyma. • Lung edema: respiratory insufficiency in the absence of other etiology, such as heart failure (ruled out by ultrasound) or volume overload. • Oxygenation (OI: oxygenation index; OSI: oxygenation index using SpO_2): Bilevel NIV or CPAP ≥ 5 cmH_2O through a full face mask: $PaO_2/FiO_2 \leq 300$ mmHg or $SatO_2/FiO_2 \leq 264$. - Mild ARDS (invasive ventilation): $4 \leq OI < 8$; $5 \leq OSI < 7.5$. - Moderate ARDS (invasive ventilation): $8 \leq OI < 16$; $7.5 \leq OSI < 12.3$. - Severe ARDS (invasive ventilation): OI ≥ 16, OSI ≥ 12.3.
Sepsis[48]	Suspected or confirmed infection and ≥ 2 SIRS criteria, one of which should be abnormal temperature or abnormal leukocyte count (the other 2 criteria are tachypnea and tachycardia or bradycardia in patients < 1 year old). Sepsis is considered severe if it occurs with cardiovascular dysfunction, ARDS or organ dysfunction in ≥ 2 of the remaining organs.
Septic shock[48]	Any type of hypotension (SBP < 5th percentile or > 2 SD below the normal value for age) or 2-3 of the following criteria: altered mental status; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or < 50 bpm in children); slow capillary refill (> 2 seconds) or warm vasodilation and preserved pulses; tachypnea; mottled skin or petechiae or purpura; increased lactate, oliguria, hyperthermia or hypothermia.

$SatO_2$: oxygen saturation; PaO_2: oxygen pressure in arterial blood; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; ARDS: acute respiratory distress syndrome; CT: computed tomography; SpO_2: peripheral oxygen saturation; NIV: non-invasive ventilation; CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; SIRS: systemic inflammatory response syndrome; SBP: systolic blood pressure; SD: standard deviation; HR: heart rate; bpm: beats per minute.

Since, in the progression of the phenotypes described above, prolonged non-invasive ventilatory support with excessive respiratory effort may be a cause of pulmonary damage, a strict failure criterion should be implemented so that treatment is not extended and invasive support can be initiated.[19]

Once invasive support is started, an attempt should be made to establish the corresponding type of presentation by measuring or estimating pulmonary compliance, which will help to choose the type of ventilatory support.[19,10]

Although it is unknown whether these pathophysiological models can be reproduced in pediatrics, they should be considered during the interpretation of the condition in order to improve how and when to provide ventilatory support.

Non-invasive ventilatory support

High-flow nasal cannulas (HFNC) and non-invasive ventilation (NIV) have demonstrated to be beneficial in the adult population,[22,23] although they increase the risk for transmission and infection as a result of high viral particle aerosolization, and may lead to a delay in invasive ventilation. However, these risks should be weighed against the added morbidity resulting from a more aggressive therapy.

The aerosolization caused by HFNC and continuous positive airway pressure (CPAP) will always be limited as long as the patient interface is adequately adjusted. However, exhaled air may leak laterally at more than 60 cm if the HFNC disengages at the point between the tubing and the patient interface.[24] In a study conducted in healthy adults, no particle aerosolization between 10 nm and 500 nm was observed when using a nasal cannula, a non-rebreather mask or a heated HFNC.[25]

The assessment of response to non-invasive support is based on oxygenation parameters, SpO_2/fraction of inspired oxygen (FiO_2) (SF) and oxygen saturation index (OSI). The use of CPAP or NIV as first-line method is recommended instead of HFNC in patients with SF > 221 and < 264.[26] HFNC with a surgical mask over the patient's face or with a protective acrylic box or other device to minimize aerosol dispersion may be a reasonable practice that would benefit hypoxemic patients with COVID-19 and prevent intubation.[27]

NIV with an oronasal or total face mask interface is recommended to minimize leakage. If possible, use a double-branch circuit (if single-branch, a filter should be placed before the leakage site -whisper swivel-) and high efficiency particulate air (HEPA) filters in expiratory tubing (both branches if using environmental air). Always humidify the NIV circuit, either actively or passively (heat and moisture exchanger [HME] filter). It is desirable to perform NIV in a negative pressure room; if not possible, in an isolated room or at least with a considerable spatial separation between patients. If oxygenation does

TABLE 3. *Endotracheal intubation procedure*

Intubation checklist
Plan ahead
1. Make sure you have practice donning and doffing PPE, and have a partner to check the procedure.
2. Allocate roles: intubator (more experienced in managing airways). Minimize staff inside the room (maximum: 3 people).
3. Negative pressure room, if possible.
4. Establish a clear communication strategy.
Intubation
1. Don PPE.
2. Determine monitoring, intravenous access, intubation equipment (consider videolaryngoscopy, if available), HME filter between the mask and the bag.
3. Preoxygenate for 3-5 minutes.
4. Plan for RSI induction, minimize self-inflating bag for ventilation.
5. Intubate and confirm (avoid using a stethoscope; use $EtCO_2$ and examination of the chest).
6. Connect to ventilator, with inline suction.
7. Wipe down relevant surfaces.
8. Disposable equipment should be discarded as per the hospital protocol.
9. Ensure proper PPE doffing, monitored by a partner.

PPE: personal protective equipment; HME: heat and moisture exchanger; $EtCO_2$: end-tidal CO_2; RSI: rapid sequence intubation. Modified from Paediatric Intensive Care Society UK: Paediatric Critical Care Coronavirus Disease 2019 Guidance.28

not improve in 30-60 minutes (oxygen saturation [$SatO_2$] 92-97 % with FiO_2 < 0.4) and respiratory rate/effort does not decrease, treatment escalation to ventilatory support should not be delayed.

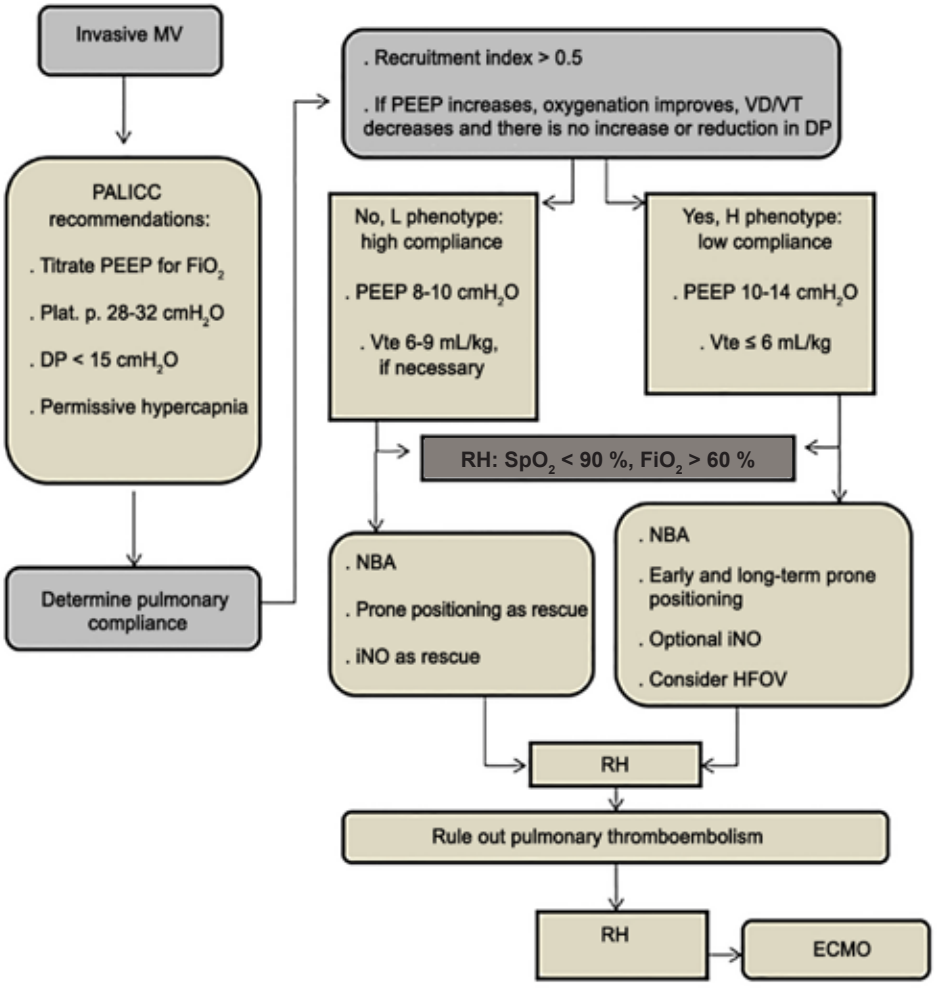
Intubation and invasive mechanical ventilation

Endotracheal intubation should be performed as soon as possible in patients who tend to a worsening SF, progressive respiratory distress, high oxygen levels (> 60 %) in HFNC/NIV, altered sensorium or multiple organ failure. An intubation checklist[28] should be used (*Table 3*).

During endotracheal intubation, an acrylic box may be used as an extra protection in addition to the standard personal protective equipment (PPE); the box may be dropped if airway management proves difficult.[29]

Ventilation should be done in accordance with the PALICC recommendations[12] (*see algorithm, Figure 1*). It is suggested to start with a positive end-expiratory pressure (PEEP) of about 10 cmH_2O. PEEP may need to be increased in the case of hypoxemia; high-PEEP strategies are recommended for FiO_2; the latter should be titrated to maintain SpO_2 at 92-96 % (in the case of severe disease:

FIGURE 1. *Invasive ventilatory support algorithm for pediatric patients with COVID-19*



MV: mechanical ventilation; PEEP: positive end-expiratory pressure; Plat. p.: plateau pressure; DP: driving pressure; VD/VT: dead space; Vte: expiratory tidal volume; RH: refractory hypoxemia; iNO: inhaled nitric oxide; NBA: neuromuscular blocking agents; ECMO: extracorporeal membrane oxygenation; HFOV: high frequency oscillatory ventilation.
Source: own creation.

88-92 %); and permissive hypercapnia (pH > 7.20) may also be necessary. An early prone positioning (12-18 hours per day)[31] and neuromuscular blocking agents (NBA) should be considered for moderate-severe ARDS (oxygen pressure in arterial blood [PaO_2]/FiO_2 < 150); oxygenation index (OI) ≥ 12; OSI ≥ 10, over 24-48 hours. Prone positioning should be discontinued when PaO_2/FiO_2 is ≥ 150.

Refractory hypoxemia and management

If the patient continues with hypoxemia, pulmonary compliance should be determined to establish the ventilation strategy based on the type of clinical presentation, as proposed by Gattinoni. The type of lung (recruitable or not) can be established in different manners. A CT is not an easy option due to the risk for infection and during transfer. A chest X-ray showing hyperinflated lungs and/or a low lung flow is an extreme factor of this outcome measure. A lung ultrasound requires trained staff; pulmonary compliance should be determined using adapted software. However, bedside monitoring and clinical parameters should be available; therefore, PEEP increases in a non-recruitable lung usually lead to a drop in mean blood pressure (MBP) and cardiac output as observed by central venous oxygen saturation (SvO_2), increased dead space (VD/VT), and increased driving pressure. Another recently disseminated option is the determination of the recruitment index[32] (*see algorithm, Figure 1*).

High frequency oscillatory ventilation in the case of refractory hypoxemia and a low pulmonary compliance may also be considered. A bacterial/viral filter system should be added to the circuit's expiratory branch to minimize the risk for aerosol contamination when using leak-free devices (SensorMedics ventilator). ECMO should be considered if refractory hypoxemia persists in spite of the actions implemented, but it should be noted that ECMO is not a first-line therapy to be indicated when all resources become occupied during a pandemic.[33]

In the case of refractory hypoxemia, the following should be considered: presence of pulmonary embolism as confirmed with a chest CT angiography, sequelae of hypercoagulability, endothelial activation at the expense of an increase in proinflammatory cytokines. If this is assumed, it is recommended to measure D-dimer and IL-6 levels and to assess anticoagulation.[34,35]

Precautions for patients with mechanical ventilation

All staff entering the room of a patient with suspected or confirmed COVID-19 should wear adequate PPE. In parallel, it is recommended to place a filter between the self-inflating bag and the mask or artificial airway.[36] For patients with an endotracheal tube (ETT), balloon pressure should be maintained between 25 and 30 cmH_2O (1 cm H_2O = 0.098 kPa). It is recommended to minimize ETT disengagement and use closed in-line aspiration, and the device should be changed once a week. Also, it is suggested to use heated, double-branch wire circuits that are only changed in the presence of visible dirt.[36] Active humidification, with heater and bacterial/viral filters in both ends, may be at risk for aerosol contamination; whereas passive humidification with a HME filter in the distal end has to be changed every 24 hours.[26] If it is necessary to take the patient off the ventilator, it is recommended to perform a full expiration with the ventilator on stand-by and, if the patient is not receiving NBAs, the ETT should be clamped before disengagement.

In the case of patients who need respiratory support during transfer, the HME filter should be placed between the ventilator and the patient. The secretions resulting from suction should be collected in the same closed containers used during surgical procedures. They have a larger storage capacity and are disposable.

For patients who need aerosol therapy, the recommendation is to use a metered-dose inhaler with spacer if the patient is breathing spontaneously or a vibrating mesh nebulizer if the patient is ventilated. It will be necessary to use an additional filter in the expiratory flow port during nebulization. Routine chest physiotherapy and cough assist devices are not recommended.[36]

Weaning from mechanical ventilation

The patient should be extubated if they will not require rescue non-invasive support. The recommendation is to perform a spontaneous breathing test with CPAP and/or support pressure not exceeding 5 cmH_2O, avoiding the use of a T-piece. When weaning patients who underwent a tracheostomy, HME filters should be used. An unnecessary bronchial hygiene therapy should be avoided.[36] Precautions to prevent aerosol dispersion are critical during extubation, so an option is to use devices like acrylic boxes, plastic shields, etc. If respiratory effort increases

following extubation, non-invasive supports may be considered.

Drug treatment[26,31,37-40]

Corticosteroids: These are not recommended for the management of viral pneumonia outside clinical trials. No benefits have been demonstrated and there may be potential damage related to their use.

Antivirals: There is no current evidence supporting a specific anti-COVID-19 treatment. Available options are derived from the experience of SARS, Middle East respiratory syndrome (MERS), and other influenza virus treatments.

Oseltamivir: It is only considered in the case of influenza co-infection because neuraminidase inhibitors have no effect against COVID-19.

Fabiravir and ribavirin: It has been reported that a combination of fabiravir and oseltamivir for severe flu accelerates recovery, as well as ribavirin and interferon-alpha for SARS, but their benefit in COVID-19 has not been clarified.[40]

Lopinavir/ritonavir: This combination was not effective for COVID-19 in a randomized study in adults with an insufficient sample size.[40] Some protocols suggested using proteases in children with underlying conditions and immunosuppression of any severity and in critically-ill children admitted to the PICU. If used, this combination is administered in an early manner upon obtaining an informed consent for its compassionate use for 14 days.

Remdesivir: Two adequately designed studies about its use are ongoing. Wang[41] did not evidence a clinical benefit, although patients receiving remdesivir had a shorter period until clinical improvement than those receiving placebo. The study was discontinued early due to major adverse events in the remdesivir group. Beige et al.[42] showed that the administration of remdesivir (loading and maintenance dose for 10 days) was associated with fewer days until recovery and a smaller incidence of lower respiratory tract infections in adult patients, without a higher number of adverse events.

Hydroxychloroquine-chloroquine: Both drugs block the membrane receptor ACE2 in SARS-CoV-2. Its use has been proposed for severe cases requiring management at the PICU or for immunocompromised patients with interstitial pneumonia. A recently published multicenter study with these drugs, in association or not with a macrolide, showed a higher rate of in-hospital mortality than in control patients, with a high number of *de-novo* ventricular arrhythmias.[43]

Intravenous immunoglobulins: These have been used in severe cases, but their indication and effectiveness still need to be assessed. There is currently not enough evidence for their indication.[44]

Convalescent plasma: A pilot study suggested that convalescent plasma administration is safe, reduces viral load, and may improve clinical outcomes.[45] However, it may only be used as part of a compassionate treatment or in the context of duly regulated clinical trials.

Other support therapies to be considered at the pediatric intensive care unit

Septic shock: The Surviving Sepsis Campaign (SSC) guidelines for COVID-19 recommend to use a conservative fluid strategy, avoid colloid solutions, and use low-dose corticosteroids for refractory shock to catecholamines. In children, epinephrine is the first-choice vasoactive drug for septic shock.[46]

Co-infections: Secondary bacterial co-infections are common; therefore, a broad-spectrum antibiotic therapy should be considered in severe cases.

Myocarditis: A report has been made of a series of 20 pediatric patients with cardiogenic shock and high troponin levels. Treatment included vasoactive support, immunomodulators (methylprednisolone and gamma globulin) and ventilatory support, with a 100 % survival.[47]

COMMENTARY/CONSIDERATION

The SARS-CoV-2 infection is an emerging pandemic, whose attributable risk and severity among children is currently difficult to establish. The small number of pediatric cases attempts against the recommendations based on strong evidence. The results of international collaborative studies that may improve the classification of clinical presentation, course, and adequate management are now expected. ■

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