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Research Article

Sars-Cov2 Infection: Clinical Approach in Pediatric Intensive Care Unit -

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ABSTRACT

As coronavirus disease 2019 (COVID 19) spreads across the world, the intensive care community must prepare for the challenges associated with this pandemic. Most reported cases of COVID 19 in children aged <18 years appear to be asymptomatic or mild, but a small proportion of infected children develop severe cases of COVID-19 that require hospitalization. One of the earliest cases of COVID-19 in central Wuhan, China, was a previously healthy 3-year-old child who was admitted to the intensive care unit (ICU) in early January 2020. Clinical approach of these patients is complex and depends on clinical, laboratorial and imagiologic findings. It includes pharmacotherapy, fluids and ventilatory support. Critical care management is challenging due to the multisystemic involvement that often occurs and also due to the management of team protection care.

Keywords: SarsCov2; COVID 19; PIMS-TS, MIS-C; Intensive Care; Ventilatory Suppor

ABBREVIATIONS:

ABG: Arterial Blood Gas; ACE: Angiotensin-converting enzyme; ALT: Alanine aminotransferase; ARDS: Acute Respiratory Distress Syndrome; AST: Aspartate aminotransferase; BNP: Brain-type natriuretic peptide; BLPAP: Bilevel Positive Airway Pressure; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; *CPAP*: Continuous positive airway pressure; CF: cardiac frequency; ECMO: Extracorporeal Membrane Oxygenation; ETT: *endotracheal tube*; FiO2: fraction of inspired oxygen; HLH: Hemophagocytic Lymphohistiocytosis; HFOT: High flow oxygen therapy; ICU: Intensive Care Unit; IL: Interleukin; IV: intravenous; IMV: Invasive Mechanic Ventilation; IPAP: Inspiratory positive airway pressure; LDH: Lactate dehydrogenase; MIS-C - Multisystem inflammatory syndrome in children; MV: Mechanic Ventilation; NIV: Non-invasive ventilation; PARDS: Pediatric Acute Respiratory Distress Syndrome P/F: Coefficient PaO_2/FiO_2; PIMS-TS - Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; PEV - Plateau Exhalation valve; PEEP: Positive end-expiratory pressure; PSILI – patient self-inflicted lung injury; RF: Respiratory frequency; S/F - coefficient SpO_2/FiO_2; SpO2: oxygen saturation; SV: Sedimentation velocity; *VP/P: ventilation*/perfusion; WHO: World Health Organization

INTRODUCTION

In the end of 2019, it was identified in Wuhan, China, a new coronavirus strain, the SarsCov2 whose infection is defined as COVID 19 [1-5]. Unofficial information reports the first identified case of COVID-19 on 17 November 2019 in the city of Wuhan. The disease was only officially recognized after epidemiological and microbiological investigation of a cluster of atypical pneumonia in late December 2019. The infection spread quickly, regionally, nationally and internationally leading the World Health Organization (WHO) to declare, on March 11 of 2020, COVID 19 a pandemic and a worldwide public health emergency [6]. Until the beginning of December 2020 it was reported almost 66 millions of cases and 1.5 millions of deaths [7].

COVID 19 infection primarily affects the respiratory system presenting in most cases as asymptomatic or mild ("flu like illness") respiratory disease with recovering in one to two weeks. Rarely may it occur moderate to severe hypoxemic pneumonia [2-12].

According to literature, 81% of COVID 19 cases are mild, 14% severe and 5% critical [13]. The mortality in hospitalized patients varies between 5 to 15% [11]. The disease incubation period is estimated to reach 14 days (with an average interval of 4 to 5 days) [12].

SARSCoV2 binds to the Angiotensin-Converting Enzyme 2 receptor (ACE2), located in type II alveolar cells, which can cause diffuse alveolar lesion due to direct cytopathic lesion. In the most severe (rare) cases, there may be a rapid progression to respiratory failure with Acute Respiratory Distress Syndrome (ARDS), which can be associated with a condition of septic shock with multiorgan failure underlying conditions. Thromboembolic events may also be present. In some cases, occurs a cytokine storm, a rare condition that consists in severe inflammatory reaction that mimics sepsis, septic shock and hemophagocytic lymphohistiocytosis (HLH) [4,5,11,15]. Risk factors for severe disease include prematurity, obesity, immunodeficiencies, chronic lung disease, renal and cardiovascular disease, hematologic or metabolic conditions and age < 1 year [10,13,16,17].

The most severe presentation occurs after a period of mild symptoms usually between 5 and 7 day of disease. [11] In pediatric age, similarly to adulthood, the situations with the worst evolution present clinical worsening after a period of mild symptoms, probably coinciding with the peak of viral replication. [18] In children, occurs around the 5th - 7th day after the onset of symptoms, just before what happens in adults (between the 6th and 10th day) [11].

On April 2020, the United Kingdom described for the first time, cases of pediatric hyperinflammatory syndrome with multisystemic involvement and major hemodynamic instability: "Pediatric inflammatory multisystem syndrome temporally associated with SARSCoV2 – PIMS-TS" or "Multisystem inflammatory syndrome in children – MIS-C" [18,19]. It appears to result from overrated response of the acquired immunity to SarsCov2 infection. Although these atypical presentations, in pediatric age the infection by SarsCov2 is less severe than in adults with better prognosis. This results from various aspects such as: better global health, thymus function, less expression of ACE receptor and crusade immunity with other coronavirus.

In this article we pretend to guide the clinical management of a critically ill patient with COVID 19 disease when intensive care is needed.

METHODS

A literature review was carried out in order to gather the most recent data available and thus elaborate a protocol for patients with COVID 19 disease admitted to intensive care unit.

RESULTS

Children in intensive care are infected only with SarsCov2 but coinfection with other pathogenic agents such as virus (Influenzae A and B, Parainfluenza, Adenovirus, Rhinovirus, Bocavirus), bacteria (Pneumococcus, Staphylococcus, H. Influenza, Mycoplasma pneumoniae) or fungi (particularly in patients under immunosuppressive therapy) occur in approximately 40-50% of the cases and also in patients with PIMS-TS. [6,20]

Initial evaluation includes clinical, laboratorial and imagiologic data that are related to worst prognosis and are enumerated below. [1-3,9,11,14,16,17].

Clinical

- Respiratory distress signs (tachypnea, nasal flaring, retractions, grouting and toraco-abdominal dissociation)
- Persistent fever
- Feeding problems
- Thoracic pain
- Cyanosis/SpO2<92%
- Altered level of consciousness
- Peripheral hypoperfusion

Laboratorial

- Arterial Blood Gas (ABG): PO_2<60 mmHg and PCO_2>50 mmHg
- Lymphopenia: <1200/mm^3 (or other cytopenia)
- D-dimer progressive elevation (>1000 µg/L)
- Lactate dehydrogenase (LDH) progressive elevation
- Impaired renal function
- Hepatic enzymes elevation and rhabdomyolysis
- Ferritin and C-reactive protein (CRP) elevation
- Elevated procalcitonin (>0,5 ng/ml): may indicate bacterial sobreinfection
- Troponin and pro-BNP elevation

Imagiologic

Chest X-ray and CT-scan

- Bilateral infiltrates (ground-glass opacification)
- Alveolar pulmonary infiltrates (ARDS)
- Pulmonary consolidations with disorganization
- Pleural effusions are rare (more frequent if hyperinflammation syndrome)

Thoracic ultrasound

- B diffuse pattern
- Alveolar consolidation
- Pleural line irregularities

Children with underlying conditions, such as immunodeficiency, cardiopathy, chronic respiratory, renal, endocrine or metabolic diseases, are more likely to have a severe disease [21-23].

SarsCov2 infection may result in a wide spectrum of clinical manifestations, involving one or various systems and different exams are needed [3,15,21].

Respiratory system (2/3 of cases) [2,6,10,25,26].

Diagnostic based on X-ray, CT scan and ultrasound images

- Bronchiolitis
- Uni or bilateral pneumonia
- ARDS/PARDS (Pediatric Acute Respiratory Distress Syndrome)
- Pulmonary hypertension
- Pulmonary embolism
- Obstructive pulmonary pattern

Hyperinflammation syndrome [2,6,11,27].

Laboratory findings and ultrasound image

- Pleural and/or pericardial effusion and ascites
- Persistent fever
- Elevated CRP with normal procalcitonin
- D-dimer>400 µg/L
- Elevated plasma fibrinogen
- Diminished albumin and proteins
- IL-6>40 pg/ml

Hemodynamic failure [2,6,10,11]

Electrocardiography and ultrasound image

- Myocarditis
- Cardiac failure
- Shock

Neurologic findings [2,6].

Lumbar puncture and neuroimage

- Seizures
- Coma
- Severe myopathy
- Thrombotic phenomena
- Cardiorespiratory distress in consequence of neurologic impairment

PIMS-TS: Related to recent or active SarsCov2 infection

Clinical findings

- Persistent fever (duration of 4 days)

- Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea)
- Myocardial dysfunction
- Shock
- Rash
- Mucous involvement
- Renal impairment
- Neurologic symptoms (headache)
- Respiratory symptoms
- Swollen of extremities
- Odynophagia

Laboratory findings

- Lymphopenia, neutropenia and thrombocytopenia
- Elevated CRP, sedimentation velocity (SV), fibrinogen, ferritin, procalcitonin, d-dimers and IL-6
- Elevated troponin, BNP or pro-BNP
- Hypoalbuminemia and hyponatremia
- Hepatic enzymes elevation
- Elevated LDH
- Elevated triglycerides

Additional investigation [28,29].

Immunoglobulin measure (IgA, IgG, IgM and IgE)

- Urine analysis
- Urine and blood culture
- Oral search for Streptococcus group A
- Serology: Cytomegalovirus, Epstein Barr, Parvovirus B19, Mycoplasma, Hepatitis A, B and C, Adenovirus and Enterovirus
- Electrocardiography and echocardiography (in all patients)
- X-ray and abdominal ultrasound

Clinical phenotypes [30] (see figures 1 and 2 and tables 3, 4 and 5)

- Kawasaki-like [31].

World Health Organization[8]	Royal College of Paediatrics and Child Health (United Kingdom)[7]	Centers for Disease Control and Prevention (United States)[9]
Children and adolescents 0-19 y of age with fever >3 d AND 2 of the following: 1. Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP) 4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers) 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome	A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features (see listed in eAppendix in Supplement 2). This may include children fulfilling full or partial criteria for Kawasaki disease[a] Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice) SARS-CoV-2 PCR test results may be positive or negative	An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 wk prior to the onset of symptoms Additional comments Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

Abbreviations: APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECHO, echocardiography; ESR, erythrocyte sedimentation rate; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PT, prothrombin time; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Criteria for Kawasaki disease include persistent fever and 4 of 5 principal clinical features: erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash (maculopapular, diffuse erythroderma); erythema and edema of the hands and feet and/or periungual desquamation; and cervical lymphadenopathy.

Figure 1: PIMS-TS definition. Adapted from Whittaker et al – JAMA (2020).

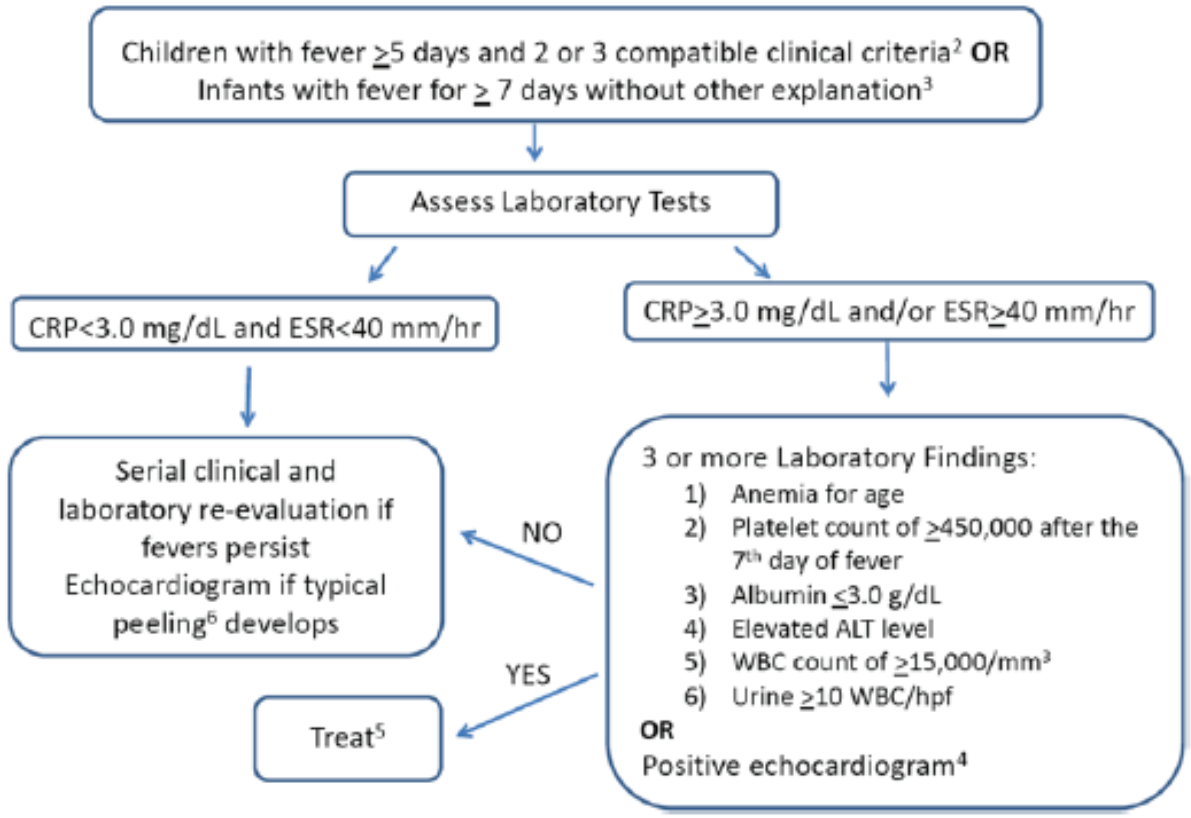

Figure 2: Incomplete Kawasaki disease approach. Adapted from AHA – Circulation (2017)

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Figure 3: PARDS (Pediatric Acute Respiratory Distress Syndrome) definition

- Non-specific: fever or shock and symptoms that include abdominal pain and other gastrointestinal symptoms, respiratory and neurologic symptoms; mimics HLH and toxic shock.

According to literature, there are specific criteria to intensive care admission. At least one of the following must be present: severe hypoxemia with no improvement with traditional oxygen therapy; severe pneumonia with hypoxemia and tachypnea; acute respiratory acidosis; recurrent apnoea; respiratory failure with mechanical ventilation need; hemodynamic instability; altered level of consciousness and/or multiorgan failure [23,425].

When intensive care is needed due to the presence of the factors mentioned above, there are some therapies that must be performed. The therapeutic approach includes pharmacological therapy and ventilatory support in most severe cases.

Pharmacological Therapy

Medical therapy depends on individual need, according to clinical presentation (see table 1), because there is no proven efficacy [10,21,23,31,33]. Available drugs include antiviral, immunomodulators, antibiotics and antipyretics.

Antiviral therapy

The only drugs of therapeutic value are Remdesivir and Oseltamivir. The last one should be use only if coinfection with Influenza [3,32,34,35]. These drugs should be initiated in the firs 7 days of the disease in order to improve their efficiency [3,23,32,36].

Lopinavir/Ritonavir, Chloroquine and Hydroxychloroquine are no longer used.

Remdesivir

Is an antiviral drug that binds to viral RNA, blocking their replication. It has been used is diseases like Ebola, Marburg, MERS and SARS [2,32].

Actually, there are only clinical trials in children with more than 12 years old, but its use before the age of 12 or weigh between 3,5-40 Kg could be done if clinical benefits [32,37].

It should be used if confirmed SarsCov2 infection and moderate to severe disease with hypoxemia and chest x-ray alterations and/or hemodynamic failure [23,36]. In PIMS-TS use only if severe disease or active infection [38,39].

Table 1: Clinical Presentation and clinical approach.

Clinic	Chest X-ray	Treatment	Considerations
Mild Mild or moderate respiratory distress without hypoxemia	No indicated unless risk factors	Symptomatic (*, **)	Outpatient, unless risk factors
Moderate Hypoxemia (SpO2<92%/ FiO2 0,21) and/ or moderate respiratory distress	Normal	Symptomatic (*, **)	Hospitalized
	Any infiltrate	Symptomatic (*, **) Consider corticotherapy	Consider Remdesivir
Severe Severe hypoxemia and respiratory distress, shock, multiorgan failure	Any infiltrate	Symptomatic (*, **) Consider corticotherapy	Consider Remdesivir and other immunosuppressors (Tocilizumab, Anakinra,…)

*Use antibiotics if bacterial sobreinfection
** Use any different drug among Remdesivir or off-label Remdesivir

Table 2: Ventilatory options

Oxygen therapy	O_2 (not humidified): target SpO_2: 92 – 96% [1,3,8,9]. • Venturi or high flow masks with reservoir [9]. • Limited use in mild hypoxemia, because not increase P/F (does not recruit alveoli). • Place surgical mask between the interface [3,50,55].
High flow oxygen therapy	• Mild to moderate hypoxemia (P/F > 200 mmHg), (S/F > 264 - FiO^2< 0,3-0,4), refractory to Oxygen therapy [3,9,10]. • Place surgical mask between the interface [50,56]. • If after 30-60 min: S/F < 220 or FiO2 > 0,4 to SpO2 > 92% [10,57].
NIV	• Alternative to IMV to alveolar recruitment [8,10,57]. • If hypoxemia - **CPAP** (PEEP > 5 cmH_20) [8,10,45]. • If hypoxemia or hypercapnia - **BLPAP** (**ST** or **PS** mode) - **IPAP** or **PS** for VC ~ 6 ml/Kg [8,58]. • Indicated if S/F > 221 e < 264, L pattern [10,57,58]. • Sedation is essential for good adaptation and decrease respiratory frequency and stop P-SILI Intubation if after 30-90 min: necessity of FiO^2 > 0,6 for SpO2 92-97% or S/F ≤ 200 or increase of respiratory effort (high FC/FR). [57,58]. Interfaces like total facial mask or Helmet, in case of need PEEP´s valvular, apply one filter between [3,9,10,56]. • Use masks no vented and without anti-chocking valvular • Useful after remove intubation to decrease respiratory failure and hospitalization in intensive care unit
IMV	• If no improvement or signs of respiratory failure and oxygenation rates, after NIV or HFOT [50]. • Early introduction if severe hypoxemia - P/F < 150 mmHg - (H pattern) [10,50,57,58].

Table 3: Kawasaki disease criteria.

Fever for 5 days and 4 of the following:
Erythema with lips fissure, oropharyngeal erythema, strawberry tongue
Bilateral conjuntivites, non exudative
Maculopapular rash, multiforme-like erythema
Hands and foot edema and erythema in acute phase and/or ungual desquamation in sub-acute phase
Enlarged lymph nodes (>/= 1,5 cm), frequently unilateral
If 4 or more than 4 criteria diagnostics is possible even though only 4 days of fever Patients that don't fulfill all the criteria may be diagnosed with incomplete Kawasaki disease
Coronary arteries abnormalities confirm Kawasaki disease diagnostic

Exclusion criteria

- High Flow Oxygen, Non-Invasive Ventilation (NIV), Mechanical Ventilation (MV) or Extracorporeal Membrane Oxygenation (ECMO) need
- Ionotropic drugs need

Table 4: Streptococcus toxic syndrome criteria.
1: S. pyogenes identification
A: Steril culture: Blood, pleural, surgical wound, cerebrospinal liquid
B: Non-steril: cutaneous wound, sputum, pharyngeal
2: Severity signals
A: Hypotension
B: 2 or more
• Fever
• Rash
• Renal impairment
• Platelets < 100000/mm^3
• Hepatic enzymes alterations
• PARDS
• Tissue necrosis
• Gastrointestinal symptoms

Table 5: Staphylococcus toxic syndrome criteria
1: Fever > 38,9ºC
2: Hypotension
3: Diffuse rash
4: Multiorgan involvement (3 or more)
• Liver (hepatic enzymes elevation)
• Blood (platelets < 100000/mm^3)
• Kidney (impaired function or pyuria with no documented infection)
• Mucous (vaginal, conjunctive, oropharynges)
• Gastrointestinal (vomiting, diarrhea)
• Muscular (CPK elevation, myalgias)
• Central Nervous System (altered level of consciousness)
• PARDS
5: Exclusion of:
• Measles
• Leptospirosis
6: Negative blood culture or cerebrospinal liquid (except for S. aureus)
Confirmed case: 6 criteria
Suspected case: 5 criteria

- AST or ALT more than 5x normal value
- Creatinine clearance <30ml/min/1,73m^2 or dialyses need
- Multiorgan failure
- Infants or pregnant women

Doses [23,35-37].

- If **weigh < 40 Kg**: First day 5 mg/kg/day; after second day use 2,5 mg/kg/day (perfusion in 30-120 minutes)
- If **weigh > 40 Kg**: First day 200 mg/day; after second day use 100 mg/day (perfusion in 30-120 minutes)

Duration of therapy: 5 days (it can be prolonged to 10 days if severe disease or persistent positive viral load without clinical improvement)

Side effects [23,35-37]

Low arterial blood pression

- Acute renal failure
- Hepatic enzymes elevation
- Nausea, vomiting, diarrhea and abdominal pain
- Coagulopathy

Oseltamivir

Use only if coinfection with Influenza virus.

Immunomodulators

Systemic Corticotherapy

Clinical trials in adults have demonstrated a decrease in mortality. Although its use is still controversial because of the effect in viral depuration [1,3,8,16,32].

It should be used in case of moderate to severe disease with hypoxemia, progressive respiratory failure and symptomatic evolution for more than 5 to 7 days; severe ARDS; septic shock resistant to treatment with catecholamines and/or with probability of adrenal insufficiency; hemophagocytic lymphohistiocytosis; severe bronchospasm; encephalitis; PIMS-TS. In the last one, there are two options: early use concomitant with immunoglobulin therapy in case of Kawasaki like disease, if elevated probability of immunoglobulin resistance (male, age < 12 months, RCP>10 mg/dL, Platelets </= 300.000/mm^3, AST>100 U/L, neutrophilia >80%, Hyponatremia < 133 mEq/L), shock, coronary dilatation or hemophagocytic lymphohistiocytosis; use as second line if no response to immunoglobulin therapy (it should be offered 24 hours after immunoglobulin). [1,12,18,23,36,39-41].

Doses: depends on disease severity [16,23,36,40]

Mild to moderate disease

- Methylprednisolone iv 1-2 mg/kg/day (each 12 hours, for 3-5 days)

If persistent symptoms or elevated inflammatory markers it should be necessary treatment for more than 6 days. In this case it should be replaced to the same dose of oral prednisolone. In the next 2-3 weeks the dose should be progressively decreased according to symptoms and inflammatory markers.

Severe disease (refractory shock, encephalitis, PIMS-TS with multiorgan involvement and myocardial dysfunction)

- Methylprednisolone iv 1-2 mg (kg/day (each 12 hours, for 3 to 5 days)
- Methylprednisolone iv 10-30 mg/kg/day (for 3 days, max 1g/day) and if positive effect it should be replaced to the same dose of oral prednisolone.
- Alternatively, it should be used dexamethasone iv 0,15 mg/kg/day (max 6mg/day and 10 days) [40]

Immunoglobulin

First line option in PIMS-TS specially if criteria for Kawasaki disease or toxic shock syndrome [23,30,38,39,4,44]

Doses

- 2 g/kg/dose, perfusion in 10 to 12 hours. If after 36 hours persists fever it could be administered a second dose.
- If hemodynamic instability the dose should be 1g/kg/day for 2 days.

Tocilizumab

Specific recombinant monoclonal antibody to IL-6 receptor. IL-6 should be measured. There is no date for its use before the age of two years [21,35].

It can be used in severe disease with persistent inflammatory status (elevated IL-6 > 40 pg/mL and d-dimmers > 400 ng/mL) and/or in PIMS-TS when there is no answer to immunoglobulin and systemic corticotherapy.

It should be administered one single dose and if no clinical response the second dose could be offered 12 hours later.

Doses:

- **If < 30Kg:** 12 mg/kg/dose iv (in 50 mL of NaCl, perfusion in 1 hour)
- **If >/= 30 Kg:** 8 mg/kg/dose iv (in 100 mL of NaCl, perfusion in 1 hour)
  - Max: 800 mg

Side effects [16,23,35,38]

Nausea, vomiting, diarrhea, abdominal pain and intestinal perforation (rare)

- Headache
- Rash
- Hypertension
- Leucopenia/Neutropenia and thrombocytopenia
- Discharged hepatic function
- Hypercholesterolemia
- HBV reactivation

Risk of opportunistic infections. It should not be use if platelets<100000/mm^3, neutrophils<500/mm^3 or hepatic enzymes elevation [23,38].

Infliximab

Monoclonal antibody anti TNF-alpha. [35] Consider administration if PIMS-TS with Kawasaki like disease resistant to immunoglobulin and systemic corticotherapy [35,38,40].

Doses

One single dose of 5 mg/kg (in 250 mL of NaCl, perfusion in 2 hours).

Pre-medication: anti-histaminic and corticoid [35,38]

Side effects [35,38].

- Anaphylaxis
- Risk of infection

Anakinra

IL-1 receptor blocker with small lifetime, rapid begin of action and less risk of bacterial infection [35,38]

It could be use if severe pneumonia associated to persistent inflammatory status with HLH criteria and/or in PIMS-TS with Kawasaki like disease resistant to immunoglobulin and systemic corticotherapy [35,38]

Doses [35,38]

- **Transcutaneous:** 2 mg/kg/day with progressive increase to 8 mg/kg/day (each 12 hours)
- **Intravenous:** This is preferred if dose>100mg/day, platelets<20000/mm^3/hemorrhagic signs or marked edema
  - NaCl dilution till concentration of 4-36 mg/ml
  - Administration = transcutaneous
  - **If < 20 Kg:** 2 mg/kg, single dose; followed by continuous perfusion of 0,02 ml/kg/hour
  - **If > 20 Kg:** 2 mg/kg, single dose; followed by continuous perfusion of 0,01 ml/kg/hour (max 400 mg/day)
  - Therapeutic for 9 days [35].

Note: if dose>100 mg/day, it should be administered each 8 to 12 hours or in continuous perfusion.

Side effects [35,38].

- Local reaction
- Flu-like disease
- Neutropenia
- Risk of infection

Antibiotics

They should be used if bacterial pneumonia or sepsis (if septic shock they should be administered in the first hour). Perform blood cultures before administration [3,21].

The choice depends on age, origin of infection, epidemiology and bacterial resistances [3,16,21,23,32,45].

Antipyretics

Paracetamol

First line option due to lack of information about the use of non-steroid anti-inflammatory drugs [1].

FLUIDS

The administration should be careful because the risk of hydric overload (lung edema) but hypovolemia status should also be avoided (tecidular hypoperfusion) [46].

If hemodynamic failure is present:

- Careful volemic perfusion (isotonic crystalloid); avoid dextrans and hydroxyethyl starches [1,21,32,36,47].
- Albumin 5% should be used in case of refractory volemic perfusion (>60 ml/kg of crystalloid), hypoalbuminemia and/or hyperchloremic metabolic acidosis [47].

- In case of refractory volemic perfusion, first line option is epinephrine (low cardiac outflow or myocardial dysfunction) or norepinephrine (if vasodilatation associated to hyperinflammatory syndrome or when sedative drugs are used) [21,46].

- In shock situations associated with hyperinflammation it's important to use anti-inflammatory drugs. [38,44].

Tromboembolic Disease Prophylxis

Severe cases of COVID 19 disease may present with elevated risk of thromboembolic phenomena due to hyperinflammation and endothelial dysregulation [21,38,48,49].

In pediatric age there are few information about this situation but pharmacological therapy should be initiated if there are some risk factors associated to thrombosis risk (personal history of thrombophilia or thromboembolic phenomena; direct familiar with thromboembolic phenomena; central venous catheter; after puberty age; immobilization; burns; neoplasic disease; severe ventricular dysfunction; estrogen therapy; obesity; severe dehydration; recent trauma or surgery) [48,49].

According to this risk factors, therapy with enoxaparin is recommended if familiar or personal history of thromboembolic phenomena; central venous catheter and 2 risk factors; or presence of 4 risk factors [48].

Anti-Xa factor should be measured after 48-72H (recommend value is 0,3-0,49) [38].

Enoxaparin (transcutaneous)

Doses

- **Age < 2 months:** 0,75 mg/kg/dose each 12 hours

- **Age > 2 months:** 0,5 mg/kg/dose each 12 hours

If platelets < 30000/mm^3 or active blood loss, thromboembolic prophylaxis should be mechanic [38,48].

Acetylsalicylic acid (aspirin)

Anti-inflammatory

Use in PIMS-TS with Kawasaki like disease: simultaneously with immunoglobulin.

30-50 mg/kg/day each 6 hours, till apyrexia for 48 hours. After this approach, use anti-aggregante dose for 6 to 8 weeks till normal platelets counts, acute phase markers and normal echocardiogram [38,40,44].

Anti-aggregante

Use in PIMS-TS if severe disease, elevated inflammatory markers and/or platelets>700000/mm^3 or in the presence of aneurysms. Use a dose of 3-5 mg/kg/day for 6 weeks (perform echocardiogram to confirm normalization). This recommendation is made due to described cases of coronary arteries alterations in PIMS-TS even though there are no criteria for Kawasaki like disease [38,44].

Personal Protection

Use individual equipment protection as recommend by World Health Organization. Play special attention to procedures associated to elevated risk of aerosol liberation [1,3,50,51].

Ventilatory Support

Oxygenation evaluation: SpO2, PaO2, PaO2/FiO2 (gold standard if hypoxemia or intrapulmonary shunt), SpO2/FiO2, Oxygenation Index, Oxygenation Index based on SpO2 [10,26,52-54]. The last two used to evaluate the severity of PARDS (see Annex 6).

There are various ventilatory options for treatment of patients in intensive care (see table 2) that should be used according to individual clinical features. These include oxygen therapy, high flow oxygen therapy, Non-Invasive Ventilation (NIV) and Invasive Mechanical Ventilation (IMV).

Invasive Ventilation

- Use high efficiency HEPA filters in the branches of ventilator that imply greater dead space and resistance in the mechanical ventilation circuit (possible impact on triggers). Replace filters of the branch of expiratory every 24 hours or before if very humid [9,45,46].

Use passive humidification devices (not active with pan) with age-appropriate HMEs heat and humidity exchangers, between interface and the circuit. Some filters include both functions – HMEFs. The humidification process is less efficient and the risk of obstruction of ETT because secretions, in this case use active humidification when changing tracheal tubes. Some protocols use acetylcysteine iv [10].

- Use closed suction circuit aspiration [9,10,45].

- ETT cuff well inflated [9,10].

- Avoid circuit disconnections [10,45], but in case of disconnection immediate clamping of ETT [10].

- If necessary, suspend positive pressure ventilation and disconnect after locating the antimicrobial filter [9,45].

Non Invasive Ventilation

- Use dual branch fans / circuits, because interfaces indicated are «non-vented» (no air leak points)[8, 9, 56] This type of ventilators are conventional and it must be choose the mood of NIV, because the only available with two branches is V680® [56].

- The filter distribution is similar to that described in invasive ventilation [9,5]

- In single-branch ventilators, the circuit is protected by placing antimicrobial filters at the ventilator outlet and close to the patient interface. Close to the patient interface, it is preferable to use a filter that incorporates HMEF function [56].

- Adjust parameters (pressure) to compensate the increase in resistance that represents the presence of 2 filters in the system (as in IMV) [56,58].

- NIV through non-vented interfaces and single branch,

requires the existence of an expiratory system (exhalation port, PEV - Plateau Exhalation valve, Whisher-Swivel valve or active valve). Placing a filter outside the patient interface minimizes contamination of exhaled air [56,58].

- Choose ventilators that offer 100% O2 (Philips V680®, Philips V60®, Philips V60 plus®, Philips Trilogy 202®, Philips Trilogy Evo O2®), or if they are home-based, that have an O2 mixer that provide at least 80% O2 [46,48].
- Before removing the interface (mask or helmet), suspend ventilation

Orotracheal intubation

There are various criteria for this procedure that include clinical, laboratorial and imagiologic findings [8-10,45,50,57]

Clinical

- Signs of severe respiratory failure (grunting, retractions, elevated respiratory rate, abdominal breathing)
- Hemodynamic instability that needs amine support
- Organic failure
- Changes in the status of consciousness

Acid-base homeostasis

- SpO_2 < 92 % with FiO_2 > 0,6
- P/F < 200 mmHg and (FiO_2 > 0,4)
- Hypercapnia and acidosis

NIV failure

No improvement after one hour: P/F and S/F < 200 (FiO_2 > 0,4), no decrease of cardiac frequency/respiratory frequency, ROX index – (S/F)/RF ≤5 (> 10 years)

Other/Imagiologic

- Thoracic X Ray and CT scan: presence of ground glass opacities and diffuse distribution of pulmonary opacities
- Thoracic ultrasound: if interstitial syndrome with B lines and conserved pleural sliding, try NIV; on the other hand, if interstitial syndrome with multiple subpleural consolidations and decreased pleural sliding, try early orotracheal intubation

Orotracheal intubation is a procedure with high risk of contamination. So it needs adequate protection [9,10], compartment with negative pressure system or in isolated room equipped with appropriate filters (HEPA: Hospigardard® or equivalent) [1,9], involve as few people as possible (should be a nurse with emergency car and airway material in the outside area) [1,9,45].

This procedure must be carried out by the most experienced doctor with videolaryngoscopy (if available and there is experience in use) [1,9,10]. Early use of Sellick maneuver [1,55]. Prefer ETT with cuff [9,10]. Avoiding supraglottic devices [38,50].

Fast orotracheal intubation sequence

- Before the procedure oxygenate for 5 minutes with a high output mask and FiO2 100%. Must be well adapted and supported with both hands of the member responsible for the airway [3,9,10,35,50].
- Avoid manual ventilation [8,50,39] and use an antimicrobial filter between the mask and the insufflation bag [9,10,31,44,50]. In case of necessity of manual ventilation, do not hyperventilate [31,50]. If possible, connect valvule of PEEP.
- Use sedoanalgesia and muscle relaxant (inhibit cough reflex): [44,48].
  - **If hemodynamic stability:** 1 a 3 mg/Kg of Propofol, 1 - 2 µg/Kg of Fentanyl, 0,6 - 1 mg/Kg of Rocuronium
  - **If hemodynamic instability:** 1 – 1,5 mg/Kg of Ketamine, 1 – 2 mg/Kg of Fentanyl, 0,6 – 1 mg/Kg of Rocuronium
- Introduce clamped ETT [9,44]. In case of use a tracheal guide, clamp the ETT as soon as possible before the complete removal of the guide [10,44].
- Unclip ETT only when the cuff is well inflated and adapted to the circuit.
- Start positive pressure ventilation only after confirming the absence of leakage and filling of ETT [10]
- Confirm adequate intubation, using direct observation of the chest expansion, use of capnography and chest radiography.
- Nasogastric intubation to decrease contacts with airways
- The reusable material must be immediately protected, sealed and sent for sterilization

Convencional MIV

The pulmonary manifestations present different stages of evolution and pathophysiological patterns, important information to take account when defining the ventilatory strategy. The severe hypoxemic respiratory failure is different from the classic forms of PARDS. The use of high PEEPs at the beginning may not be the most correct strategy. Some patients haven´t pulmonary compliance as low as initially thought. Two basic pathophysiological patterns have been suggested in the evolution to severe hypoxemia (respiratory failure type I), both present decrease of P/F with different radiological images:

1. Presence of dysregulation of pulmonary perfusion and vascular microthrombosis. Important compromise in pulmonary perfusion (Q), increase of alveolar volume dead space and increase V/Q ratio (decrease PaO2 and increase PaCO2) [10,24].

Pulmonary compliance and the level of alveolar recruitment are relatively preserved. These patients have a limited response to alveolar recruitment techniques (increase of PEEP, prone and recruitment maneuvers) - «*limited PEEP response*» .. This type of mechanism is suspected when hypoxemia is important and chest X-ray presents little interstitial infiltrate («Black X ray»), despite the highly altered CT-scan [24,45]. There are some improvement with inhaled nitric oxide and/or systemic vasoconstrictors, especially it there are signs of Pulmonary hypertension on cardiac ultrasound [10,24,45]

2. Alteration of the permeability of the alveolar capillary membrane (inflammation), with decrease in the V/Q ratio and intrapulmonary shunt, similar to classic PARDS [10,24].

These patients have decreased pulmonary compliance, need alveolar recruitment and respond to increase of PEEP - "higher PEEP response". On chest radiography, bilateral interstitial alveolar infiltrates compatible with acute lung involvement («White X ray») are observed [24,45].

See PARDS criteria and stratification according to severity- Berlin definition and PALICC 2015 definition [12,40,45,49].

The ventilation strategy will have to be adapted to each patient and in general includes:

- Adequate sedoanalgesia (decrease of PSILI – patient self-inflicted lung injury). Muscle relaxants if sedation alone is sufficient to achieve effective ventilation. Some studies, demonstrate decrease of mortality, when used in the early stage of moderate to severe PARDS (first 24-48hours) [3,9,10,45,48].

Prefer in bolus [1,8]. The objective is decrease transpulmonary pressures, minimize the possibility persisted and facilitate adaptation of the prone position.

Evaluation of brain activity, using sedation scales (Comfort-B, Ramsay, Evans) or *Bispectral Index* (POC.SNCIP(UCIPED). GER.001- sedation in pediatric intensive care unit.

Stop if: P/F ≥ 150; OI > 12 and OSI > 10

- Although there is no consensus regarding the mandatory ventilation mode, take into account that volume-controlled ventilation allows assessing lung static complicance. Under flow conditions = 0, determine the value of the plateau pressure (through the inspiratory pause) – Static compliance (ml/cm$H_2$0) = VC / (Plateau pressure – PEEP)

- Protective ventilation

- PEEP for P/F > 150 - 175 mmHg (shunt < 40-33,5 %) and plateau pressure < 28 - 32 cmH_2O.

- PEEP ~ 8 -12 cm$H_2$0

- Less risk of atelectasia and of VILI – ventilator induced lung injury [1,12].

- PEEP value depends on the pulmonary pathophysiology pattern [24].

- Initial PEEP of ~10cmH2O is consensual [10,24,45].

- **Prono position:** [1,3,9,10,37,45,48].

If: refractory hypoxemia (P/F ≤ 150 mmHg with FiO_2 ≥ 0,6 and PEEP > 5), after the first 4-6 hours of IMV (after parameter optimization, sedoanalgesia and adequadte curarization) [48].

Durations: 16 a 20 h/day [1,8,12,16,48].

Contraindicated: shock, major acute hemorrhage, polytraumatized, spinal instability, Intracranial hypertension, abdominal surgery, malignant arrhythmias [16].

Criteria for remove progressively ventilation: [10,25,59].

No progression lung lesions at radiological level

- PaO2 > 55 – 60 mmHg (P/F > 150 mmHg) with FiO_2 < 0,4 and PEEP < 10 cmH_2O

- Hemodynamic stability (no need for a high dose vasopressor)

- Without high fever and elevated inflammatory biomarkers that can compromise the effectiveness of ventilation

In this phase, the support pressure mode must be used, in a closed circuit with no spontaneous breathing test with T-piece [3].

In case of refractory hypoxemia, after optimization of ventilation, use of rescue and prone therapies, consider institution of ECMO [3,9,12,48].

Extubating

- Stop as soon as possible. Target SpO2 88-96%. Try to minimize the injury associated with ventilation. [1,8]

- Caution with individual protection and only 2 elements (one that manipulate airway and other to administers drugs) [1,3,12,44].

- Consider the use of drugs that reduce cough reflex and if the patient is reactive: fentanyl, lidocaine (1mg/Kg), dexmedetomidine and propofol [44].

- Placement protective barrier before handling the airway, between the patient and the professionals. [44]

- Effective aspiration through ETT (closed system) before the procedure [44].

- Put the ventilator in standby mode and turn off the suction system. Remove the ETT connected to the respiratory system after deflating cuff [44].

- Put material directly in trash [44].

- Minimize time between extubation and the application of 02 administration interface, to reduce facial manipulation

- The patient must use surgical mask over the O2 administration interface [31,44].

Inhalatory Therapeutics

If necessary, use an expander chamber inhaler on the patient breathing spontaneously or through the inspiratory branch on the ventilated patient, after an HMEF filter [3,9].

Pneumatic, ultrasonic or oscillatory membrane systems should not be used due to the high risk or aerosol generation. [3]

CONCLUSION

The patient with COVID-19 with criteria for Intensive Care admission requires a complex and specific approach in terms of therapeutic strategy, namely in relation to the type of ventilatory support. It is a recent, multifaceted, multi-organ disease, and there is still much to know. In these patients, the participation of a multi-

disciplinary and experienced team is essential to the objectives of the interventions and subsequent follow-up.

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