

Caring for Critically Ill Children With Suspected or Proven Coronavirus Disease 2019 Infection: Recommendations by the Scientific Sections' Collaborative of the European Society of Pediatric and Neonatal Intensive Care*

OBJECTIVES: In children, coronavirus disease 2019 is usually mild but can develop severe hypoxemic failure or a severe multisystem inflammatory syndrome, the latter considered to be a postinfectious syndrome, with cardiac involvement alone or together with a toxic shock like-presentation. Given the novelty of severe acute respiratory syndrome coronavirus 2, the causative agent of the recent coronavirus disease 2019 pandemic, little is known about the pathophysiology and phenotypic expressions of this new infectious disease nor the optimal treatment approach.

STUDY SELECTION: From inception to July 10, 2020, repeated PubMed and open Web searches have been done by the scientific section collaborative group members of the European Society of Pediatric and Neonatal Intensive Care.

DATA EXTRACTION: There is little in the way of clinical research in children affected by coronavirus disease 2019, apart from descriptive data and epidemiology.

DATA SYNTHESIS: Even though basic treatment and organ support considerations seem not to differ much from other critical illness, such as pediatric septic shock and multiple organ failure, seen in PICUs, some specific issues must be considered when caring for children with severe coronavirus disease 2019 disease.

CONCLUSIONS: In this clinical guidance article, we review the current clinical knowledge of coronavirus disease 2019 disease in critically ill children and discuss some specific treatment concepts based mainly on expert opinion based on limited experience and the lack of any completed controlled trials in children at this time.

KEY WORDS: children; coronavirus; hypoxemic respiratory failure; multisystem inflammatory syndrome, pediatric intensive care

Peter C. Rimensberger, MD¹
 Martin C. J. Kneyber, MD, PhD, FCCM^{2,3}
 Akash Deep, FRCPCH⁴
 Mehak Bansal, DNB⁵
 Aparna Hoskote, MD⁶
 Etienne Javouhey, MD, PhD^{7,8}
 Gilles Jourdain, MD⁹
 Lynne Latten, RD¹⁰
 Graeme MacLaren, MB BS, MSc, FCCM^{11,12}
 Luc Morin, MD¹³
 Marti Pons-Odena, MD, PhD^{14,15}
 Zaccaria Ricci, MD¹⁶
 Yogen Singh, MD¹⁷
 Luregn J. Schlapbach, MD, PhD, FCICM^{18,19}
 Barnaby R. Scholefield, MD, PhD^{20,21}
 Ulrich Terheggen, MD, PhD²²
 Pierre Tissières, MD, DSc²³
 Lyvonne N. Tume, RN, PhD²⁴
 Sascha Verbruggen, MD, PhD²⁵
 Joe Brierley, FRCPCH²⁶
 on behalf of the European Society
 of Pediatric and Neonatal Intensive
 Care (ESPNIC) Scientific Sections'
 Collaborative Group

*See also p. 127.

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Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is usually mild in children, few require hospitalization and/or intensive care (1, 2), and death is rare (3). Like in adults, it is mainly, but not obligatorily, characterized by respiratory illness, fever, flu-like or abdominal symptoms, including diarrhea (1, 4).

Respiratory involvement varies from mild upper respiratory tract symptoms to severe acute respiratory distress syndrome (ARDS). Gattinoni et al (5)

proposed two adult ARDS phenotypes of COVID-19 that may coexist: “Type L COVID-19 ARDS” characterized by intrapulmonary shunting, preserved compliance, less potential for lung recruitability, and increased alveolar dead space due to pulmonary microthrombi formation; “Type H”, a more “traditional” ARDS characterized by low compliance. These phenotypes have not been described in children, although some with multisystem inflammatory syndrome (MIS) (see below) show reduced lung compliance but near normal oxygenation (PC Rimensberger, unpublished observations, 2020 and reported by Chao [6]).

Recently, Pediatric MIS-Temporally associated with COVID-19 (PIMS-TS, later termed MIS-C in the United States and MIS by World Health Organization, which we use in this international article) has been reported (7–12). It is unknown if MIS is a postinfectious immune reaction with aberrant development of acquired immunity or a novel disease (11, 12).

A prodrome of lethargy and high temperature, with half reporting acute abdominal pain and diarrhea, is followed by a marked inflammatory multisystemic syndrome with either 1) a refractory “toxic” shock-like (TSS) syndrome with predominantly vasoplegic or cardiogenic shock or 2) a Kawasaki-like syndrome including coronary dilatation/aneurysms or a combination of both. MIS can occasionally be the “initial” presentation of COVID-19 (7, 9). Respiratory symptoms may not be present (11). Increased C-reactive protein, interleukin (IL) 1 and 6, mild to moderately elevated troponin, and high pro-BNP can be found (8–11).

This European Society of Pediatric and Neonatal Intensive Care (ESPNIC) statement provides recommendations for caring for children with suspected or proven SARS-CoV2 in intensive or intermediate care units. It builds on previous ESPNIC statements or consensus paper recommendations (13) unless otherwise stated, including pediatric guidance on septic shock (14), acute lung injury (15), noninvasive and invasive mechanical ventilation (16, 17), extracorporeal respiratory and/or circulatory support (extracorporeal membrane oxygenation [ECMO]) (18, 19), acute kidney injury (AKI) (20), nutrition (21, 22), Kawasaki disease (KD) (23), and emergency mass critical care (24).

METHODOLOGY

The ESPNIC scientific group collaborative (two leading/writing members per section) worked with a

4-week timeline to draft recommendations. Given the paucity of pediatric COVID-19 outcome studies, the National Institutes of Health (NIH) consensus statement standards and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach are not yet suitable (25).

Main PubMed search terms for repeated searches included coronavirus, COVID-19, SARS-CoV2, critical-illness, children, Kawasaki-like disease, MIS/PIMS-TS & MIS-C, and terms related to each section topic. Section leads selected section members based on their expertise for advice and validation of drafted recommendations. The authors (P.C.R., M.C.J.K., J.B.) coordinated the work and edited draft recommendations. Each modification was sent back to section leads for final approval.

Basic Rules—Protect Yourself and Your Team

One or repeated nasal swab specimen negative polymerase chain reaction may occur and does not rule out COVID-19 (26). Thus, full personal protective equipment (PPE) should always be worn when caring for COVID-19 positive or suspected children. Aerosol-generating procedures (AGPs) (**Table 1**) are high-risk interventions and must be reduced to an absolute minimum.

Respiratory Illness and Support

Pediatric Acute Lung Injury Consensus Conference and Pediatric Mechanical Ventilation Consensus Conference recommendations on respiratory support modes, strategies, and pulmonary ancillary treatment apply (15, 16). Of note, there is an increased risk of air-borne disease dissemination using noninvasive respiratory support (**Table 2**). Ideally, an adequate interface seal should be assured (e.g. helmet, nonvented oronasal or full-face mask) (27). Bacterial/viral filters (high-efficiency particulate air filter) must be placed at least on the expiratory limb of the patient circuit for invasive and noninvasive mechanical ventilation.

Delayed intubation is usually avoided in children with marked hypoxic-respiratory failure ($SpO_2/FiO_2 < 221$) or with no improvement with NIV within 60–90 minutes (16, 17). However, higher intubation thresholds may be reasonable in proven COVID-19 hypoxic respiratory failure with low work of breathing and/or no pathologic hyperventilation.

TABLE 1.
Common Aerosol-Generating Events

High-flow nasal cannula.
Continuous positive airway pressure or noninvasive ventilation without an adequate seal.
Bag-mask ventilation.
Intubation.
Any advertent or inadvertent circuit or endotracheal tube disconnection.
Tracheal suction (without a closed system).
Extubation.
Coughing/sneezing or any procedure inducing this.
Chest physiotherapy.
Delivery of nebulized medications (unless via closed circuit).
Cardiopulmonary resuscitation (prior to intubation).

Intubation should be performed by an expert in airway management in a closed environment with minimal staff present. Video laryngoscopy, rapid sequence induction, and avoiding bag/mask ventilation are recommended (28). If bag/mask ventilation cannot be avoided, the “two-person technique” is preferable to ensure better mask seal. Cuffed endotracheal tube should be used irrespective of patient age.

Measuring the quasi-static respiratory system compliance (Crs) under zero flow conditions after intubation, and then daily, allows identification of the clinical phenotype (i.e. with preserved or decreased Crs) and guides ventilator settings (Table 3).

Microvascular Pulmonary Thrombosis, Pulmonary Embolism, and Thromboprophylaxis

Hypercoagulability, common in adults with COVID-19, has been observed in severely affected children, in whom we recommend a daily coagulation screen (D-dimer, prothrombin time, platelet count) (33) and pharmacologic thromboprophylaxis with either low weight molecular weight or unfractionated heparin (34)—based on renal function (creatinine clearance cut off value 30 mL/min).

TABLE 2.
General Recommendations for Patients Requiring Respiratory Support

Strict personal protection equipment is mandated when managing patients, especially when handling airways, with suspected or confirmed coronavirus disease 2019.
Assure an adequate seal of the interphase for noninvasive ventilation.
Use cuffed ETTs for invasive ventilation.
Use bacterial/viral filters (high-efficiency particulate air filter) on the expiratory limb of the patient circuit.
Minimize ETT disconnections and use inline, closed suctioning.
Use airway humidification (active or passive), beware of endotracheal tube occlusion due to plugging caused by tenacious secretions.
Supportive care: fluid management, hemodynamic management, transfusion strategies, nutritional management, and sedation and analgesia practices should also be applied per Pediatric Acute Lung Injury Consensus Conference recommendations.

ETT = endotracheal tube.

In children with refractory hypoxia or right heart strain on electrocardiogram/echo, inferior vena cava signs, or raised D-dimers, we recommend screening for pulmonary embolism (PE) (e.g. ultrasound and/or CT-angiogram) and if found aggressive treatment: systemic anticoagulation is first line, but consider systemic thrombolysis or interventional radiology after multidisciplinary consultation for PE-induced hemodynamic compromise (34).

Cardiovascular Involvement

There is no change to the 2020 Surviving Sepsis Campaign (SSC) “pediatric septic shock guidance” (14) recommended in children with COVID-19. Of note, hypovolemia is common following the vomiting and diarrheal prodrome with reduced fluid intake before ICU admission.

Specific MIS treatment (Fig. 1) should follow a multidisciplinary approach involving infectious diseases specialists, rheumatologists, cardiologists, and

TABLE 3.
Practice Recommendation for Coronavirus Disease 2019 Children on Invasive Mechanical Ventilation

Ventilator settings	Initial settings
Vt–expiratory	5–7 mL/kg ideal bodyweight, lower Vt may be targeted if decreased lung compliance.
PEEP and FiO ₂	Initial PEEP ± 8–10 cm H ₂ O ^a —further increase based on guidance from the low PEEP/FiO ₂ grid (29) ^b . Titration of PEEP/FiO ₂ to maintain oxygen saturation 92–96% for moderate or 88–92% for severe pediatric acute respiratory distress syndrome
Goals and limits	Values
Driving pressure	≤ 15 cm H ₂ O
Pplat	< 28–32 cm H ₂ O
pH	> 7.20
Supportive measures	Specific recommendation
Neuromuscular blockade	Consider early use of neuromuscular blocking agents for 24–48 hr if PaO ₂ /FiO ₂ < 150; OI ≥ 16; OSI ≥ 10, and/or if there is spontaneous breathing at high (esophageal) transpulmonary pressures, minimizing ventilator dyssynchrony, prone positioning, and avoiding high Pplat.
Prone positioning	Consider prone positioning if PaO ₂ /FiO ₂ < 150; OI ≥ 16; OSI ≥ 10, especially if there is concomitant reduced lung compliance.
Escalating therapies for refractory hypoxemia	Proposed clinical approach
PEEP/recruitment	Titrate PEEP, balancing oxygenation, and hemodynamics. High PEEP may be necessary if low lung compliance.
iNO	Use iNO if documented pulmonary hypertension and/or right ventricular dysfunction/failure. Consider iNO if alteration in hypoxic pulmonary vasoconstriction is presumed (i.e. lack of improvement in oxygenation despite all other measures). With acute onset of marked hypoxemia consider pulmonary embolism (D-dimers, ultrasound, CT thorax).
HFOV	HFOV may be considered in patients with poor lung compliance (i.e. requiring inspiratory airway pressures during conventional mechanical ventilation of 30 cm H ₂ O or higher to maintain acceptable ventilation ([i.e. pH > 7.20]) and/or oxygenation despite adequate PEEP settings. We recommend staircase titration of mean airway pressure according to the oxygenation response (30, 31).
Respiratory ECMO	May be considered if refractory hypoxemia persists despite all measures used.

HFOV = high-frequency oscillatory ventilation, iNO = inhaled nitric oxide, OI = oxygenation index, OSI = oxygen saturation index, PEEP = positive end-expiratory pressure, Pplat = plateau pressure, Vt = tidal volume.

^aLower initial PEEP levels should be considered in patients with preserved compliance (“Type L” lung disease [5]) indicating “non”-recruitable lung disease.

^bPEEP levels below the PEEP/FiO₂ grid have shown to be associated with increased mortality in pediatric acute respiratory distress syndrome (32).

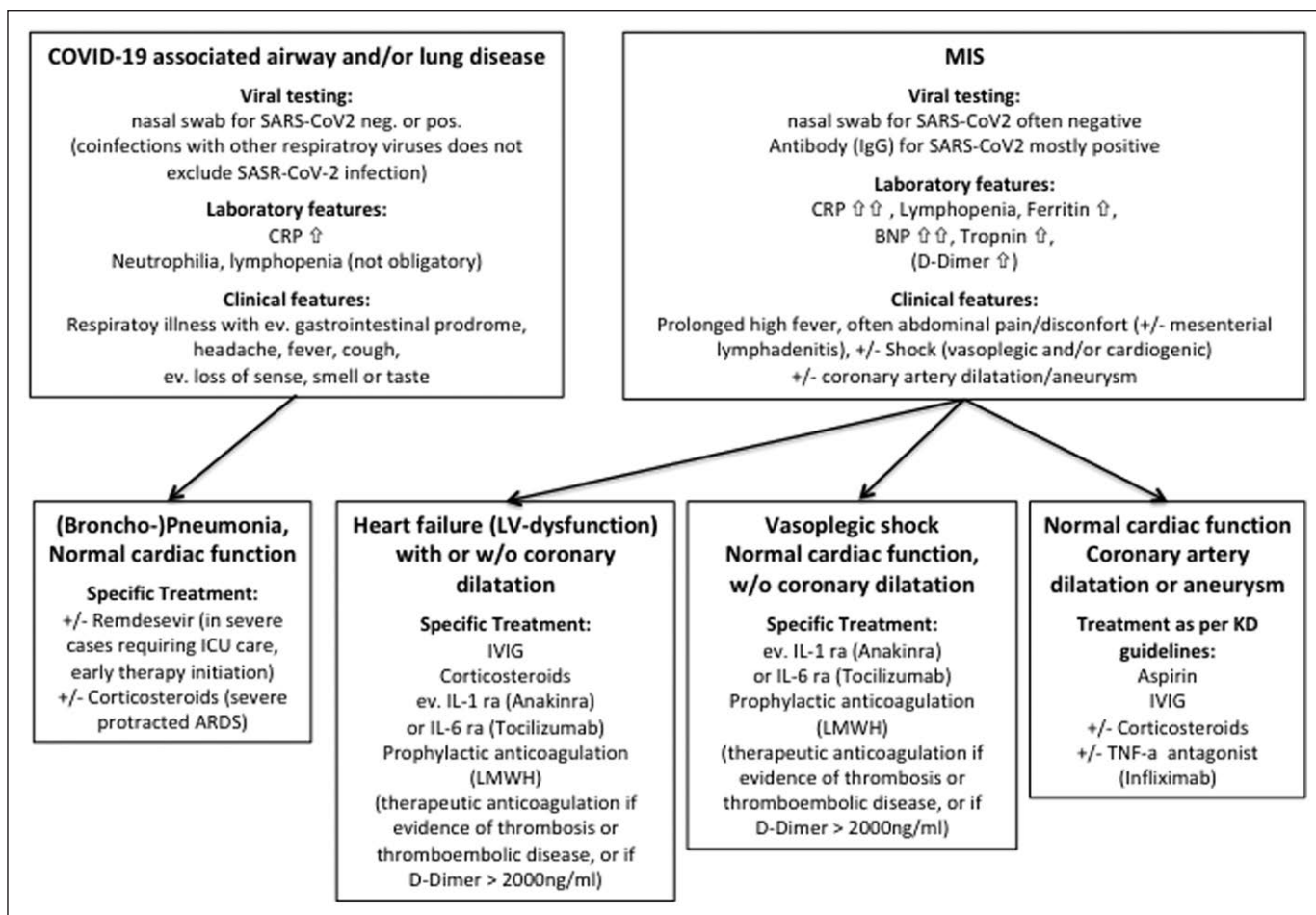


Figure 1. Proposed specific treatment options (beyond basic ICU treatment concepts) for coronavirus disease 2019 (COVID-19)–related severe respiratory disease (SARS) and multisystem inflammatory syndrome (MIS). ARDS = acute respiratory distress syndrome, BNP = brain natriuretic peptide, CRP = C reactive protein, CoV2 = coronavirus 2, KD = Kawasaki disease, IgG = immunoglobulin G, IL = interleukin, IVIG = IV immunoglobulin, LMWH = low molecular weight heparin, LV = left ventricular, TNF-a = tumor necrosis factor-alpha.

intensivists. In Kawasaki-like or TSS presentations (e.g. hyperinflammatory shock) especially when myocardial dysfunction is documented, successful use of IV immunoglobulin administered early as per KD guidelines (23) has been reported (9–11) and can be recommended, acknowledging this is not based on data for the TSS-like presentation. Besides IVIG, steroids are the most frequently used anti-inflammatory drug (8–11). In the event of resistance to IVIG and persistent high inflammatory markers, anti-IL-6 monoclonal antibody (Tocilizumab, Sarilumab), IL-1 receptor antagonist (Anakinra), or tumor necrosis factor-α antagonist (Infliximab) has been used on an empirical basis (9, 11). However, according to NIH COVID-19 treatment guidelines (July 17, 2020), there are insufficient data yet to recommend for or against the use of either IL-6 or IL-1 inhibitors (35).

In cardiovascular compromise/hemodynamic instability, repeated multimodal hemodynamic monitoring, including point of care ultrasound (36), can optimize therapy. With documented myocardial and/or coronary involvement, serial and follow-up echocardiography by a pediatric cardiologist is important and might allow for an eventual better understanding of this novel disease for which the Initial early prognosis seems good (9).

COVID-19 is not a contraindication to ECMO in children, the present indications and thresholds for ECMO as per currently published extracorporeal life support organization (ELSO) guidelines apply (18). Shock refractory to standard management should prompt early consultation with ECMO providers (19) although specific COVID-19 ECMO data in the context of MIS are sparse (9, 11). In line with interim ELSO

COVID-19 guidelines (18), we do not recommend extracorporeal cardiopulmonary resuscitation outside an ICU setting and without an experienced team.

AKI and Renal Replacement Therapies

Although the epidemiology and etiology of COVID-19 AKI may differ slightly from other types of critical illness, management is essentially the same (20). Unless there is a situation such as severe sepsis where continuous renal replacement therapy (CRRT) is clearly superior to peritoneal dialysis (PD) allowing hemodynamic stability and more accurate fluid removal (37), both methods are equally efficacious (38).

Given the COVID-19 cytokine storm, other extracorporeal therapies (e.g. hemoperfusion and cytoabsorption) have been proposed in COVID-19 ICU patients with AKI to remove proinflammatory cytokines (39), thereby reducing cytokine storm induced organ damage. With minimal supportive data and the risk of therapeutic drug removal, as well as poor availability, we do not currently recommend them.

Adaptation of Renal Replacement Therapy Regimens With Resource Limitation. With resource limitations, renal replacement therapy (RRT) regimens can be adapted. 1) Single machine use for two or more patients by increasing exchange rates to compensate for decreased RRT time (31). 2) Use of lower rates after achieving metabolic control to limit consumable waste (32). 3) If CRRT unavailable, PD may be used (38).

Risks of Filter Clotting During CRRT. The hypercoagulable COVID-19 state means frequent filter clotting, and vascular thrombosis can be an issue, so the usual approach of prefilter heparin is recommended (20) (Table 4). Many adults with COVID-19 have had deranged liver function tests (LFTs) (40), so citrate has been relatively contraindicated. Cautious use in children is permitted, although few have had deranged LFTs to date. Alternatively, a combination of prostacyclin and unfractionated heparin (both pre filter) can be used.

Neurologic Involvement

COVID-19, as with other viral infections, can cause rare but important neurologic manifestations in children (e.g., meningitis, encephalitis, acute disseminated encephalomyelitis, postinfectious brainstem encephalitis, Guillain-Barre syndrome, myositis, acute

TABLE 4.
Measures to Reduce the Risk of Filter Clotting During Continuous Renal Replacement Therapy

Address all issues related to vascular catheter—size, location, bending, kinking, leakage.

Higher blood flow rates and predilution replacement fluid administration reduces the chances of clotting of the filter.

Preferring filters with larger surface area to reduce transmembrane pressure.

While using continuous veno-venous hemodiafiltration, reduce the postfilter component to avoid clotting in the bubble trap.

Dose heparin infusion appropriately. Follow practical tips from the Kidney Disease Improving Global Organization guidelines [18].

Consider using a heparin bolus 20 U/kg.

Start prefilter heparin at higher than usual rates 20–30 U/kg/hr (usual 10–20 U/kg/hr).

Maintain ACT 180–220 s, if ACT is low and the filter clots- increase the dose by 10–20% of the previous dose.

Heparin 10 U/kg/hr and prostacyclin 4 ng/kg/min can be combined as anticoagulants.

While using citrate regional anticoagulation, aim for lower ionized calcium levels in the circuit: 0.2 mmol/L instead of the usual 0.3–0.4 mmol/L.

Heparin and citrate can be combined as well. Unfractionated heparin is infused directly into the patient at a dose of 10 U/kg/hr whilst citrate is administered regionally at the usual dose $-1.5 \times$ blood flow rate (citrate dose might have to be increased) with calcium infusion (calcium chloride or calcium gluconate).

ACT = activated clotting time.

necrotizing hemorrhagic encephalopathy, and anoxia [41–43]).

COVID-19 can present atypically in both adults and children with nonspecific neurologic symptoms (e.g. headache, dizziness, impairment of taste and smell, seizures, neck stiffness, photophobia, altered mental state, behavioral changes, and movement disorders [9, 11, 43]). Thus, clinicians should consider COVID-19

in children presenting with new-onset neurologic symptoms. Infant COVID-19–associated seizures have been reported (44), and current status epilepticus management guidelines should be followed and neurophysiologic monitoring considered in high-risk patients (45, 46). Hypercoagulable state in COVID-19 predispose patients to a risk of acute cerebrovascular disease (23) and early neuroimaging with CT or MRI in patients with neurologic symptoms will assist diagnosis.

Anti-Inflammatory, Antiviral Treatment, and Antibacterial Treatment

Evidence for best practice and recommendations around antiviral and anti-inflammatory treatment in COVID-19 is rapidly evolving, and—given the relative rarity of severe COVID-19 presentations in children—infectious diseases and immunology experts should be consulted early and treatments determined by consensus with families. For compassionate use, bioethics support is also warranted, and the risk of innovative therapy must be fully explained to the family. However, if formal clinical trials are available, children should be enrolled (47).

Antibacterial Treatment. Critically ill children with respiratory or systemic disease are much more likely to suffer from bacterial or other viral infections, which should be promptly treated as per the SSC guidelines even during the COVID-19 pandemic (14). The principals of antimicrobial stewardship should be followed.

Anti-Inflammatory Treatment. Consider systemic anti-inflammatory treatment (e.g. high-dose steroids) in unstable patients with MIS. Immunomodulation (e.g. targeted IL-6 antagonists such as Tocilizumab or IL-1 receptor antagonist [Anakinra]) in patients with hyperexpression of several cytokines including IL-6 and IL-1 β , hyperferritinemia, and thrombocytopenia (i.e. cytokine storm) should remain limited to clinical trials (47).

Antiviral Therapies. In severe COVID-19–related respiratory illness, empirical antiviral agents can be considered, whereas as MIS is likely to be a postinfectious syndrome they should not (11, 12).

Based on adult data, remdesivir is the preferred antiviral drug for compassionate use in children (48). The U.S. Food and Drug Administration has authorized it as an investigational antiviral drug (emergency use authorization May 1, 2020) (49). Lopinavir/ritonavir, a

protease inhibitor, may be considered if remdesivir is unavailable (50).

Nutritional Support

Usual ICU nutritional practice (21, 22) is recommended. Specific COVID-19 aspects are as follows: Enteral feeding tube placement and aspiration are potential AGP so 1) decrease exposure by quicker gastric tube placement rather than postpyloric tubes and 2) avoid measuring gastric residual volumes, which has limited evidence.

Neonatal and Pediatric Transport: Specific Considerations

Additional recommendations to existing transport policies for the transport of both suspected and SARS-CoV2 proven children, either inside or between hospitals, are necessary, primarily to protect the team involved.

SARS-CoV2 status of an infant or child must be determined at referral, so staff, PPE, and equipment can be prepared as well as referring and receiving unit secure pathways for the transfer team within the hospital to avoid cross-contamination of clean areas/staff. We recommend that the team transporting children with suspected/confirmed COVID-19 must wear full PPE. For staff (i.e. ambulance drivers, paramedics) not directly involved inpatient care but coming into their close proximity (< 2 m) (e.g. loading/unloading stretcher), at least reduced PPE is mandatory. Patients, if self-ventilating, should wear a surgical mask whenever feasible to minimize aerosol spread. The risk of AGP during transport conditions, with staff wearing full PPE, is greater than in ICU; hence, a lower threshold for pretransport intubation to avoid emergency intubation during transport is justified.

For pediatric stretcher transports closed transport capsules, if available and the child's condition allows, reduce aerosol spread. Air conditioning/ventilation must, if possible, be set to extract to avoid air recirculation. Counterintuitively as it is contrary to family centered care, infants and children should be transported without their parents or relatives present.

At the destination, designated areas must be available for PPE doffing by transport staff. After the transport exposed transport equipment including equipment left in the transport vehicle (i.e. not within closed compartments) requires decontamination with a universal detergent, followed by cleaning of the entire interior

of the vehicle with a chlorine-based solution at 1,000 parts per million (51).

Nursing Care

Protection of nursing personnel is paramount, with full PPE available and used effectively to minimize contamination. The primary goals of nursing care must be rethought during a pandemic (e.g. organization and function of a unit and its staff [24]), with some nursing protocols adapted or modified.

The number of caregivers and time in a bed-space can be minimized, for example, use of extenders (deployed personnel) who remain outside patient's immediate area/dedicated "infectious" zone to prepare drugs, organize/set-up devices, and communicate between ward control/nurse in charge and the bedside nurse.

The use of consumables such as in-line suction catheters and ventilator circuits must be considered both are able to be used for up to 7 days (52, 53). Fundamental nursing care should be clustered (12 hr) to reduce nursing exposure and promote physiologic stability. This includes eye care, oral care, washing, and pressure area prevention to reduce iatrogenic injury (54). Safe and prolonged prone positioning is also helpful in pediatric COVID-19 pneumonitis and safer using a checklist (55).

The nursing workload model must change from usual patient-centered model to task delivery allocation ensuring vital care (e.g. proning, medication) is completed safely and effectively despite fewer qualified staff. Reduced nurse:patient ratios place significant stress on the whole team, changing standards from "ideal" to best possible critical care with the resources available.

Finally, a vital nursing role during COVID-19 is to promote and optimize family/parent involvement in care despite significantly restricted visitation. Consistent daily family communication is essential, that is, video-conferencing (56, 57). Reducing the child and family's fear of staff in full PPE is essential, requiring careful developmentally appropriate explanations and the use of play (56).

Visiting and Spiritual Care

Restrictions on visiting are at odds with usual PICU family-centered care. Families in self-isolation or with COVID-19 are usually not permitted into hospitals to protect other children, parents/families, and staff from

infection. In exceptional circumstances, such as imminent or actual bereavement, full PPE can be worn by the individuals affected. Otherwise restricted visiting, such as one parent and no siblings, has become usual. Novel ways to enable contact such as video-conferencing with boyfriend/girlfriend and school friends should be instituted for teenagers. The psychologic distress for the parents of critically ill children, compounded by the removal of primary support mechanisms, is being witnessed by many of us and worthy of formal study. The dehumanizing effects of PPE, the absence of relatives, and even personal effects are concerning too. Compassionate exceptions to restricted visiting policies should be considered in specific situations, but the risk to healthcare teams is also worrying (58).

Spiritual support should be offered on request given that as religion and spirituality provide the foundation for many people's morality. Consultation with faith or nonfaith (philosophical, psychologic or pastoral) support must be offered and can include religious rites performed by video link. Faith/spiritual/other supportive care must also be available for staff, particularly those struggling with the dehumanizing aspect and the tough decisions being made and their results.

Ethical Considerations

The COVID-19 triaging decisions required by "adult" colleagues have not been necessary in children with their lower disease severity. It is worth noting the complex pediatric population may become an issue in another pandemic or even a second wave (59).

Rather than direct infection, the COVID-19 ethical issues affecting children and PICU teams are the loss of other healthcare opportunities with major cancelled surgery, clinics and other issues, social isolation, and education issues, and for staff, PPE availability, reduced parent presence with sick children, and moral injury to those deployed to adult services who have seen/made rapid existential decisions.

Difficult treatment decisions during a pandemic must comply with relevant ethical principles, and independent ethics support must be available for both clinicians and families (60).

CONCLUSIONS

COVID-19 in children has been thought to be mild and mainly, yet not obligatory, characterized by

respiratory illness, fever, flu-like symptoms, and only rarely progressing to severe hypoxic-respiratory failure. However, recently the MIS was described in children, although whether this represents an acute inflammatory manifestation of COVID-19, a postinfectious immune reaction or different disease remains unclear. Suitable registries are urgently required for this purpose.

The majority of our recommendations for children with COVID-19 are essentially the same as for any critically ill child, for example, noninvasive or invasive mechanical ventilation, cardiac failure, pediatric sepsis, and multiple organ failure. We have highlighted those areas where there is enough clinical experience or specific concern to amend current recommendations.

Many involve the risk to staff, for example, PPE and transport and reduced staff and family numbers in PICU. Anti-inflammatory and infective approaches, for example, immunomodulation and antiviral therapies, are suggested but are largely considered on a compassionate basis as controlled studies do not exist.

- 1 *Division of Neonatology and Paediatric Intensive Care, Department of Paediatrics, University Hospital of Geneva, University of Geneva, Geneva, Switzerland.*
- 2 *Division of Paediatric Critical Care Medicine, Department of Paediatrics, Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands.*
- 3 *Critical Care, Department of Anaesthesiology, Peri-operative & Emergency Medicine, University of Groningen, Groningen, The Netherlands.*
- 4 *Paediatric Intensive Care Unit, King's College Hospital, London, United Kingdom.*
- 5 *Paediatric Intensive Care, SPS Hospitals, Ludhiana, India.*
- 6 *Cardiac Intensive Care Unit, Heart and Lung Directorate, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, United Kingdom.*
- 7 *Paediatric Intensive Care Unit, Hospices Civils de Lyon, University of Lyon, Lyon, France.*
- 8 *University Claude Bernard Lyon 1, Hospices Civils of Lyon, Lyon, France.*
- 9 *Division of Paediatrics, Neonatal Critical Care and Transportation, Medical Centre "A.Béclère", Paris Saclay University Hospitals, APHP, Paris, France.*
- 10 *Critical Care, Nutrition and Dietetics, Alder Hey Children's, NHS Foundation Trust, Liverpool, United Kingdom.*
- 11 *Cardiothoracic ICU, National University Hospital, Singapore, Singapore.*
- 12 *Paediatric Intensive Care Unit, Royal Children's Hospital, Melbourne, VIC, Australia.*
- 13 *Paediatric Intensive Care, AP-HP Paris-Saclay University, Bicêtre Hospital, Le Kremlin-Bicêtre, France.*
- 14 *Department of Paediatric Intensive Care and Intermediate Care, Sant Joan de Déu University Hospital, Universitat de Barcelona, Esplugues de Llobregat, Spain.*
- 15 *Immune and Respiratory Dysfunction, Institut de Recerca Sant Joan de Déu, Santa Rosa 39-57, 08950 Esplugues de Llobregat, Spain.*
- 16 *Paediatric Cardiac Intensive Care Unit, Department of Pediatric Cardiology and Cardiac Surgery, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy.*
- 17 *Department of Paediatrics—Paediatric Cardiology and Neonatology, Cambridge University NHS Foundation Trust, Hospitals and University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom.*
- 18 *Child Health Research Centre, The University of Queensland, and Paediatric Intensive Care Unit, Queensland Children's Hospital, Brisbane, QLD, Australia.*
- 19 *Department of Intensive Care Medicine and Neonatology, and Children's Research Centre, University Children's Hospital of Zurich, University of Zurich, Zurich, Switzerland.*
- 20 *Department of Paediatric Intensive Care, Birmingham Children's Hospital, Birmingham, United Kingdom.*
- 21 *Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom.*
- 22 *Department of Critical Care, Paediatric and Cardiac Intensive Care Unit, Al Jalila Children's Hospital, Dubai, United Arab Emirates.*
- 23 *Paediatric Intensive Care, AP-HP Paris-Saclay University, Bicêtre Hospital, Le Kremlin-Bicêtre, France.*
- 24 *University of Salford, Manchester UK and Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom.*
- 25 *Intensive Care Unit, Department of Paediatric Surgery and Paediatrics, Erasmus Medical Centre, Sophia Children's Hospital, Rotterdam, The Netherlands.*
- 26 *Paediatric Intensive Care Unit, NIHR Great Ormond Street Hospital Biomedical Research Centre, London, United Kingdom.*

Members of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) Scientific Sections' Collaborative Group are listed in the **Appendix**.

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For information regarding this article, E-mail: peter.rimensberger@hcuge.ch

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APPENDIX

Participants from the ESPNIC scientific sections collaborative group: Cardiovascular Dynamics Section and Cardiac ICU and Mechanical Circulatory Support Section: Joe Brierley (London, United Kingdom), Aparna Hoskote (London, United Kingdom), Joris Lemson (Nijmegen, The Netherlands), Uri Pollak, (Jerusalem, Israel), Peter C. Rimensberger (Geneva, Switzerland), Yogen Singh (Cambridge, United Kingdom), Javier Urbano Villaescusa (Madrid, Spain). CRRT/Renal Section: Mehak Bansal (Ludhiana, India), Joe Brierley (London, United Kingdom), Akash Deep (London, United Kingdom), Zaccharia Ricci (Rome, Italy). Ethics Section: Joe Brierley (London, United Kingdom), Marek Midgal (Warsaw, Poland), Anna Zanin (Vicenza, Italy). Infection, Systemic Inflammation, and Sepsis Section: Etienne Javouhey (Lyon, France), Luc Morin (Paris, France), Luregn Schlapbach (Brisbane, Australia), Pierre Tissières (Paris, France). Metabolism, Endocrinology, and Nutrition Section: Lynne Latten (Liverpool, United Kingdom), Sascha Verbruggen (Rotterdam, The Netherlands). Neuro Critical Care Section: Hari Krishnan (Birmingham, United Kingdom), Karl Reiter (Munich, Germany) Barnaby R Scholefield (Birmingham, United Kingdom). Nursing Science Section and Pediatric and Neonatal Intensive Care

Nursing Section: Orsola Gawronski (Rome, Italy), Joseph C. Manning (Nottingham, United Kingdom), Julie Menzies (Birmingham, United Kingdom), Anne-Sylvie Ramelet (Lausanne, Switzerland), Paulien Raymakers-Jansen (Utrecht, The Netherlands), Lyvonne N Tume (Liverpool, United Kingdom). Respiratory Failure Section: Robert Blokpoel (Groningen, The Netherlands), Joe Brierley (London, United Kingdom), Cristina Camilo (Lisbon, Portugal), Giovanna Chidini (Milan, Italy), Daniele de Luca (Paris, France), Mireia Garcia Cuscó (Bristol, United Kingdom), Jürg Hammer (Basel, Switzerland), Martin C.J. Kneyber (Groningen, The Netherlands), Yolanda M. Lopez Fernandez (Barakaldo, Spain), Alberto Medina (Oviedo, Spain), Christophe Milesi (Montpellier, France), Vicent Modesto Alapont (Valencia, Spain), Marti Pons MD (Barcelona, Spain), Peter C. Rimensberger (Geneva, Switzerland), Lyvonne Tume (Liverpool, United Kingdom). Transport Section: Morten Breindahl (Copenhagen, Denmark), Christian Heiring (Copenhagen, Denmark), Mattias Kjellberg (Uppsala, Sweden), Gilles Jourdain (Paris, France), Padmanabhan Ramnarayan (London, United Kingdom), Ulrich Terheggen (Dubai, United Arab Emirates), Johannes van den Berg (Umea, Sweden).