Extracorporeal Membrane Oxygenation in Children with Coronavirus Disease 2019: Preliminary Report from the Collaborative European Chapter of the Extracorporeal Life Support Organization Prospective Survey

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Since the declaration of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic,[1] a small percentage of children with coronavirus disease 2019 (COVID-19) infection have required intensive care unit (ICU) admission with an even smaller percentage needing extracorporeal membrane oxygenation (ECMO) support.[2,3] To provide contemporaneous data on ECMO utilization and activity during the COVID-19 pandemic, the European Chapter of the Extracorporeal Life Support Organization (EuroELSO) established a prospective survey among European neonatal and pediatric centers from the 15th of March to the end of June 2020. The survey was approved by the Maastricht University Medical Centre Ethics Committee. Centers reported anonymized data weekly through the EuroELSO website (www.euroelso.org). We report the preliminary data from 52 neonatal and pediatric ECMO centers across Europe during the first wave of the COVID-19 pandemic.

Seven children (<18 years of age) from four countries received ECMO support for SARS-CoV-2 infection. The demographics, clinical details, and pre-ECMO characteristics of these seven children supported on ECMO are shown in Table 1. The median age was 11.5 years (range 54 days to 16 years), three (43%) were male, and two (29%) had underlying comorbidities. These significant comorbidities included one infant with transposition of great arteries diagnosed at 5 weeks of age and another child who received hematopoietic stem cell transplant (HSCT) for primary immunodeficiency disease (STAT-3 mutation). The indications for ECMO were hypoxemia (n = 3, 43%), shock associated with Pediatric Multisystem Inflammatory Syndrome Temporally Associated With SARS-CoV-2 (PIMS-TS)[4,5] (n = 3, 43%), and septic shock (*Staphylococcus aureus*) (*n* = 1, 14%). The median time from the onset of symptoms to ECMO deployment was 5 days (range 2–32 days), while median time from intubation to ECMO was 34 hours (range 10–624 hours). All patients were ventilated in pressure-controlled mode in the 6 hours pre-ECMO deployment. Adjunctive respiratory therapies pre-ECMO such as prone positioning (*n* = 2, 28%), inhaled nitric oxide (*n* = 2, 28%), and high-frequency oscillatory ventilation (*n* = 1, 14%) were tried. In the three children supported for hypoxemia, the median oxygenation index was 29 (range 24–41) and the partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio was 65 (range 37–82). In the three patients with PIMS-TS and in the one with sepsis, supported for hemodynamic collapse, the median Vasoactive-Inotropic Score was 160 (range 142–220) and the median lactate was 7 mmol/L (range 4–9 mmol/L). All, except the patient number 6, had signs of hyperinflammatory state.[4,6] In particular, children with PIMS-TS reported higher levels of inflammatory proteins before ECMO: C-reactive protein 306 mg/L (range 300–463 mg/L), ferritin 2,185 ng/mL (range 845–4,815 ng/mL), and fibrinogen 5.8 g/L (range 5–9.5 g/L). Patient 2 with *S. aureus* septic shock reported lower level of inflammatory proteins (C-reactive protein 184 mg/L, fibrinogen 3.7 g/L, and ferritin 1,100 ng/mL).

The ECMO characteristics, treatment, and outcome of these children are described in Table 2. The initial ECMO mode was predominantly venoarterial (VA) ECMO in six (85%) and

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Table 1. Demographics, Clinical Details, and Pre-ECMO Characteristics of Children Supported on ECMO for SARS-CoV-2 Infection

Case/ Country	Age/Sex/BMI	Diagnosis and Comorbidities	Covid-19 Status: SARS-CoV-2 PCR	Worst Ventilation Parameters (6 Hours Pre-Cannulation)	Worst ABG Parameters (6 Hours Pre-Cannulation)	Onset of Symptoms to ECMO (Days)	Intubation to ECMO (Hours)	Inflammatory State	Immunomodulatory Therapy Before ECMO	Antiviral Therapy (Yes/No)
1/Spain	16 years/ female/27.3	pARDS, obesity	Positive	PIP: 34 PEEP: 14 Dynamic driving pressure: 20 OI: 41	pH: 7.29 $PaCO_2$: 55 PaO_2:FiO_2: 67 Lactate: 1.3	11	96	Yes CRP: 192.9 Fibrinogen: 7.9 Ferritin: 283	No	Yes (lopinavir-ritonavir→ remdesivir)
2/France	6 years/ female/14.9	Septic shock *Staphylococcus aureus* co-infection	Positive	PIP: 26 PEEP: 7 Dynamic driving pressure: 19 OI: 5	pH: 7.33† $PaCO_2$: 55 PaO_2:FiO_2: 100 Lactate: 4.0	2	34	Yes CRP: 184 Fibrinogen: 3.7 Ferritin: 1,100	No	No
3/United Kingdom	14 years/ male/29.9	PIMS-TS, none	Positive	PIP: 30 PEEP: 10 Dynamic driving pressure: 20 OI: 4.8	pH: 7.14 $PaCO_2$: 38 PaO_2:FiO_2: 185 Lactate: 5.9	7	34	Yes CRP: 463 Fibrinogen: 9.5 Ferritin: 2,185	Yes IVIG and low dose of steroids	No
4/United Kingdom	11 years/ female/17.8	PIMS-TS, none	Positive	PIP: 24 PEEP: 10 Dynamic driving pressure: 14 OI: 17	pH: 7.0 $PaCO_2$: 51 PaO_2:FiO_2: 186 Lactate: 9.0	3	10	Yes CRP: 300 Fibrinogen: 5.0 Ferritin: 845	Yes IVIG	No
5/United Kingdom	12 years/ female/15	PIMS-TS, none	Negative*	PIP: 20 PEEP: 5 Dynamic driving pressure: 15 OI: 3.1	pH: 7.14 $PaCO_2$: 36 PaO_2:FiO_2: 100 Lactate: 8.0	5	20	Yes CRP: 306 Fibrinogen: 5.8 Ferritin: 4,815	Yes IVIG, steroids, and high dose of aspirin	No
6/United Kingdom	54 days/ male/NA	pARDS in TGA, late presentation of congenital heart disease	Positive	PIP: 16 PEEP: 5 Dynamic driving pressure: 11 OI: 29	pH: 7.14 $PaCO_2$: 80.2 PaO_2:FiO_2: 37 Lactate: 2.4	1.4	31	No CRP: 51.6 Fibrinogen 0.9 Ferritin: 55.8	No	Yes (remdesivir)
7/Spain	8 years/ male/21	pARDS, hematopoietic stem cell transplantation	Positive	PIP: 40 PEEP: 8 Dynamic driving pressure: 32 OI: 24	pH 7.1 $PaCO_2$: 83 PaO_2:FiO_2: 65 Lactate: 0.5	32	624	Yes CRP: 1.2 Fibrinogen: 5.8 Ferritin: 10,000	Yes Tocilizumab and anakinra	Yes (lopinavir-ritonavir→ remdesivir)

Units of measure: PaO_2 and $PaCO_2$ (mm Hg); PIP, PEEP, and dynamic driving pressure (cm H_2O); C-reactive protein (mg/L [range: 0–5]); fibrinogen (g/L); lactate (mmol/L); and ferritin (ng/mL).
*Positive on serology for SARS-CoV-2.
†Only venous gas.
ABG, arterial blood gas analysis; BMI, body mass index; Covid-19, coronavirus disease 2019; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; FIO_2, fraction of inspired oxygen; IVIG, intravenous immunoglobulin; NA, not applicable; OI, oxygenation index; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; pARDS, pediatric acute respiratory distress syndrome; PCR, polymerase chain reaction; PEEP, positive end-expiratory pressure; PIMS-TS, Pediatric Multisystem Inflammatory Syndrome Temporally Associated With SARS-CoV-2; PIP, peak inspiratory pressure; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TGAs, transposition of great arteries.

Table 2. ECMO Characteristics, Treatment, and Outcome of Children Supported on ECMO for SARS-CoV-2 Infection

Case/ Country	ECMO Initial Mode	Cannulation Site	Time of ECMO Conversion and New ECMO Mode	ECMO Duration (Days)	Immunomodulatory Therapy During ECMO	Cardiac Injury/ Myocarditis	Complications on ECMO	Outcome (Survival to Hospital Discharge)/ Cause of Death
1/Spain	VV	Fem-Jug	NA	7	Yes: Tocilizumab	NA	None	Survived
2/France	VA	RIJV-CA	48 hours VA to VV	9	Yes: IVIG, steroids	Troponin: 337	Major intraventricular and intraparenchymal hemorrhage	Died Cerebral hemorrhage
3/United Kingdom	VA	Fem-CA	NA	6	Yes: Steroids	Yes Troponin: 675	Right MCA and ACA ischemic infarction	Died Cerebral infarct
4/United Kingdom	VA	RIJV-CA	NA	11	Yes: IVIG, steroids	Yes Troponin > 2,000, endomyocardial biopsy: lymphocytic infiltrate consistent with partially treated myocarditis	None	Survived
5/United Kingdom	VA	RIJV-CA	87 hours VA to VV	7	Yes: IVIG, steroids, infliximab	Yes Troponin: 110	Thrombus in right atrium	Survived
6/United Kingdom	VA	RIJV-CA	NA	7	No	NA	None	Survived
7/Spain	VA	Fem-Fem	24 hours VA to VV	30	Yes: Anakinra, convalescent plasma, mesenchymal stromal cells	Yes Troponin: 24.7	Pulmonary embolism and cardiac arrest	Died Pulmonary embolism

Units of measure: Troponin: ng/L (normal value <26 ng/L).

ACA, anterior cerebral artery; CA, carotid artery; ECMO, extracorporeal membrane oxygenation; Fem, femoral; IVIG, intravenous immunoglobulin; Jug, jugular; MCA, middle cerebral artery; NA, not applicable; RIJV, right internal jugular vein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VA, venoarterial; VV, venovenous.

venovenous (VV) ECMO in one patient (15%). Of the six children supported on VA ECMO, three were converted to VV ECMO after a median of 48 hours (range 24–87 hours) following: differential hypoxemia (Harlequin syndrome) (n = 1) and improvement of cardiac function with lag in lung recovery (n = 2). During ECMO, all children were managed with lung rest settings in pressure-controlled mode to maintain a median tidal volume of 5 ml/kg (range 4–6 ml/kg), a respiratory rate of 18 (range 15–20), a positive end-expiratory pressure of 7 cm H_2O (range 5–10 cm H_2O), and a FiO_2 of 0.25 (range 0.21–0.40). One child (patient 7) received a tracheostomy while on ECMO.

The management of ECMO was standard with staff in full personal protective equipment, and enhanced vigilance for thrombotic complications was maintained by the treating centers. All children were anticoagulated with unfractionated heparin as per their institutional protocol. Two children (patients 3 and 5) developed thrombosis while on ECMO despite having activated partial thromboplastin time ratios of 1.6 and 2.7, respectively, before clot formation.

All with PIMS-TS presentation were treated with intravenous immunoglobulin (IVIG) and steroids. Among these, one (patient 4) underwent a cardiac biopsy at the time of left atrial decompression procedure that showed an infiltration of lymphocytes suggestive of partially treated myocarditis. Two children required continuous renal replacement therapy, both died. Three patients (43%) received antiviral therapy: lopinavir/ritonavir pre-ECMO and then remdesivir on ECMO, two survived. Immunomodulation with tocilizumab, anakinra, or infliximab (Table 2) was used in three patients (43%), two survived. Convalescent plasma and infusion of mesenchymal stromal cells were administered to the child post HSCT. Surfactant therapy, plasma exchange, or cytokine adsorption filters were not used.

Five children (71%) were successfully decannulated, but four (57%) survived to hospital discharge. The median ECMO duration was 7 days (range 7–11 days) with a median ICU stay of 16 days (range 7–20 days). Three children (43%) died—two died on ECMO and a third died post decannulation before pediatric intensive care unit discharge (Table 2).

The child post HSCT (patient 7) died for refractory cardiac arrest due to pulmonary embolism after 30 days of ECMO. Patient 3 reported an ischemic stroke involving both the anterior and middle cerebral artery on day 2 of ECMO, while patient 2 reported severe intraventricular and intraparenchymal hemorrhages after 7 days of ECMO. In these three patients, high D-dimers levels 13,500 mcg/L (range 2,200–14,994 mcg/L) were reported suggesting an abnormal activation of the hemostatic system.

In contrast to adult data,[4] we report that the use of ECMO in children with COVID-19 infection patients in Europe is both scarce and of diverse etiology. An age-specific immune-protective mechanism[5] to SARS-CoV-2 may explain this low occurrence of severe disease. Our survey has highlighted: 1) SARS-CoV-2 infection may be associated with comorbid conditions in children, 2) a temporal increase in the ECMO utilization may have been associated with the emergence of PIMS-TS,

3) the risk of thrombotic complications is high when on ECMO support, and 4) the role of adjunctive therapies (antiviral and immunomodulation therapy) remains unclear, however, IVIG and judicious use of steroids may benefit those presenting with PIMS-TS. Early referral before circulatory collapse and multiple organ dysfunction may be advocated in these children.

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