# Successful use of ECMO in the treatment of acute respiratory distress syndrome associated with SARS-CoV-2 in two pediatric cases

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### Abstract

SARS-CoV-2 infection, in the vast majority, affects adult patients. The severity of COVID-19 and mortality are directly correlated with the increasing age of patients and the number of comorbidities. However, with the further development of the COVID-19 pandemic, severe cases of COVID-19 have been reported in children. About 0.8-1% of sick children require hospitalization in an intensive care unit. The main syndromes that cause disease severity and mortality in children are acute respiratory distress syndrome, multisystem inflammation syndrome and multiple organ failure. The rapid development of severe respiratory failure and hypoxemia in respiratory distress syndrome leads to the use of various methods of respiratory therapy, and in case of their ineffectiveness to extracorporeal membrane oxygenation (ECMO). In our report, we present two clinical cases of successful use of ECMO in children with COVID-19, who developed severe ARDS.

Keywords Children, COVID-19, acute respiratory distress syndrome, ECMO.

## Introduction

Since the beginning of the COVID-19 pandemic caused by SARS-CoV-2, low morbidity has been reported in children.<sup>1</sup> Thus, among pediatric patients, an average of 2.5% of patients diagnosed with SARS-CoV-2 required hospitalization, and 0.8% of children required admission to the intensive care unit (ICU). The mortality in the pediatric population of patients with COVID-19 was <0.1%. Among children and adolescents. the highest percentage of

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Article downloaded from www.germs.ro Published June 2022 © GERMS 2022 ISSN 2248 - 2997 ISSN - L = 2248 - 2997 hospitalizations (4.6%) was in patients aged 0-4 years.<sup>2</sup> The main complications of SARS-CoV-2 that cause mortality in children are respiratory distress syndrome, multiorgan failure and multisystem inflammatory syndrome.<sup>3</sup>

Since the main target organ in COVID-19 is the lungs, it is the acute respiratory distress syndrome that is the main cause of deterioration in patients and their admission to the ICU. According to an international survey examining the availability of extracorporeal membrane oxygenation (ECMO) in pediatric ICU (PICU) that treated patients with COVID-19, admission (multiple choice question) to the PICU was most frequently due to respiratory failure (n=50, 76.9%), followed by multisystem inflammatory syndrome in children (MIS-C, 27.7%, n=18) and cardiac failure (26.2%, n=17).<sup>4</sup> The rapid development of severe respiratory failure (RF) and hypoxemia leads to the use of various methods of respiratory therapy, and in case of their ineffectiveness, extracorporeal membrane oxvgenation is used as the final possible rescue technology.<sup>3,5</sup>

In our report, we present two clinical cases of successful use of ECMO in children with COVID-19, who developed severe ARDS and critical hypoxemia, which could not be corrected by traditional methods of respiratory therapy.

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## Case reports Case 1

A three-year-old girl (body weight 15 kg) was admitted to the ICU with severe signs of RF. Physical examination revealed shortness of breath, respiratory rate (RR) 72 /min, retraction of intercostal spaces, heart rate (HR) 170/min, sinus tachycardia, SpO<sub>2</sub> 87%, and body temperature 36.8°C. Crackles on both sides of the lungs were detected during the auscultation. The chest radiography revealed right-sided focal pneumonia (Figure 1).



Figure 1. Right-sided focal pneumonia

The child had been ill for two days, when she developed a low-grade fever.

The next day, the temperature rose to 37.6°C, there were weakness and coughing. On the third day of the disease there was breathlessness, which progressed rapidly and led to hospitalization.

A week previously, the girl's father had been diagnosed with COVID-19 confirmed by a positive PCR test for SARS-CoV-2.

Oxygen was administered through facemask (O<sub>2</sub> flow at 10 L/min). Ceftriaxone, azithromycin and dexamethasone were administered, and correction of fluid and electrolyte disorders were performed. As the oxygen therapy was not accompanied by a significant improvement in oxygenation (SpO<sub>2</sub> 90-91%, PaO<sub>2</sub> 68 mmHg, PaCO<sub>2</sub> 55 mmHg, pH 7.27), dyspnea with

retraction of muscles, after 5 hours non-invasive ventilation was transitioned: NIV CPAP/PSV (FiO<sub>2</sub> 60%, PEEP 8 cmH<sub>2</sub>O, PIP 5 cmH<sub>2</sub>O). A temporary improvement in oxygenation was achieved:  $PaO_2/FiO_2$  133,  $PaO_2$  80 mmHg,  $PaCO_2$  57 mmHg.

There was a further progression of RF and hypoxemia ( $PaO_2/FiO_2$  117) on the background of NIV CPAP/PSV in the child, as well as the deterioration of the neurological status of the patient on the Glasgow scale (the decrease in the GCS score from 14 to 12). The control chest X-rays (performed in 24 hours) revealed a deterioration of the radiological imaging (Figure 2).



Figure 2. The increase of the intensity of opacities on the right side, the appearance of new bilateral infiltrates

In 25 hours, the patient was administered mechanical ventilation: P/SIMV,  $FiO_2$  50%, PIP 12 cmH<sub>2</sub>O, PEEP 10 cmH<sub>2</sub>O, TV 6 mL/kg, RR 25/min, I/E 1: 1.5. Given SvO<sub>2</sub> 63%, the infusion of dobutamine 5 µg/kg/min was prescribed. The dynamics of laboratory parameters is shown in Table 1.

After 36 hours, a positive PCR test for SARS-CoV-2 was received.

For the next 96 hours, the child was on the mechanical ventilation: P/SIMV in prone position, and required myoplegia and fixed parameters of mechanical ventilation: Ppeak 29 cmH<sub>2</sub>O, PIP15 cmH<sub>2</sub>O, PEEP 14 cmH<sub>2</sub>O, TV 6

	Reference	ECMO	Post-							
	range	day 0	day 1	day 2	day 3	day 4	day 5	day 6	day 7	ECMO
Hemoglobin (g/L)	120-145	97	91	93	88	85	97	92	89	110
Leukocytes	4.4-9	2.5	11.8	11.1	10.5	12.8	17.6	15.4	12.2	9.3
(×10 <sup>9</sup> /L)										
Neutrophils (%)	47-72	78	77	75	78	77	76	68	65	61
Lymphocytes (%)	19-37	19	17	18	18	22	18	27	30	32
Platelets (×10 <sup>9</sup> /L)	130-400	320	335	283	265	170	150	152	170	230
C-reactive protein (mg/L)	0-7	32		145		160			25	11
Ferritin (mg/dL)	15-150	225								24
Procalcitonin	0-0.5	0.28		0.5		1.1			0.8	0.02
(ng/mL)										
Fibrinogen (g/L)	2-4	6		8		2.5	1.5		1.8	4
D-dimer (ng/mL)	20-500	1334	1554	1288	1155	1234	1115	1227	1106	986
APTT (s)	28.2-40.2	22	81	91	85	81	84	91	82	52
INR	0.8-1.2	0.6	2.0	2.3	2.1	2.0	2.15	2.3	2.1	1.4
ALT (U/L)	5-35	22		32		47			52	48
Creatinine	70-110	99		78		115			88	86
(mkmol/L)										
Glucose (mmol/L)	4.4-6.2	7.8	11.1	12.7	12.3	11.7	10.3	11.5	9.8	6.1
Sodium (mmol/L)	135-145	138	143	144	135	138	148	133	136	140
Potassium	3.5-5.5	4.0	4.3	3.7	3.9	4.2	5.0	4.1	4.4	5.1
(mmol/L)										
PaO <sub>2</sub> (mmHg)	80-100	60	170	185	168	166	176	165	168	124
PaCO <sub>2</sub> (mmHg)	35-45	69	32	30	35	37	41	38	35	44
ECMO blood			0.8	0.78	0.81	0.8	0.75	0.71	0.68	
flow (L/min)										
Sweep gas flow			1.5	1.6	1.4	1.4	1.35	1.3	1.2	
(L/m)										
ECMO FiO <sub>2</sub> (%)			100	100	100	100	80	80	60	
Ventilator FiO <sub>2</sub>		100	40	40	40	40	35	35	35	40
(%)										
PaO <sub>2</sub> /FiO <sub>2</sub>		60								310
Tidal volume		6.1	4	4	4	4	4	4	4	6
(mL/kg)										
Cstat		8	7	8	12	15	15	`17	18	22
$(mL/smH_2O)$										

Table 1. The dynamics of laboratory parameters. ECMO settings and mechanical ventilat	tion. Case 1.
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APTT – activated partial thromboplastin time; ALT – alanine transaminase; INR – international normalized ratio;  $PaO_2$  – partial pressure of oxygen;  $PaCO_2$  – partial pressure of carbon dioxide;  $PaO_2/FiO_2$  – pressure of arterial oxygen to fractional inspired oxygen concentration.

mL/kg, RR 25/min, I/E 1:1.2. The patient's condition deteriorated, the patient needed an increase in FiO<sub>2</sub> from 60% to 100%. The negative dynamics of PaO<sub>2</sub>/FiO<sub>2</sub> from 117 to 80 was noted. The ultrasound examination of the lungs showed signs of the interstitial syndrome (a large number of B-lines, single A-lines) and a

symptom of consolidation in the basal areas of the lungs on both sides. The reduced ejection fraction of the left ventricle (IF 45%) was observed. The child received meropenem, fluconazole, dobutamine 7.5  $\mu$ g/kg/min, furosemide 7 mg/kg/d, dexamethasone 8 mg/d, heparin 5 IU/kg/h. On the 5<sup>th</sup> day after the start of mechanical ventilation, the child was transitioned to high-frequency oscillatory ventilation (HFOV): FiO<sub>2</sub> 100% Paw 25 cmH<sub>2</sub>O,  $\Delta$ P33%, frequency 7Hz. However, no significant improvement in oxygenation was achieved (PaO<sub>2</sub>/FiO<sub>2</sub> 72).

For the next 48 hours, a decrease in oxygenation was observed  $(PaO_2/FiO_2 60)$ . It was decided to transition the child to V-V ECMO (7 days from the beginning of mechanical ventilation). The right internal jugular vein (return cannula: 14 Fr) and the left femoral vein (access cannula: 16 Fr) were cannulated. V-V ECMO settings: – RPM (pump speed) 3125, LPO (blood flow rate) 0.7-0.8, FiO<sub>2</sub> 100%. Protective mechanical ventilation was performed: P/SIMV, FiO<sub>2</sub> 40%, PIP 14 cmH<sub>2</sub>O, PEEP 10 cmH<sub>2</sub>O, TV 4 mL/kg, RR 15/min, I/E 1:1.5. The child required prolonged analgesia and sedation, heparinization (heparin 10-15 units/kg/h, target values of APTT 80-90 s).

As a result of V-V ECMO, there was an improvement in oxygenation of  $PaO_2$  170-180 mmHg, and also respiratory mechanics; static lung compliance (Cstat) increased from 8 mL/cmH<sub>2</sub>O to 22 mL/cmH<sub>2</sub>O. The duration of V-V ECMO was 7 days. Subsequently, the convection ventilation continued. P/SIMV: PIP 18 cmH<sub>2</sub>O, PEEP 10 cmH<sub>2</sub>O, FiO<sub>2</sub> 40%, RR 20/min. Satisfactory oxygenation rates (PaO<sub>2</sub>/FiO<sub>2</sub> 310) were achieved – Table 1.

After six days, the child was weaned from mechanical ventilation.

The following complications were observed in the course of treatment in the ICU: thrombocytopenia, short-term steroid diabetes and cognitive disorders, hematoma of the anterior abdominal area. Hematoma developed after cannulation of the femoral artery on the background of heparin therapy. The volume of the hematoma was 250-300 mL, it led to intraabdominal hypertension. The size of the hematoma, its anatomical location was diagnosed by ultrasound examination. The child underwent surgical drainage of the hematoma. After ten days, she was transferred from the ICU.

The child had mild neurological disorders. Thus, we observed a decrease in the strength of the muscles of the lower and upper extremities, impaired articulation and difficulty forming long sentences, as well as fine motor skills such as inability to draw simple pictures, hold a pencil, brush your teeth.

The total duration of treatment in the hospital was 67 days.

## Case 2

A 17-year-old girl (body weight - 50 kg) was admitted to the admission department with complaints of dyspnea, a cough, fever 38.5°C, and general fatigue. Physical examination: RR 24/min, HR 111/min, BP 100/60 mmHg, SpO<sub>2</sub> 97%. The patient was hospitalized in the pediatric department. A positive PCR test for SARS-CoV-2 was received.

The child's condition deteriorated within three days. The RF progressed; RR 35/min, SpO<sub>2</sub> 86%, oxygen dependence, HR 110/min, BP 100/60 mmHg, the symptom of capillary refill > 3 s, cold extremities. Bilateral polysegmental pneumonia was detected on the chest radiograph (Figure 3). The lung ultrasound showed signs of interstitial syndrome on both sides, alveolar consolidation on the left, left-sided hydrothorax.

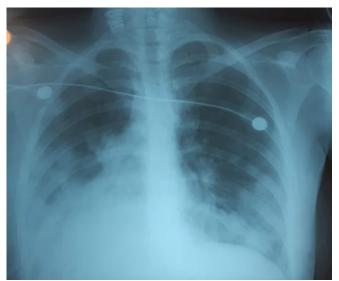


Figure 3. Bilateral polysegmental pneumonia

The patient was transferred to the ICU. Noninvasive lung ventilation was administered: NIV BiPAP, PIP 12 cmH<sub>2</sub>O. PEEP 7 cmH<sub>2</sub>O. FiO<sub>2</sub> 60%. Acid-base balance: pH 7.4 pCO<sub>2</sub> 30, PaO<sub>2</sub> 86, PaO<sub>2</sub>/FiO<sub>2</sub> 143. After 16 hours of non-invasive mechanical ventilation, due to the progression of RF (dyspnea 43/min, retraction of respiratory muscles, no improvement PaO<sub>2</sub>), the child was transitioned to mechanical ventilation: P/SIMV, FiO<sub>2</sub> 60%, PIP 15 cmH<sub>2</sub>O, PEEP 10 cmH<sub>2</sub>O, I/E 1-1.5, TV 320 mL/kg, RR 16/min. The ventilation was performed using prone position as well as myoplegia.

The following drug therapy was administered: remdesivir, cefepime, ciprofloxacin, dexamethasone 6 mg/d, enoxaparin 0.4 mL/d, nutritional therapy (enteral feeding through a tube), and sedation.

On the third day of mechanical ventilation, the girl had a complication – left-sided pneumothorax. The urgent drainage of the pleural cavity (Figure 4) was performed, as well as reduction of mechanical ventilation parameters: P/SIMV, FiO<sub>2</sub> 80%, PIP 12 cmH<sub>2</sub>O, PEEP 8 cmH<sub>2</sub>O, I/E 1-1.5, TV 300 mL/kg.



Figure 4. Left-sided pneumothorax

Over the next 24 hours, there was a progressive decrease in oxygenation:  $PaO_2/FiO_2$  81,  $PaO_2$  80 mmHg,  $PaCO_2$  61 mmHg. The chest radiograph showed that the left lung was partly collapsed; there was an active air discharge through the drainage. The drainage of the left pleural cavity and the second drainage were performed (Figure 5).

There was no positive dynamics within the next 24 hours. The need for ECMO was considered. Ventilation: P/SIMV, FiO<sub>2</sub> 100%,

PIP 11 cmH<sub>2</sub>O, RR 25 PEEP 8 cmH<sub>2</sub>O, I/E 1-1.5, TV 240 mL/kg, which led to the deterioration of oxygenation of  $PaO_2/FiO_2$  74.



Figure 5. The left lung was partly collapsed

On the fifth day from the beginning of mechanical ventilation, there was a further decrease in oxygenation:  $PaO_2/FiO_2$  75,  $PaO_2$  75 mmHg,  $PaCO_2$  61 mmHg, the child received V-V ECMO. The patient was cannulated vena saphena magna dextra (return cannula: N $\ge$ 22) and vena saphena magna sinistra (access cannula: N $\ge$ 22). Productivity of 2.2 - 2.5 L/min.

V-V ECMO settings: RPM (pump speed) 3440, LPO (blood flow rate) 2.5-3 L/min, FiO<sub>2</sub> 100%. The protective mechanical lung ventilation: P/SIMV, FiO<sub>2</sub> 40%, PIP 12 cmH<sub>2</sub>O, PEEP 8 cmH<sub>2</sub>O, TV 300 mL/kg, RR 12 min, I/E 1: 1.5.

The child required prolonged analgesia and sedation and heparinization. The dynamics of laboratory parameters is shown in Table 2.

As a result of the use of ECMO, the oxygenation indicators were improved:  $PaO_2/FiO_2$  264,  $PaO_2$  132 mmHg,  $PaCO_2$  38 mmHg. The positive dynamics on pulmonary mechanics was also noted: Cstat increased from 17 mL/cm H<sub>2</sub>O to 57 mL/cmH<sub>2</sub>O. The duration of ECMO was seven days. Eight days after weaning from ECMO, the child was extubated and performed spontaneous breathing. Two days later, the child was transferred from the ICU to

	,					0				
	Reference	ECMO	Post-							
	range	day 0	day 1	day 2	day 3	day 4	day 5	day 6	day 7	ECMO
Hemoglobin (g/L)	120-145	88	84	115	109	97	93	94	97	109
Leukocytes (×10 <sup>9</sup> /L)	4.4-9	15.5	16.8	19.1	20.5	15.9	15.6	13.4	12.8	11.5
Neutrophils (%)	47-72	71	78	74	80	77	78	71	69	63
Lymphocytes (%)	19-37	13	15	18	17	18	18	22	32	28
Platelets (× $10^9/L$ )	130-400	346	280	215	190	167	158	169	170	250
C-reactive protein	0-7	48		198		192			55	32
(mg/L)										
Ferritin (mg/dL)	15-150	246								21
Procalcitonin (ng/mL)	0-0.5	0.125		0.2		0.5			0.2	0.079
Fibrinogen (g/L)	2-4	4.4		5		3.5	2.1		1.4	3.5
D-dimer (ng/mL)	20-500	1866	1564	1367	1370	1238	1119	1221	1122	1007
APTT (s)	28.2-40.2	30.5	100	89	85	97	101	91	88	52
INR	0.8-1.2	1.1	1.5	1.4	1.4	2.0	2.1	1.5	1.4	1.3
ALT (U/L)	5-35	44		45		47			52	51
Creatinine (mkmol/L)	70-110	64		77		91			85	76
Glucose (mmol/L)	4.4-6.2	7.8	10.1	6.7	10.3	7.7	6.3	5.5	5.8	5.1
Sodium (mmol/L)	135-145	136	133	144	135	137	142	139	137	145
Potassium (mmol/L)	3.5-5.5	5.1	4.8	4.7	3.8	4.9	5.0	4.1	4.4	3.8
PaO <sub>2</sub> (mmHg)	80-10	75	110	126	120	132	123	115	95	106
PaCO <sub>2</sub> (mmHg)	35-45	61	39	33	34	37	44	37	35	38
ECMO blood flow (L/min)			3	2.5	2.5	2.4	2.2	2.2	2.1	
Sweep gas flow (L/m)			4	4.6	4	3.5	3.3	3.3	2.8	
ECMO FiO <sub>2</sub> (%)			100	100	100	100	80	80	60	
Ventilator FiO <sub>2</sub> (%)		100	40	40	40	35	30	35	35	40
PaO <sub>2</sub> /FiO <sub>2</sub>		75								264
Tidal volume (mL/kg)		4.5	4	4	4	4	4	4	4	6
Cstat (mL/smH <sub>2</sub> O)		17	15	16	22	25	32	37	41	57
2 ,										

**APTT** – activated partial thromboplastin time; **ALT** – alanine transaminase; **INR** – international normalized ratio;  $PaO_2$  – partial pressure of oxygen;  $PaCO_2$  – partial pressure of carbon dioxide;  $PaO_2/FiO_2$  – pressure of arterial oxygen to fractional inspired oxygen concentration.

the pediatric ward. After 12 days, the child was discharged in satisfactory condition. The following side effects were observed: thrombocytopenia and transient cognitive impairment. The total duration of hospitalization was thirty-nine days.

## Discussion

The ECMO should be considered as an option for rescue therapy in patients when

mechanical ventilation, nitric oxide, and HFOV, do not provide adequate blood oxygenation. According to EuroELSO (Extracorporeal Life Support Organization), the frequency of ECMO use during the COVID-19 pandemic was 0.5-1% of all patients hospitalized in the ICU. Although cases of pneumonia caused by SARS-CoV-2 have been reported in infants, children and young adults, these patients generally performed well and rarely required extracorporeal life support.<sup>2,5</sup> According to the EuroELSO survey, which was conducted on January 28, 2021, in European countries, only ten cases of ECMO treatment in children were officially registered, while in adult patients more than a thousand cases of ECMO were registered. As of April 20, 2022, the number of children who received ECMO had increased to 47 children, 17 of whom had ARDS.<sup>6</sup>

As for the survival of children, the results of ECMO treatment in the pediatric population are better than in adults, on average 57%.<sup>7</sup> The predictors of mortality in patients who required ECMO are mechanical ventilation that exceeds two weeks before ECMO, multiple organ failure, and comorbid conditions. Therefore, it is important to take a timely decision to start ECMO, before the onset of dysfunction of other vital systems of the body.

According to the recommendations of ELSO (2015), Indications for Pediatric Respiratory Extracorporeal Life Support, "the decision to start ECMO should be based on the negative dynamics of oxygenation before reaching the critical values of PaO2/FiO2".<sup>8</sup> At the same time, according to the guidelines of the ELSO Coronavirus Disease 2019 Interim Guidelines, if the medical institution is not equipped with ECMO, the decision to transfer to the ECMO center can be made at  $PaO_2/FiO_2 \le 100$ , without waiting for the  $PaO_2/FiO_2$  criteria <80.<sup>9</sup> The purpose of protective lung ventilation is to minimize development of ventilator-associated lung injury (VALI). The main manifestations of VILI include pulmonary barotrauma and biotrauma of the lungs. Biotrauma is associated with oxidative stress and activation of proinflammatory cytokines. According to current data, the main factors causing VALI are tidal volume (VT)> 6 mL/kg, excessive inspiratory airway pressure (Pinsp >35 cm  $H_2O$ ), too low or incorrectly set positive end-expiratory pressure (PEEP), and also usage of high concentrations of oxygen (FiO<sub>2</sub>). After the start of ECMO, we applied protective ventilation to both patients. We reduced the TV to 4 mL/kg, PEEP was selected using the PV loop of graphical monitoring of ventilation. We also tried to keep the driving pressure (plateau pressure minus PEEP) <15 cmH<sub>2</sub>O. After achieving satisfactory

oxygenation thanks to ECMO, we reduced  $FiO_2$  to 40%.<sup>10-13</sup>

A team of cardiac surgeons performed vascular cannulation for our patients using such equipment (Cardiohelp, Maquet Cardiopulmonary AG, Germany).

The most common complication developing in children on ECMO is the threatening bleedings that result from anticoagulant therapy. According to H. J. Dalton et al., bleedings occurred in 70.2% of children on ECMO, including intracranial hemorrhage in 16% of patients, which was independently associated with a higher daily risk of death.<sup>14</sup> Our patient developed a large hematoma of the anterior abdominal area, probably due to vessel injury during cannulation. As the result of hematoma, intraabdominal hypertension developed and required surgical drainage.

Cognitive disorders in children have been reported in a review by J. Ju-Ming Wong et al., who state that more than a third of infants who received ECMO had cognitive impairment.<sup>15</sup> In another review, John C Lin reports that 42% of children who were treated with ECMO had cognitive impairment.<sup>16</sup>

## Conclusions

COVID-19-associated life-threatening conditions are much less common in children compared to adults. Nevertheless, in certain cases where critical hypoxemia cannot be corrected by traditional respiratory support, ECMO may represent a saving technology and it has been observed that subject to its timely use in pediatric patients the treatment was successful in more than half of cases.

Authors' contributions statement: MS and HL were involved in conception, literature review, and writing. NB contributed to data collection and processing. VM contributed to writing, supervision and critical review. All authors read and approved the final version of the manuscript.

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