CASE REPORTS

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Challenges in therapy of severe COVID-19 pneumonia with giant pneumatocele in a preterm newborn: how to optimize mechanical ventilation?

Izazovi u terapiji teške COVID-19 pneumonije sa džinovskom pneumatocelom kod preterminskog novorođenčeta: kako optimizovati mehaničku ventilaciju?

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Abstract

Introduction. Coronavirus disease 2019 (COVID-19) pneumonia is a potentially life-threatening condition that can require the use of mechanical ventilation (MV) and is rare in the neonatal population. Giant pneumatocele is an extremely rare complication of MV, which is practically unknown in neonates. **Case report.** We report a case of a two-week-old premature infant who developed severe acute respiratory distress syndrome (ARDS) due to COVID-19 and pneumatocele as a complication of MV. The newborn was admitted in a life-threatening condition with persistent hypercapnia, which, therefore, required prolonged MV. Chest computed tomography (CT) was done to assess the degree of fibrosis caused by COVID-19, and as an accidental finding, a pneumatocele was observed. The patient was immediately started on high-frequency oscillatory ventilation as a way of conservative treatment. After prolonged duration and gradual separation from MV, the patient was extubated, and oxygen therapy was gradually discontinued. The patient was discharged in good condition, and the follow-up chest CT showed complete regression of pneumatocele. **Conclusion.** Optimization of MV parameters and adequate treatment of complications such as ARDS or giant pneumatocele in neonates is an area that still requires further research, primarily due to the specificity of the neonatal age compared to adult patients.

Key words:
computed tomography; covid-19; infant, premature; pneumonia; respiratory distress syndrome, newborn; ventilator-induced lung injury.

Apstrakt

Uvod. Pneumonija u sklopu koronavirusne bolesti 2019 (COVID-19) je stanje koje je potencijalno opasno po život u čijem lečenju može biti neophodna primena mehaničke ventilacije (MV), ali se retko javlja u neonatalnoj populaciji. Džinovske pneumatocele su izuzetno retka komplikacija MV, praktično nepoznata kod novorođenčadi. **Prikaz bolesnika.** Prikazan je slučaj prevremeno rođenog novorođenčeta starosti dve nedelje, kod koga se u okviru COVID-19 razvio težak akutni respiratorni distres sindrom (ARDS) i pneumatocela nastala kao komplikacija MV. Novorođenče je primljeno u životno ugrožavajućem stanju sa perzistentnom hiperkapnijom zbog čega je bila neophodna produžena MV. Urađena je kompjuterizovana tomografija (KT) grudnog koša kako bi se procenio stepen fibroze izazvane COVID-19 i tom prilikom uočena je pneumatocela. Odmah je, kao metod konzervativnog lečenja, započeta visokofrekventna oscilatorna ventilacija. Nakon produženog trajanja i postepenog odvajanja od MV, bolesnik je ekstubiran i postepeno mu je ukinuta i terapija kiseonikom. Bolesnik je otpušten u dobrom opštem stanju, a kontrolnom KT utvrđena je kompletna regresija pneumatocele. **Zaključak.** Optimizacija parametara MV i adekvatno lečenje komplikacija kao što su ARDS ili džinovska pneumatocela kod novorođenčadi je oblast koja zahteva dalje istraživanje, prevashodno zbog specifičnosti neonatalnog uzrasta u odnosu na odrasle bolesnike.

Ključne reči:
tomografija, kompjuterizovana; covid-19; nedonošče; pneumonija; novorođenče, respiratorni distres sindrom; pluća, oštećenje izazvano respiratorom.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread across the globe since it was first identified in Wuhan, China, in December 2019. So far, it has affected over 600 million people and caused 6 million deaths worldwide [1]. However, not all age groups are affected in the same way. The pediatric population is shown to have an asymptomatic or mild clinical presentation, shorter disease duration, and positive outcomes with seldom-seen complications [2]. Amongst this population, SARS-CoV-2 infected newborns might be observed as a separate group with its specific traits, including possible methods of transmission, ranging from intrauterine, intrapartum, to postnatal transmission [3, 4]. Even though maternal SARS-CoV2 infection has been associated with higher rates of preterm delivery and newborns' admission to the neonatal intensive care unit (NICU), no differences were observed in neonatal mortality or length of hospital stay [4]. In the majority of cases, newborns had an asymptomatic, mild, or atypical clinical presentation, including fever, rhinorrhea, feeding difficulties, tachypnea, and dyspnea [5]. However, severe cases of neonatal COVID-19 have also been reported, with neonates requiring NICU stay and, in some cases, even noninvasive or invasive ventilation [6]. Invasive mechanical ventilation (MV) can lead to several complications, one of them being the development of pulmonary pneumatoceles, thin-walled air-containing cystic formations within the lung parenchyma. Pneumatoceles in neonatal age are usually caused by inadequate delivery of volumes or pressures during MV. Pneumatoceles are mostly asymptomatic but sometimes can have grave complications due to lung and mediastinum compression. We present a preterm newborn with severe COVID-19, requiring invasive ventilation, who developed a pneumatocele as a complication of MV.

Case report

A late preterm male neonate was born in 35/36 gestational week *via* an uncomplicated vaginal delivery to a COVID-19-positive mother, with a birthweight of 2,580 g and an Apgar score of 9. Due to the transient tachypnea of the newborn, he required oxygen supplementation during the first 24 hrs of life but had no further complications. On the 7th day of life, he was discharged from the hospital in a good clinical condition. The baby was tested for SARS-CoV-2 at birth and at discharge from the hospital using reverse transcription polymerase chain reaction tests. Both results were positive, but the baby had no symptoms of COVID-19 or any other infection.

On the 12th day of life, the baby developed feeding difficulties, became hypothermic (33 °C), and was tachypneic. Grunting and acrocyanosis were also observed, as well as a drop in oxygen saturation (SpO_2) (58%, normal values for SpO_2 are > 92%). After the initial workup at the regional medical center, the baby was urgently transferred to the COVID-19 NICU of the University Children's Hospital, Belgrade, Serbia.

On admission, the newborn was afebrile, tachypneic, and moderately dyspneic with mild subcostal retractions. Examination of the respiratory system revealed symmetrical lower-intensity breathing sounds followed by inspiratory crackles. The rest of the physical exam findings were unremarkable. Thorough laboratory as well as radiographic examinations were performed. Antigen test for SARS-CoV-2 was positive, C-reactive protein value was within the normal range (< 10 mg/L), procalcitonin, interleukin (IL)-6, and fibrinogen values were slightly above the upper limit [reference range (RR) < 0.5 ng/mL, 0–7 pg/mL, and 3.1–6.1 g/L, respectively]. Ferritin and D-dimer were elevated (2,056.3 ug/L and 6.9 mg/L, RR 13–150 ug/L and < 0.5 mg/L, respectively). Chest X-ray revealed bilateral lung opacities. Continuous fentanyl sedation and low molecular weight heparin were started. Due to the worsening of the baby's breathing pattern shortly after admission, as well as respiratory acidosis observed in arterial blood gases (ABGs), oxygen therapy *via* nasal cannulas was aborted, and the patient non-invasive ventilation (NIV) was started. Soon after, he was orally intubated, and pressure control – assist control mode of MV was introduced with initial settings raised to peak inspiratory airway pressure of 20 cm H_2O and a fraction of inspired oxygen (FiO_2) of 100% (Table 1). Twenty-four hours after starting the treatment, his ABG values improved, showing a lowering of hypercapnia but also persistent moderate hypoxia. This allowed for a change in the mode of MV to pressure control – synchronized intermittent mandatory ventilation (PC-SIMV) with a reduction of ventilation parameters (Figure 1). Systemic corticosteroids were started in regular therapy.

On the 4th day of hospitalization, significant acute respiratory distress syndrome (ARDS) progression was observed (with zones of hypoventilation, hyperinflation, and consolidation on chest X-ray). Hence, surfactant was administered, methylprednisolone dosage was increased, and immunoglobulins were started. Despite all undertaken measures, respiratory failure progressed even further over the next two days. Parameters of MV had to be significantly increased [peak inspiratory pressure of 25 mm H_2O (RR 20–25 cm H_2O), positive end-expiratory pressure of 7 mm H_2O (RR 4–6 cm H_2O), and FiO_2 of 100%] with a change in the mode of ventilation to pressure control – continuous mandatory ventilation. Second and third doses of surfactant were administered, and the dose of systemic corticosteroid was further increased. Only four days after, inhaled nitric oxide (iNO) therapy of 20 ppm was initiated as well due to suprasystemic pulmonary tension. The unwavering requirement for high MV parameters, persistent bilateral lung opacities observed on the follow-up chest X-ray, and unchanging clinical findings on the examination of the respiratory system led to a decision to apply the fourth dose of surfactant on the 11th day of hospitalization. This caused a significant increase in oxygenation, with SpO_2 values mostly above 92%. Throughout the hospitalization, the patient required intermittent administration of furosemide in order to maintain adequate diuresis, short-term inotropic support due to hypotension, as well as several erythrocyte transfusions due to anemia verified in complete blood count. Sildenafil was included in regular

Table 1

Breaking points of the patient's stay in the Intensive Care Unit

Parameter	Day of hospitalization												
	1	2	4	6	10	12	14	40	56	62	81	84	89
SPO_2 (%)	80%		90–98	77–92	77–96	88%	94%	75–82	86–92	85–99		85%	88–100
CRP (mg/L)		2.1						168.5	54.3			3.5	
Surfactant		1st dose		2nd & 3rd dose		4th dose		5th dose					
Antibiotics			amikacin ampicillin					ciprofloxacin vancomycin	amikacin piperacillin				
Corticosteroids (mg/kg of BW)		1	2	3		2							
Dobutamine						5 mcg/kg/min		starting again 7 mcg/kg/min					
Sildenafil								starting		ex			
iNO (ppm)					20		10	ex					
Immunoglobulins		pentaglobine						pentaglobine					
Mode of MV	PC-AC	PC-SIMV		CMV	CMV		SIPPV	HFOV	HFOV	SIMV	CPAP/PSV	HFNC	NC
PIP	21	26		28	23		23			23			
PEEP	5	6		6	6		5			6	7		
FiO_2	80	100		100	100		90	100	60	85	75		
OI	9	13.62		16.66	14.42		13.48	27.04	12.2	9.6	5.5		
Amplitude								45	38				
CDP								24	19				
Flow (L/min)												10	3
pH	7.27	7.31		7.46	7.44		7.34	7.27	7.32	7.43	7.43	7.41	
pCO_2 (mmHg)	55	45		47	48		59	94	88	71	44	63	
pO_2 (mmHg)	40	64		62	71		77	77	99	77	79	92	

Note: reference range (RR) for dobutamine is 2–25 mcg/kg/min, OI < 17, CDP 12–17 cm H_2O, amplitude 20–40 cm H_2O, flow for HFNC 6–10 L/min, pH 7.35–7.45, pCO_2 35–45 mmHg, pO_2 50–80.

SPO_2 – oxygen saturation; CRP – C-reactive protein; BW – body weight; iNO – inhaled nitric oxide; MV – mechanical ventilation; PIP – peak inspiratory pressure; PEEP – positive end-expiratory pressure; FiO_2 – fraction of inspired oxygen; OI – oxygenation index; CDP – continuous distending pressure; pH – potential of hydrogen; pCO_2 – partial pressure of carbon dioxide; pO_2 – partial pressure of oxygen; PC-AC – pressure control assist control; PC-SIMV – pressure control – synchronized intermittent mandatory ventilation; CMV – continuous mandatory ventilation; SIPPV – synchronized intermittent positive pressure ventilation; HFOV – high-frequency oscillatory ventilation; CPAP/PSV – continuous positive airway pressure/pressure support ventilation; HFNC – high flow nasal cannula; NC – nasal cannula.

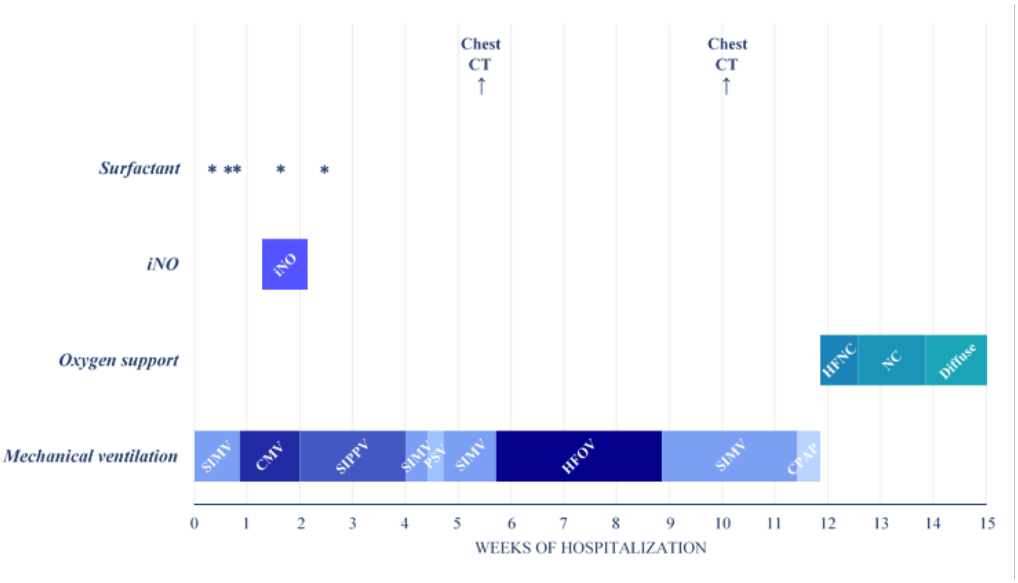


Fig. 1 – Timeline of the patient's stay in the Intensive Care Unit.
CT – computed tomography; Diffuse – diffuse oxygen therapy; * – administration of surfactant; For other abbreviations, see Table 1.

therapy on the 14th day, and usage of iNO was aborted the day after. The described improvement of oxygenation was short-lived, and on the 17th day, the 5th dose of surfactant was administered, and beta-2 agonist-anticholinergic inhalations were started. Acetylcysteine inhalation was also administered to help eliminate the abundance of secretion present in the airways from the start of the treatment. Compensated respiratory acidosis with refractory hypercapnia and hypoxemia was a persistent finding in ABGs. During the next ten days, ventilatory support was gradually reduced all the way down to pressure support ventilation mode, and both corticosteroid and sildenafil doses were decreased. However, on the 32nd day of hospitalization, the patient's clinical aspect worsened due to developing sepsis, so the requirement for ventilatory support once again increased, and he was changed back to PC-SIMV mode of ventilation. The obtained chest X-ray showed no signs of improvement in comparison to previous X-rays, and the image of the III phase of ARDS was still present.

In order to evaluate the degree of lung fibrosis, on the 36th day of hospitalization, a chest computed tomography (CT) scan was obtained, which corresponded to the already established diagnosis of ARDS. Additionally, it showed a large air collection (pneumatocele) in the anterior part of the right hemithorax with a polycyclic outline, spreading from the diaphragm to the upper half of the sternum and communicating with airways (Figure 2). Diffuse bilateral ground glass lung opacities and thickened peribronchial connecting tissue were noted as well.

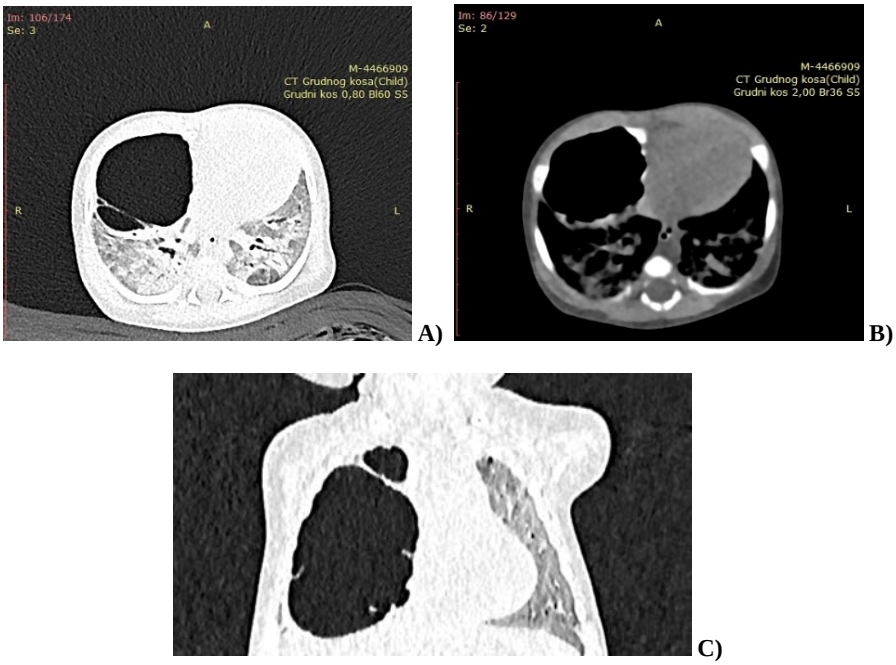


Fig. 2 – Computed tomography of the chest. Pneumatocele observed in transverse (A and B) and coronal plane (C).

The high-frequency oscillatory ventilation (HFOV) mode was started and kept for the next 22 days. This gradually led to an improvement in gas exchange and made it possible for ventilatory support to be reduced first to PC-SIMV. Over the next 19 days, it dropped down to pressure-controlled – continuous positive airway pressure. Even though follow-up chest CT scan findings showed further progression of the changes in the lung parenchyma, the clinical aspect of the patient, as well as his oxygenation and ventilation, were good enough to allow for extubation after 83 days of MV. Complete supportive therapy was initiated to improve respiratory function (such as beta-2 agonist-anticholinergic inhalations, corticosteroid inhalations, aminophylline, and IV corticosteroids). Oxygen support was gradually decreased from high flow nasal cannula to diffuse application of 4 L/min of oxygen. The baby was discharged from the Intensive Care Unit after 106 days (Table 1, Figure 1) and moved to the Pulmonology Department for further treatment using inhaled and systemic corticosteroids, a decrease in oxygen therapy, and physical rehabilitation.

The third chest CT scan performed was the first to show an improvement. Findings described in previous CT scans were in regression – pneumatocele was smaller, but ground glass opacities were persistent with fibroadhesive strips and consequential bronchiectasis. At no time was there any indication for an operative approach to the described pneumatocele. Considering that the mother was trained during the hospitalization to provide adequate physical rehabilitation treatment, as well as percutaneous drainage of secretion from the airways and application of oxygen therapy, and seeing that the clinical aspect of the patient was significantly improved, the baby was discharged home after 144 days in the hospital, from October 2021 to April 2022.

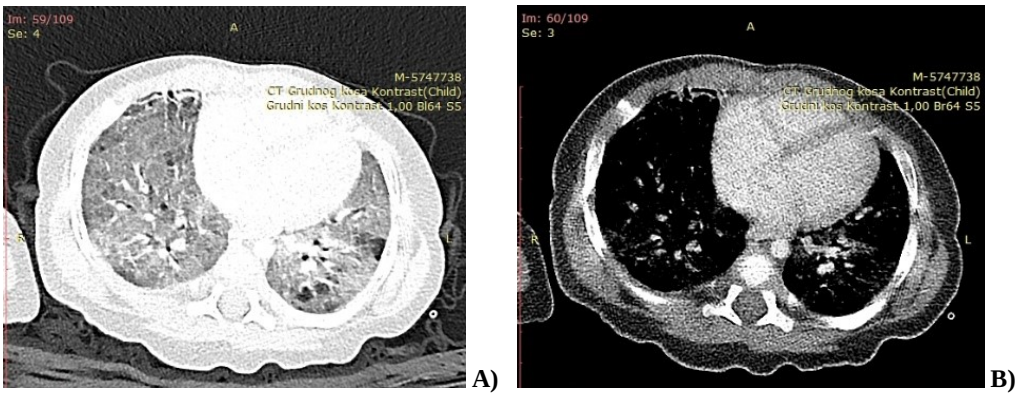
Systemic and inhaled corticosteroids were prescribed in regular therapy, along with the usage of a home oxygen concentrator as required.

Follow-up chest CT performed two months after hospital discharge showed no signs of previously described pneumatocele and no change in the rest of the findings regarding lung fibrosis (Figure 3). On the follow-up examination five months after discharge, the mother reported that the baby did not require oxygen support, so systemic corticosteroid therapy was aborted, and inhaled corticosteroids were tapered off.

Discussion

The available literature on severe cases of COVID-19 in newborns is scarce since clinical presentation in this population is usually asymptomatic or mild, with the most common symptoms being fever, rhinorrhea, feeding difficulties, and cough [5]. Severe cases of pulmonary involvement require respiratory support, but oxygen therapy or noninvasive ventilation is mostly a sufficient manner of respiratory treatment [7]. Only a small number of critically ill newborns require invasive MV [7]. Changes in lung radiographs, such as ground glass opacities, were also commonly described in patients with pulmonary involvement and severe clinical presentation. However, even though it has been one of the most common clinical entities observed in severe COVID-19 patients over the previous three years, not many newborns were classified as having ARDS since this diagnosis is not so common during the neonatal period. The Montreux definition of neonatal ARDS states that ARDS is characterized by qualitative or quantitative surfactant dysfunction and extensive lung tissue inflammation. It has acute onset from a known or suspected clinical insult. Conditions such as respiratory distress syndrome, transient tachypnea of the newborn, or congenital anomalies have to be excluded as a primary cause of acute respiratory condition [8].

MV is an important method of ARDS treatment when NIV is insufficient, but it must be highlighted that the lungs of these patients are even more prone to ventilator-induced lung injuries (VILI): volumes/pressures required to expand collapsed alveoli lead to overexpansion of normal, unaffected alveoli and cause lung injuries such as pneumothorax or pneumatocele. Therefore, a crucial point in ARDS treatment is balancing MV parameters with low tidal volume (4 mL/kg) and limited platform pressure (up to 25 mm H_2O) to provide adequate ventilation and oxygenation, prevent respiratory acidosis, and, on the other hand, avoid any potential VILIs [9]. MV leads to an increase in levels of pro-inflammatory cytokines (IL-6, IL-8 and tumor necrosis factor-α) and a decrease of anti-inflammatory cytokine IL-10, which, in addition to already elevated levels of pro-inflammatory cytokines due to primary disease, increases lung vulnerability and propensity towards complications [10].



A) **B)**

Fig. 3 – Follow-up computed tomography of the chest. No signs of pneumatocele were observed (A and B).

Additionally, in newborns, especially premature infants, MV carries even higher risks since it can potentially harm lung development and lead to histological changes in airways and alveoli [11]. Pneumothorax has been described in the literature as a complication of MV in SARS-CoV-2 positive newborns [6], but to our knowledge, pneumatocele in newborns has not been described in relation to COVID-19 so far.

Pulmonary pneumatoceles in neonatal age are most commonly caused by MV, specifically by inadequate delivery of volumes or pressures. They are typically observed in the right lower lobe or the right middle lobe due to the anatomy of airways and distribution of ventilatory pressure and volumes [10]. Pneumatoceles are mostly asymptomatic and discovered as incidental findings on chest X-rays. However, they can sometimes compress the adjacent lung and the mediastinum, leading to the development of atelectasis of the lung parenchyma, consequential respiratory failure, pulmonary hypertension, and death. Common complications are the rupture of the pneumatocele into the pleural space, tension pneumothorax, and secondary infection. It is, therefore, important to start adequate treatment for pneumatocele as soon as the diagnosis is established. Although there are no clear guidelines, therapeutic options range from conservative management, such as lung protective ventilation strategies, unilateral intubation, positioning of the patient, and fluid restriction, to invasive approaches, such as percutaneous drainage, lobectomy, or even pneumonectomy for patients who develop complications refractory to conservative management [10, 12]. Lung protective ventilation strategies imply the reduction of mean airway pressure and the usage of HFOV or volume-controlled modes as a guarantee of adequate volume delivery. HFOV delivers small tidal volumes, maintains constant alveolar inflation, prevents the lung "inflate-deflate" cycle, and improves oxygenation [13]. This ventilation mode uses the effects of permissive hypercapnia to provide ventilation support while maintaining normal cellular function and potential of hydrogen value. It is the best ventilation mode to reduce the risk of VILI as it improves lung recruitment while avoiding overdistension. HFOV is also the best and most recommended conservative treatment method in patients with pneumatocele, where it is usually the only method of treatment. It may take up to several months for complete resolution, but in cases of uncomplicated pneumatoceles, complete recovery with no residues is the most common outcome [10].

Conclusion

This case report provides insight into severely ill COVID-19 newborns requiring intensive respiratory support and developing lung complications. Even though they are described in the adult population, entities such as pneumatocele, COVID-19-caused ARDS, and respiratory insufficiency in newborns are still an area that lacks clear guidelines and requires further research.

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A signed informed consent for writing and publishing this paper was obtained from the patient's legal guardian (parent).

Conflict of interest

The authors declare no conflict of interest.

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