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Surfactant lung lavage in neonatal meconium aspiration syndrome as a life-saving respiratory strategy: literature review and a case report

Aleksei V. Mostovoi[1,2,3], Anna L. Karpova[1,2,3], Igor V. Popov[1], Lubov' A. Anikeeva[1], Nikolai Yu. Karpov[4]

[1]Vorokhobov City Clinical Hospital № 67, Moscow Healthcare Department; 2/44 Salyama Adilya Str., Moscow 123423, Russia;

[2]Russian Medical Academy of Continuous Professional Education, Health Ministry of Russian Federation; 2/1 bldg. 1, Barrikadnaya Str., Moscow 123993, Russia;

[3]Yaroslavl State Medical University, Health Ministry of Russian Federation; 5 Revolutsionnaya Str., Yaroslavl 150000, Russia;

[4]Tutaev Central District Hospital; 104 Komsomolskaya Str., Tutaev, Yaroslavl Region 152303, Russia

***Corresponding author:** Aleksei V. Mostovoi, e-mail: valmost@mail.ru*

Abstract

Here, we review the latest available studies on using surfactant lavage in newborns with severe manifestations of meconium aspiration syndrome (MAS), illustrated by a representative clinical case. Meconium-stained amniotic fluid may be found in 8–20 % of all births, with the incidence reaching 23–52 % after a full 42 weeks of gestation. From 2 to 9 % of newborns with meconium-stained amniotic fluid subsequently develop MAS clinical signs. About a third of newborns with MAS require tracheal intubation and mechanical ventilation. MAS-related mortality rate due to severe injuries of the lung parenchyma and the development of pulmonary hypertension, can exceed 20 %. Other complications, including air leak syndrome (ALS), occur in 10–30 % of children with MAS. Surfactant lavage may be one of the clinical tools that avoids extracorporeal membrane oxygenation (ECMO) in severe MAS cases. This clinical observation is also of interest because a mature, even post-term newborn with MAS subsequently developed a typical bronchopulmonary dysplasia (BPD), which required proper treatment.

Keywords: post-term pregnancy, poractant alpha, surfactant-BL, tauractant, acute neonatal distress syndrome, persistent pulmonary hypertension of newborns, high frequency oscillatory ventilation

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Лаваж легких сурфактантом при неонатальном синдроме аспирации мекония как жизнеспасающая респираторная стратегия: обзор литературы и клинический случай

А.В. Мостовой[1,2,3], А.Л. Карпова[1,2,3], И.В. Попов[1], Л.А. Аникеева[1], Н.Ю. Карпов[4]

[1]ГБУЗ «Городская клиническая больница № 67 имени Л.А. Ворохобова Департамента здравоохранения города Москвы»; Россия, 123423 Москва, ул. Саляма Адиля, д. 2/44;

[2]ФГБОУ ДПО «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации; Россия, 123995 Москва, ул. Баррикадная, д. 2/1, корп. 1;

[3]ФГБОУ ВО «Ярославский государственный медицинский университет» Министерства здравоохранения Российской Федерации; Россия, 150000 Ярославль, ул. Революционная, д. 5;

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[4]ГБУЗ Ярославской области «Тутаевская центральная районная больница»; Россия, 152303 Тутаев, ул. Комсомольская, д. 104

Для контактов: *Алексей Валерьевич Мостовой, e-mail: valmost@mail.ru*

Резюме

Представлен обзор современных исследований о применении сурфактантного лаважа новорожденным с тяжелыми проявлениями синдрома аспирации мекония (САМ), иллюстрированный описанием клинического случая. Околоплодные воды могут быть окрашены меконием в 8–20 % всех родов, причем после полных 42 недель гестации частота САМ достигает 23–52 %. От 2 до 9 % новорожденных, у которых воды были окрашены меконием, впоследствии отмечаются клинические проявления САМ. Около трети новорожденных с САМ нуждаются в интубации трахеи и искусственной вентиляции легких. Летальность при САМ в связи с тяжелыми повреждениями паренхимы легких и развитием легочной гипертензии может превышать 20 %. Другие осложнения, включая синдром утечки воздуха (СУВ), встречаются у 10–30 % детей с САМ. Лаваж сурфактантом может быть одним из клинических инструментов, который позволяет избежать использования экстракорпоральной мембранной оксигенации (ЭКМО) в тяжелых случаях САМ. Приведенное клиническое наблюдение представляет интерес еще и тем, что у зрелого, даже переношенного ребенка с САМ в последующем сформировалась типичная бронхолегочная дисплазия (БЛД), которая требовала соответствующего лечения.

Ключевые слова: переношенная беременность, поракtант альфа, Сурфактант-БЛ, тауpактант, острый неонатальный дистресс-синдром, персистирующая легочная гипертензия новорожденных, высокочастотная осцилляторная искусственная вентиляция легких

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Introduction / Введение

Meconium aspiration syndrome (MAS) is considered to be a neonatal respiratory distress linked to the meconium-stained amniotic fluid and typical clinical and radiological symptoms unexplained by any other cause [1]. Meconium-stained amniotic fluid may comprise 8–20 % total births [1–4], with MAS incidence reaching 23–52 % after 42 full weeks of gestation [5, 6]. Between 2 and 9% of neonates with meconium-stained amniotic fluid subsequently developed clinical MAS [2, 7, 8]. About one third of neonates with MAS require tracheal intubation and mechanical ventilation [8]. MAS mortality due to severe damage to the lung parenchyma and developing pulmonary hypertension can exceed 20 %. Other complications, including air leak syndrome (ALS), occur in 10–30 % of infants with MAS [9].

Emergence of meconium in the amniotic fluid results from stimulated gut maturation due to hypoxic stress able to induce peristalsis and relaxation of the rectal sphincter followed by meconium passage. Aspiration of meconium-containing fluid may occur if fetal distress develops in relation to progressive hypoxia, leading to development of a gasping respiration pattern [10]. Aspiration triggers post-natal hypoxia due to the four pulmonary effects: airway obstruction, surfactant dysfunction, chemical pneumonitis, pulmonary hypertension [11].

Meconium aspiration syndrome is characterized by development of respiratory failure, typical radiographic symptoms and complications within the first 48 hours of life. Based on respiratory failure severity, MAS is subdivided into mild form with oxygen dependence persisting for less than 48 hours, requiring less than 40 % oxygen supply; moderate form requiring more than 40 % oxygen supply for more than 48 hours, with no ALS signs; severe form, when mechanical ventilation (MV) is required for more than 48 hours. A frequent complication in severe cases is presented as a persistent pulmonary hypertension of the newborn (PPHN) [2]. Characteristic radiographic symptoms for MAS include diffuse, polymorphic, heterogeneous nodular infiltrates, localized or generalized, asymmetric or symmetric; increased airiness of unchanged lung tissue; signs of air leakage; pleural effusion; cardiomegaly [12].

Due to developing respiratory failure, neonates with MAS often require some respiratory support. However, the use of continuous positive airway pressure (CPAP) therapy is not recommended, since there no evidence of its effectiveness in MAS exists, whereas CPAP in MAS patients may increase pneumothorax risk [13]. MV is needed in about 30–40 % of newborns with MAS [1, 14]. With elevating need to increase the parameters of conventional MV (CMV), high frequency oscillatory ventilation (HFOV) [15, 16] or high frequency jet MV [17] may be required. Available publications show that about 20–30 % of all children with MAS on MV require HFOV [7, 11, 18]. The main indications for switching from CMV to HFOV are presented by refractory hypoxemia and/or high fractional oxygen in the inspired mixture (FiO_2) = 0.4 or more, as well as respiratory acidosis. In case of developing PPHN, inhalation nitric oxide (iNO) therapy can be administered [19, 20]. A more objective dia-

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Highlights

What is already known about this subject?

- Every third newborn with meconium aspiration syndrome (MAS) requires tracheal intubation and start of mechanical ventilation, with mortality rate reaching as high as 20 %.
- In order to avoid the use of extracorporeal membrane oxygenation (ECMO), surfactant replacement therapy is often used worldwide: surfactant lung lavage or bolus injection. Surfactant therapy of neonatal acute respiratory distress syndrome (ARDS) in MAS reduces mortality and disability.
- Most researchers use a surfactant solution for lavage in a volume of 15–20 ml/kg, and cases of repeated bolus surfactant administration after lavage have also been described. No similar studies on this topic were found among studies published in Russian.

What are the new findings?

- This review and the case report provide an insight about safe and effective use of the respiratory strategy of surfactant lung lavage in the amount of 15–20 ml/kg and/or bolus surfactant administration in severe MAS.
- A successful experience of using surfactant lung lavage with subsequent bolus surfactant injection in a newborn complicated with air leak syndrome (ALS), persistent pulmonary hypertension of newborns and neonatal ARDS in MAS is presented.
- For the first time in Russia, the algorithm of surfactant lung lavage with bolus surfactant administration has been described to improve oxygenation and prevent ECMO.

How might it impact on clinical practice in the foreseeable future?

- Our experience provides additional opportunities for surfactant therapy in neonatal clinics in the case of severe MAS, when the start of ECMO and/or transportation to the ECMO center is not possible due to the severity of patient's condition.
- Such respiratory strategy in neonatology can reduce a risk of ECMO and lead to improved oxygenation as well as rapid stabilization of patients with MAS, lower ALS risk.
- Our study may represent a successful application of this respiratory strategy in newborns with severe MAS.

Основные моменты

Что уже известно об этой теме?

- Каждый третий ребенок с синдромом аспирации мекония (САМ) требует интубации трахеи и перевода на искусственную вентиляцию легких, а летальность может достигать 20 %.
- Для того чтобы избежать применения экстракорпоральной мембранной оксигенации (ЭКМО), в мире часто используют заместительную терапию сурфактантом: легочным лаважом или болюсным введением. Терапия сурфактантом острого респираторного дистресс-синдрома (ОРДС) при САМ позволяет снизить летальность и инвалидность.
- Большинство зарубежных исследователей применяют сурфактантный раствор для проведения лаважа в объеме 15–20 мл/кг, также описаны случаи повторного болюсного введения сурфактанта после лаважа. Среди российских публикаций на эту тему подобных исследований не было найдено.

Что нового дает статья?

- Представлен обзор литературы, дающий представление о безопасном и эффективном применении респираторной стратегии сурфактантного лаважа в объеме 15–20 мл/кг и/или болюсного введения сурфактанта при тяжелой форме САМ.
- Представлен собственный успешный практический опыт применения сурфактантного лаважа с последующим болюсным введением сурфактанта у ребенка с синдромом утечки воздуха (СУВ), персистирующей легочной гипертензией новорожденных и неонатальным ОРДС при САМ.
- Впервые в отечественной неонатальной практике подробно описан алгоритм проведения сурфактантного лаважа с последующим болюсным введением сурфактанта с целью улучшения оксигенации и профилактики перевода пациента на ЭКМО.

Как это может повлиять на клиническую практику в обозримом будущем?

- Описанный нами опыт открывает дополнительные возможности неонатальным клиникам проведения заместительной терапии сурфактантом в случае тяжелой формы САМ, когда перевод на ЭКМО или транспортировка в ЭКМО-центр невозможна из-за тяжести состояния больного.
- Применение описанной респираторной стратегии в неонатальной практике позволит снизить риск перевода пациентов на ЭКМО, а также может привести к улучшению оксигенации и последующей быстрой стабилизации пациентов с САМ, снизить риск развития СУВ.
- Наша публикация может послужить примером успешного применения данной респираторной стратегии у новорожденных с тяжелым течением САМ.

gnosis of PPHN severity and choice of treatment tactics in newborns may be established by calculating the oxygenation index (OI): $OI = FiO_2 \times MAP \times 100\ \%/PaO_2$, where MAP is the mean airway pressure (cm H_2O), PaO_2 is the partial arterial blood oxygen pressure (mm Hg) [21]. According to the Montreux definition, severe respiratory failure in neonates is diagnosed when the OI increases to more than 16 [22]. In case OI reaches 40 or more, the predicted mortality in such patients can exceed 80 %, therefore allowing to recommend extracorporeal membrane oxygenation (ECMO) [23–25].

Among the respiratory strategies for MAS treatment, surfactant therapy is also commonly used worldwide: surfactant lavage, bolus surfactant administration (es-

pecially in cases where ECMO is not possible). All studies aimed to assess surfactant therapy in MAS indicate that this treatment strategy is carried out only in case of severe MAS. Thus, H.C. Lin et al. (2005) used early surfactant replacement therapy or surfactant lavage in MAS only in case of OI exceeding 20 after HFOV and/or iNO at the age of 6 hours of life [16].

P.A. Dargaville actively popularized the technique of surfactant lavage in newborns and was among those who proposed an innovative surfactant therapy for MAS [26, 27]. In the study by P.A. Dargaville et al. (2011), during lung lavage procedure there was administered two aliquots of 15 ml/kg diluted bovine surfactant to 66 newborns with MAS that was then recovered. The median duration of respiratory support was comparable in children who underwent lung lavage and in control group (5.5 and 6.0 days, respectively; p = 0.77). The need for HFOV and iNO did not differ between the groups. Fewer newborns who underwent lavage subsequently died or required ECMO: 10 % (3/30) vs. 31 % (11/35) in control group (odds ratio (OR) = 0.24; 95 % confidence interval (CI) = 0.060–0.97). The lavage procedure was associated with lowered blood oxygen saturation (SpO_2) without a prominent effect on heart rate (HR) or blood pressure (BP). After lavage, mean airway pressure decreased more rapidly. It was concluded that lung lavage with diluted surfactant did not affect duration of respiratory support, but may reduce mortality, especially in medical facilities lacking available ECMO [26, 27]. Subsequently, S. Hahn et al. (2013) in a meta-analysis investigating surfactant lavage in MAS found a marked effect in favour of tracheobronchial tree (TBT) lavage assessing a collective outcome as death or ECMO use [28].

S. Arayici et al. (2019) carried out a randomized controlled trial comparing the effectiveness of lung surfactant lavage and bolus surfactant administration for therapeutic purpose in newborns who underwent mechanical ventilation for MAS [29]. Treatment was carried out in accordance with the technique described by P.A. Dargaville et al. [26]. Before the lavage procedure, newborns were sedated and/or muscle relaxation. Newborns underwent lung lavage received two aliquots (multiple fractions) of diluted porcine surfactant poractant alfa (Curosurf, Chiesi Farmaceutici SpA, Italy) were sequentially administered into the TBT at a dose of 15 ml/kg with a phospholipid concentration of 5.0 mg/ml, with a recovery period after administration until the saturation (SpO_2) being increased to a level of more than 80 %. The washing fluid (poractant alfa diluted in saline at 1:15 ratio) was administered for 15–20 seconds through a catheter inserted into the lumen of the endotracheal tube (ETT), after which three MV movements with positive pressure using a breathing bag were applied. After high-pressure inspiration, open suctioning was performed using a standard catheter under negative pressure of –150 mm Hg with evacuation of washing fluid until the flow of secretions from the TBT ceased. After lavage, MV was continued using previous modes. Chest radiography was performed for 2–4 hours after surfactant administration. No advantage was found while using diluted surfactant compared with its bolus administration assessing duration of respiratory support in newborns with MAS. However, incidence of pneumothorax and surfactant re-administration tended to decrease as noted in newborns underwent lung lavage [29].

Moreover, there was described an approach of using surfactant lavage in MAS with subsequent bolus administration of undiluted surfactant, assessing the effectiveness of various surfactant preparations. It is assumed that lung lavage with diluted surfactant followed by bolus surfactant administration can consolidate the positive impact of lung lavage and affect overall disease course by reducing pneumothorax incidence and rate of repeated bolus surfactant administration in MAS. Thus, Y. Xu et al. (2023) investigated the efficacy of bronchopulmonary lavage with diluted artificial surfactant CHF5633 (5.0 mg/ml; 20 ml/kg) alone or followed by bolus undiluted surfactant (100 or 300 mg/kg) administration in an experimental MAS model in near-term neonatal rabbits by intratracheal administration of reconstituted human meconium. Hence, it was concluded that CHF5633 improves survival and positively acted on meconium-induced lung tissue injury, and that CHF5633 TBT lavage followed by bolus surfactant represents the optimal regimen for MAS treatment [30]. C. Rey-Santano et al. (2011) found that lung lavage with diluted lucinactant (10 mg/ml) in neonatal lambs with respiratory failure and MAS-caused pulmonary hypertension markedly improves gas exchange compared to bolus (30 mg/ml) instillation ($p < 0.05$), and is therefore an effective and safe strategy [31].

The sole Russian study analyzing surfactant therapy in newborns with MAS and published in 2011 by I.V. Vinogradova and G.I. Nikiforova included 100 newborns with severe MAS (main group or group with lavage – 41 children). The subjects underwent lung lavage followed by bolus drug Surfactant-BL (OOO Biosurf, Russia) administration. Bovine surfactant (75 mg per vial) was diluted in 2.5 ml of physiological solution, according to the manufacturer's instructions [32]. Next, 20 % of the drug (0.5 ml) from the resulting emulsion was used and additionally diluted 10 times with 0.9 % NaCl solution (to 5.0 ml). The remaining 2.0 ml (60 mg) of the emulsion was administered bolus through an aspiration catheter alternately, 1.0 ml at a time, into the left and right bronchi. The second preparation vial was administered by microjet, so that the total dose was 50 mg/kg. It was concluded that two-component surfactant therapy in the form of TBT lavage with diluted Surfactant-BL followed by low-dose preparation administration allows to significant-

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ly shorten duration for achieving a non-toxic oxygen concentration in the supplied gas mixture and MV length [33].

Characteristics of the main studies assessing surfactant lavage in MAS included in the meta-analysis published by R. Hui et al. in 2020 [34] are summarized in **Table 1**.

The most effective volume of diluted surfactant lavage in MAS has been searched for worldwide. Experimental work by M.J. Jeng et al. (2009), inducing MAS in 24 newborn piglets (human meconium was introduced into the lungs), attempted to compare 3 volumes of diluted surfactant "Survanta": 10 ml/kg (lavage-10), 20 ml/kg (lavage-20) and 30 ml/kg (lavage-30). Changes in oxygenation and lung compliance in lavage-20 and lavage-30 groups were significantly better than in control group (without lavage) and in lavage-10 group ($p < 0.05$). It was concluded that 20 ml/kg diluted surfactant in two aliquots was as effective as 30 ml/kg dose [45]. H.Y. Hung et al. (2006) compared the treatment results for 11 full-term newborns with MAS using 20 ml diluted surfactant at phospholipid concentration of 10 mg/ml with those for 9 infants previously receiving 40 ml (5.0 mg/ml) instillation. Both preparation volumes were equally effective, but 20 ml was associated with fewer side effects (hypoxemia in 3 infants and white spots on chest radiograph in 5 cases), which were recorded only in the 40 ml group [46].

A search for data on using surfactant lavage in severe MAS over the past 10 years in the Russian medical libraries eLibrary.ru and CyberLeninka was unsuccessful finding not a single work published, so we considered necessary to share our own experience by presenting one of the most complex clinical cases in which TBT surfactant lavage in a post-term child with severe MAS predetermined the outcome of the disease and allowed not only to save a life, but also to improve the prognosis.

Clinical case / Клиническое наблюдение

The mother's medical history describes right eye orbit tumor removal in 2021. The first pregnancy woman was observed at the antenatal clinic since 20-week gestational age, proceeded with edema and oligohydramnios in the third trimester. Streptococcus agalactiae test result was negative. She was admitted to the perinatal center at 43-week gestational age with signs of fetal distress, so she was delivered almost immediately by cesarean section. This is the first post-term birth, in the occipital presentation. The amniotic fluid was densely meconium stained. The newborn's birth body weight was 4200 g, height 55 cm, Apgar score – 3/4/5 points.

After imbilical cord clamping (30 sec), the baby was transferred under a radiant warmer to be monitored. Given the large amount of thick meconium fluid in the oropharynx, the upper respiratory tract (URT) was sanitized, and thick dark green amniotic fluid was obtained. Since birth, the child had rare gasps, HR over 100 bpm, atony, adynamia, and areflexia. MV was started using a manual device with a T-shaped connector in the open resuscitation system Resuscitaire® RW (Dräger, Germany) through a face mask with the following parameters: positive inspiratory pressure (PIP) = 25.0 cm H_2O, positive end expiratory pressure (PEEP) = 6.0 cm H_2O, respiratory rate (RR) = 40 per min, FiO_2 gradually increased to 0.5. Given the absence of regular breathing (HR over 100 bpm), tracheal intubation with a No. 3.5 endotracheal tube was performed at 3 minutes of life, MV was started via ETT with the following parameters: PIP = 25–35 cm H_2O, PEEP = 7.0 cm H_2O, RR = 45–60 per min, FiO_2 up to 1.0. A gastric tube was inserted, and 5.0 ml of dark-green amniotic fluid were obtained. Given the progression of hypoxemia, tracheal suction was performed twice via ETT using a meconium aspirator, and an abundant amount of green amniotic fluid was obtained. By the minute 10 of life, the need for 100 % oxygen remained, SpO_2 was within 60–80 %. Attempts to increase peak inspiratory pressure and switch to HFOV were ineffective, SpO_2 did not rise above 60–70 %. Heart sounds were muffled and were heard in the typical location. Breathing was heard equally on both sides. According to the acid-base balance (ABB) assessment data, severe metabolic disturbances were detected in the umbilical cord blood: pH = 6.97, pCO_2 = 50.4, lactate = 10.3 mmol/l, BE = –18.3 mmol/l.

At the age of 15 minutes of life, umbilical vein catheterization was performed, 0.9 % sodium chloride solution was slowly administered intravenously by jet stream at a dose of 10 ml/kg. Hypoxemia progressed. By the minute 40 of life, SpO_2 was within 48–75 %, total cyanosis, prominent mottling, convulsions, rare gaspings. In the operating delivery room, the baby was transferred to HFOV using the SLE 5000 device in the high frequency ventilation (HFV) mode with the following parameters: MAP = 18 cm H_2O, amplitude (delta P) = 40 cm H_2O, frequency (f) = 9 Hz, FiO_2 = 1.0, inspiratory to expiratory ratio (I:E) = 1:2. In this regard, SpO_2 fluctuated within 48–70 %. Heart sounds were muffled and heard in the typical location. Breathing on the right side became worse. According to the acid-base balance analysis, a severe hypercapnia and metabolic disorders (pH = 6.83, pCO_2 = 31 mm Hg, lactate = 25 mmol/l, BE = –12.2 mmol/l) were recorded. Chest X-ray data detected free gas in both pleural cavities. A puncture of both pleural cavities was performed, 40 ml of air was removed from each side. A pediatric surgeon was called, pleural drains were installed on both sides, with starting passive aspiration. HFOV parameters were changed as follows: MAP = 22 cm H_2O, delta P = 50 cm H_2O, f = 9.0 Hz, FiO_2 = 1.0, I:E = 1:2. No positive effect was achieved from the performed manipulations, a progressively increasing hypoxemia and bradycardia was noted. Critical bradycardia

Table 1. Main characteristics of the studies included in the meta-analysis [34].

Таблица 1. Основные характеристики исследований, включенных в метаанализ [34].

Study Исследование	Experiment / control (gestational age) Эксперимент / контроль (гестационный возраст)	Patient age of lavage procedure (hour) Возраст проведения лаважа (час)	Lavage volume Объем лаважа	Lavage type Вид лаважа	Surfactant, preparation concentration, country of origin Сурфактант, концентрация препарата, страна-производитель
Lam B.C. et al. (1999) [35]	6/6 (39,3 ± 0,2 / 40,8 ± 0,4 weeks) (39,3 ± 0,2 / 40,8 ± 0,4 нед)	3 (2–6)	15 mL/kg 15 мл/кг	Not available Не указано	Survanta (bovine), 5.0 mg/mL, USA Сурванта (бычий), 5,0 мг/мл, США
Kowalska K. et al. (2002) [36]	11/11 (> 35 weeks) (> 35 нед)	< 6	15 mL/kg 15 мл/кг	0.9 % NaCl + surfactant 0,9 % NaCl + сурфактант	Survanta (bovine), 5.0 mg/mL, USA Сурванта (бычий), 5,0 мг/мл, США
Schlösser R.L. et al. (2002) [37]	11/7 (38–42 weeks) (38–42 нед)	Not available Не указано	20 mL 20 мл	Diluted surfactant Разведенный сурфактант	Survanta (bovine), 5.0 mg/mL, USA Сурванта (бычий), 5,0 мг/мл, США
Wiswell T.E. et al. (2002) [38]	15/7 (39,9 ± 1,2 / 39,4 ± 1,9 weeks) (39,9 ± 1,2 / 39,4 ± 1,9 нед)	14–15	16 mL/kg for the three times 16 мл/кг за 3 введения	Diluted surfactant Разведенный сурфактант	Surfaxin (synthetic), 2,5–10 mg/mL, USA Сурфаксин (синтетический), 2,5–10 мг/мл, США
Chang H.Y. et al. (2003) [39]	12/10 (39,3 ± 0,6 / 39,7 ± 1,6 weeks) (39,3 ± 0,6 / 39,7 ± 1,6 нед)	4,2 (2–7) or 5,2 (2–9) 4,2 (2–7) или 5,2 (2–9)	6–7 or 12–14 mL/kg 6–7 или 12–14 мл/кг	Разведенный сурфактант Diluted surfactant	Survanta (bovine), 5.0 or 10 mg/mL, USA Сурванта (бычий), 5,0 или 10 мг/мл, США
Salvia-Roigés M.D. et al. (2004) [40]	7/6 (39–41 weeks) (39–41 нед)	6	15 mL/kg 15 мл/кг	0.9 % NaCl + surfactant 0,9 % NaCl + сурфактант	Survanta (bovine), 3.0 mg/mL, USA Сурванта (бычий), 3,0 мг/мл, США
Dargaville P.A. et al. (2007) [41]	8/34 (37–42 weeks) (37–42 нед)	23 (8–83)	15 mL/kg for the three times 15 мл/кг за 3 введения	0.9 % NaCl + surfactant 0,9 % NaCl + сурфактант	Survanta (bovine), 5.0 mg/mL, USA Сурванта (бычий), 5,0 мг/мл, США
Lee S.M. et al. (2008) [42]	7/8 (37–42 weeks) (37–42 нед)	10,35 ± 6,35	20 mL/kg for the three times 20 мл/кг за 3 введения	0.9 % NaCl + surfactant 0,9 % NaCl + сурфактант	Newfactan (bovine), 5.3 mg/mL, South Korea Ньюфактан (бычий), 5,3 мг/мл, Южная Корея
Dargaville P.A. et al. (2011) [26]	30/35 (38–41 weeks) (38–41 нед)	14,0 ± 5,9	15 mL/kg for the two times 15 мл/кг за 2 введения	0.9 % NaCl + surfactant 0,9 % NaCl + сурфактант	Survanta (bovine), 5.0 mg/mL, USA Сурванта (бычий), 5,0 мг/мл, США
Gu H.R. (2018) [43]	51/51 (40,37 ± 1,10 / 40,33 ± 1,05 weeks) (40,37 ± 1,10 / 40,33 ± 1,05 нед)	Not available Не указано	3–5 mL once, three times 3–5 мл однократно, 3 раза	0.9 % NaCl + surfactant 0,9 % NaCl + сурфактант	Curosurf (pork), 12 mg/mL, Italy Куросурф (свиной), 12 мг/мл, Италия
Bandiya P et al. (2019) [44]	31/29 (38–39 weeks) (38–39 нед)	≤ 2	20 mL/kg 20 мл/кг	0.9 % NaCl + surfactant 0,9 % NaCl + сурфактант	Survanta (bovine), 5.0 mg/mL, USA Сурванта (бычий), 5,0 мг/мл, США

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developed at the minute 70 of life (HR less than 60 bpm). Chest compression was started in parallel with MV at FiO_2 = 1.0; every 3 minutes, a 0.1 % adrenaline solution at a dilution of 1:10000 was administered intravenously at a dose of 0.2 ml/kg/once; 8.0 minutes after the onset of resuscitation procedure, HR increased to more than 100 bpm; chest compression was stopped; SpO_2 gradually increased to 80–85 %. The development of bradycardia was assessed as possible sequelae of HFOV, so the child was transferred to CMV in Assist Control (AC) mode with the parameters: PIP = 38–40 cm H_2O, PEEP = 8.0 cm H_2O, RR = 60 per min, FiO_2 = 1.0. SpO_2 was possible to maintain within 80–88 % only by using such MV parameters, otherwise it decreased to 45–50 %. Given the observed decompensated metabolic acidosis, 4.0 % sodium bicarbonate was administered intravenously at a rate of 4.0 ml/kg/once.

To exclude a critical congenital heart defect (CHD), echocardiography (Echo-CG) was performed in the operating room, revealing a prominent myocardial hypertrophy of both ventricles and the interventricular septum with outflow tract obstruction in the both ventricles. Blood pressure monitoring was started, not measured at the first two hours of life. A decision was made to perform combined inotropic and vasopressor support in the operating delivery room. BP was gradually increased to 66/27 mm Hg. To prevent hypoglycemia, intravenous administration of a 10 % glucose solution was started. To optimize cardiotonic and infusion therapy, catheterization of the right jugular vein was performed under ultrasound (US) control; during X-ray control, the catheter was installed correctly, the outflow was confident. SpO_2 gradually increased to 88 %, periodically to 90–91 %. According to the ABB data, before the child was transferred from the operating room to the neonatal intensive care unit (NICU), positive dynamics was noted: pH = 7.12, pCO_2 = 51 mm Hg, lactate = 7.0 mmol/l, BE = –11.7 mmol/l.

The child had total skin, nails and hair stained with green amniotic fluid since birth, marked green meconium-stained skin peeling in large layers all over the body, "bath attendant" feet and "washerwoman" palms, dense skull bones were observed. After extremely serious condition of the baby was stabilized at the age of 4 hours of life in transport incubator on CMV with the parameters PIP = 38 cm H_2O, PEEP = 7.0 cm H_2O, RR = 60 per min, FiO_2 = 1.0, under continuous monitoring and ongoing cardiotonic therapy, the patient was transferred to the NICU. Immediately upon admission, HFOV with the following parameters was started: MAP = 22 cm H_2O, delta P = 50 cm H_2O, f = 9 Hz, FiO_2 = 1.0, I:E = 1:2. However, hypoxemia persisted with a stably decreased SpO_2 to 80–84 % or less. Increasing the HFOV parameters did not improve SpO_2, leading to decreased BP. Attempts to switch to CMV were unsuccessful; a marked decline in SpO_2 was noted. According to Echo-CG, PPHN signs were detected with increased mean pulmonary artery pressure to 90 mm Hg, inhalation of nitric oxide (iNO) was started using the AIT-NO-01 Tianox device (RFNC-VNIIEF, Russia) with 20 ppm (parts per million). Positive dynamics in oxygenation was not obtained. In parallel, the child's arterial hypotension progressed, which was alleviated using combined cardiotonic support; levosimendan was added to PPHN treatment.

In the treatment of pneumothorax, it was necessary that passive-to-active air aspiration from the pleural cavities was performed. At the age of 12 hours of life OI was 48. According to the chest and abdominal cavity radiography at the age of 12 hours of life, areas of moderate-intensity darkening were found spread throughout all parts of the lung fields, a positive symptom of air bronchograms, mediastinum shadow not expanded, the diaphragm, sinuses not traced, ETT in the Th2 projection, free air in the pleural cavities not determined, pneumatization of intestinal loops not observed (**Fig. 1**).

Taking into account deteriorating hypoxemia and the presence of typical clinical and radiological MAS signs in the child, the medical consultative board decided to perform surfactant lung lavage at the age of 12 hours of life (medical consultative board protocol on "off-label" drug prescription, neonatology subgroup of the Vorokhobov City Clinical Hospital No. 67, No. 656A dated of August 11, 2023). For this, poractant alpha at a dose of 100 mg/kg and at the rate of 15 ml/kg was diluted in physiological sodium chloride solution (poractant alpha was first drawn into a 60 ml syringe, and then a 0.9 % sodium chloride solution). The resulting surfactant solution was mixed carefully without shaking. Then, through a thin 5Fr-diameter catheter, the prepared solution was quickly instilled (in 30–40 sec) into the ETT of the newborn followed by its removal by open active aspiration using an aspiration catheter with vacuum control, connected to a sterile disposable transparent container. TBT sanitization was performed after 10 second-manual vibrating chest compression. About 25–30 ml of pink-colored content with meconium admixture was obtained from the ETT during TBT sanitization. During TBT lavage, the child showed a short-term (within 50 seconds) decrease in SpO_2 to 75 % and HR from 180 to 120 bpm, followed by rapidly recovered examined parameters. After TBT surfactant lavage, SpO_2 gradually, over 5–7 minutes, rose to 96–98 %, allowing for slowly reducing MAP first to 18 cm H_2O, and then gradually to 15 cm H_2O and less. OI 1 hour after TBT lavage (at the age of 13 hours of life) decreased first to 30, then to 20, and over several days, OI gradually decreased to 10. After TBT surfactant lavage, lung field pneumatization improved. No further episodes of severe hypoxemia with

SpO_2 lowered below 90 % were observed. Two days after TBT lavage, nitric oxide inhalation was discontinued. Central hemodynamics also gradually normalized in parallel with hypoxemia relief. On day 7 of life, cardiotonic therapy was completely discontinued.

On day 5 and day 10 of life, the left-sided and right-sided pneumothorax, respectively, was arrested. Up to the day 15 of life, the child required HFOV with FiO_2 = 1.0, then was transferred to CMV. On day 18 of life, the child was extubated and transferred to non-invasive 7 day-long HFOV. Then the child was transferred to non-invasive respiratory support at the DuoPAP mode (biphasic positive airway pressure), but continued to require additional oxygen supply, FiO_2 = 0.4, hypercapnia persisted within 55–60 mm Hg. On day 39 of life, it was possible to switch to high-flow cannulas using the AIRVO™ 2 device (Fisher&Paykel Healthcare, New Zealand) with the following parameters: FiO_2 = 0.3, oxygen flow = 12.0 L/min. At the age of 60 days of life, the child was transferred to breathing through oxygen cannulas with an oxygen flow of 1.0 L/min and FiO_2 = 1.0.

Later, the child was gradually transferred to mask oxygen therapy with a flow of 0.5 L/min, oxygenation remained stable, SpO_2 more than 95 %, the level of blood carbon dioxide decreased to 40–50 mm Hg. However, during mask oxygen therapy, at the age of 80 days of life, the child began to suck worse, weight gain decreased, although dyspnea, participation of accessory muscles and the need for additional oxygen did not increase, so the child was transferred back to oxygen cannulas with a flow of 0.5–1.0 L/min. According to chest X-ray examination **(Fig. 2**), at the second month of life, symptoms typical to bronchopulmonary dysplasia (BPD) appeared.

At second and third months of life, inhalation therapy with fenoterol and ipratropium bromide (Berodual®, Boehringer Ingelheim International, Germany) and budesonide (Pulmicort®, AstraZeneca, Sweden), systemic steroid therapy with dexamethasone (two 10-day courses with 1-month interval) were carried out in accordance with the clinical guidelines “Bronchopulmonary dysplasia” [47].

In parallel, 72 hour-long general therapeutic hypothermia was observed within the first two hours of life, because the child was born in severe asphyxia. In the neurological status, coma occurred from birth, clonic seizures confirmed by the amplitude-integrated electroencephalography (aEEG) data were stopped at the first week of life during combined anticonvulsant therapy. Subsequently, seizures did not recur later, anticonvulsant therapy was gradually discontinued by the end of the second month of life. According to brain magnetic resonance imaging (MRI), isolated microhemorrhages were noted in the substance of the parietal and occipital lobes, hypoplasia of the corpus callosum, mildly dilated external and internal cerebrospinal fluid spaces, and a retrocerebellar arachnoid cyst were found. Child enteral feeding was started from day 5 of life by using expressed breast milk, followed by a rapid increase in feeding volume to the age range. At the second month of life, the child began to suck effectively from a bottle, however, due to persistent severe respiratory failure during BPD, enteral feeding was carried out mainly through a gastric tube until the age of almost three months to reduce physical activity.

During the first month of life, the child required antibacterial therapy with drug correction based on the clinical, instrumental and laboratory symptoms, taking into

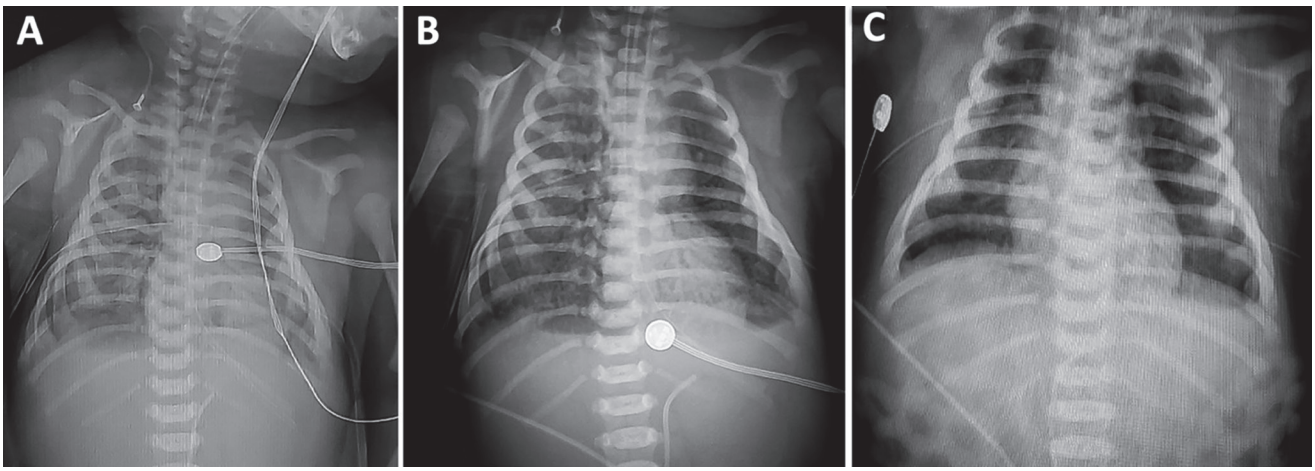

Figure 1. A series of radiographs of the child during the first day of life: **A** – the condition of the lungs after tension pneumothorax relief in the delivery room at the child's age of the first two hours of life; **B** – the patient's lungs immediately after the surfactant lung lavage procedure; **C** – the condition of the lungs by the end of the first day of life (artifacts – a water mattress of the hypothermia system).

Рисунок 1. Серия рентгенограмм ребенка в течение первых суток жизни: **A** – состояние легких после купирования напряженного пневмоторакса в родильном зале в возрасте первых двух часов жизни; **B** – легкие пациента сразу после процедуры сурфактантного лаважа; **C** – состояние легких к концу первых суток жизни (артефакты – водяной матрасик системы гипотермии).

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account severe lung damage and persistence of bilateral pneumonia, the presence from birth and dynamic persistence of laboratory systemic inflammatory markers: at the first week of life, higher C-reactive protein (CRP) to 80 mg/L, procalcitonin (PCT) level up to 30 pg/ml, interleukin (IL) IL-6 level more than 1000 pg/ml, neutrophilic index (NI) on day 2 of life reached 0.6, with thrombocytopenia persisted. Examination for intrauterine infections (cytomegalovirus, herpes simplex virus type 1, 2, toxoplasmosis, ureaplasmosis, chlamydia, mycoplasmosis, listeriosis) from various sites (including sterile sites) revealed none of such pathogens in the child. Bacteriological examination of material from various sites (oropharynx, anus, blood, sputum), collected at the first hours of life, found no microbial growth.

The child was discharged home at the age of 3.5 months of life, weighing 5064 g (3.5 month-long weight gain was 864 g) without additional oxygen supply; when breathing room air SpO_2 was consistently over 95 %. The child actively and completely sucked all additional enteral nutrition from the bottle. Throughout the entire hospitalization period, the mother was with the child for care. At the age of 8 months of life, the child's neuropsychic development was age-matched, with mild protein-energy deficiency observed.

Discussion / Обсуждение

Here, we presented a clinical observation demonstrating severe combined perinatal pathology (severe intranatal asphyxia, cerebral ischemia, meconium aspiration syndrome) with severe MAS, which accounted for developing critical condition of the child at the second hour of life requiring even cardiopulmonary resuscitation paralleled with progressive hypoxemia due to cardiopulmonary failure. We believe that the primary factor underlying development of multiple organ failure in this clinical case resulted from lung damage due to meconium aspiration. The major risk factor in arising MAS was postmaturity. An increase in the oxygenation index to 48 at the first 12 hours of life evidenced about respiratory failure refractory to traditional therapy and, in essence, served an indication for ECMO procedure [25, 48], which, however, was unavailable in the perinatal center where the child was medically assisted. Unfortunately, rehospitalization to a medical facility able to provide ECMO was impossible due to patient's extremely severe unstable condition. Selection of medical strategy, modes and parameters of invasive respiratory therapy (CMV, HFOV, iNO), correction of hemodynamic disorders were poorly efficient in alleviating hypoxemia, which persisted and progressively deteriorated.

We consider using TBT lavage with poractant alfa surfactant in this clinical case was a desperate procedure, which ultimately resulted in prominent rapid positive effect and ensured not only patient survival, but also sustained prognosis without the ECMO being associated with serious technical difficulties and complication risks [48, 49]. Indeed, meta-analysis by Al. El Shahed et al. (2014) [50] and study by H.C. Lin et al. (2005) [16] corroborate that surfactant preparations used in MAS may reduce respiratory disease severity and the rate of progressive respiratory failure requiring ECMO-based support.

The positive effect after using surfactant lung lavage might be achieved because meconium sorbed on particles of exogenously administered surfactant was removed more effectively during the procedure [28]. The effectiveness of such therapeutic approach is related to compensated secondary deficiency of endogenous surfactant inevitably developing in MAS, because meconium deactivates surfactant and may inhibit its own production [51], which can be additionally contributed by hemoglobin and plasma proteins flooding into the lungs during MAS [52, 53]. Some meconium components, especially free fatty (palm, stearic, oleic) acids have a minimal surface tension higher than surfactant, so that the alveolar surface decreases and triggers diffuse atelectasis [54].

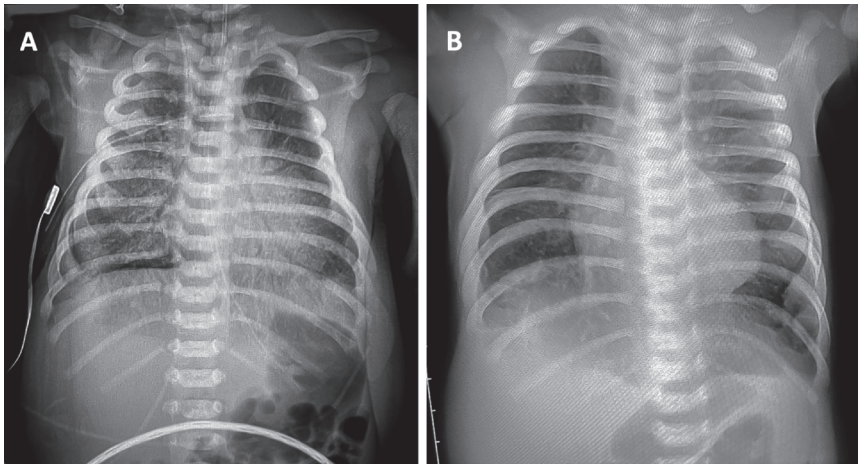

Figure 2. X-ray lung imaging of the patient at the age of the end of the first week of life (**A**) and at the age of 34 days of life (**B**).

Рисунок 2. Легкие пациента на рентгенограмме в возрасте конца первой недели жизни (**A**) и в возрасте 34 суток жизни (**B**).

I.V. Vinogradova and G.I. Nikiforova (2011) concluded that the positive effects after using surfactant emulsion are primarily coupled to its high sorption capacity [33]. Electron microscopy of the Surfactant-BL emulsion reveals vesicles 0.2–0.5 μm in size, forming 1.6–1.8 μm aggregates, so that about 10^8 particles are contained per 1 mg preparation [55], serving as a sorption platform for meconium during bronchoalveolar lavage.

The doubts regarding potential alterations in poractant alpha properties diluted with 0.9 % sodium chloride solution may be dispelled by referring to the drug instruction indicating that the main solvent for poractant alpha is 0.9 % physiological sodium chloride solution. Hence, a decrease in surfactant preparation concentration or an increase in its volume using this solvent should not be considered as the measures affecting preparation structure. Previously, A.V. Mostovoi et al. (2023) conducted a prospective randomized controlled trial demonstrating safety and better poractant alfa rheological properties after dilution. In this regard, a viscosity level for two-fold diluted poractant alfa almost reached that of ordinary water, and improved clinical outcomes in premature infants while maintaining standard dosing [56].

Moreover, according to J. van der Bleek et al. (1993), using large volume for surfactant lavage leads to a more homogeneous/uniform surfactant distribution and deposition in the lungs [57]. Importantly, a clinical effect is accounted for by surfactant lavage volume. In this regard, P. Bandiya et al. (2018) failed to show a positive effect from lung surfactant lavage in newborns with moderate or severe MAS on the length of respiratory support primarily due to usage of small volume diluted bovine surfactant. In addition, it was also noted that the lavage procedure *per se* was well tolerated by children [44]. At the same time, G. Lista et al. (2006) [58] as well as T. Lejeune and R.E. Pfister (2005) [59] observed better oxygenation after lung lavage even using porcine surfactant at small volume in newborns with MAS.

However, in 2019 S. Arayici et al. in one of the first prospective randomized studies used high-volume (15 ml/kg) vs. bolus porcine surfactant lung lavage in treatment of newborns with MAS [29]. Unlike G. Lista et al. [58], T. Lejeune and R.E. Pfister [59] and P. Bandiya et al. [44], S. Arayici et al. [29] believe that it is the large volume of "flushing" solution exerts most beneficial effect with sustained improvement of oxygenation. In our clinical observation, we used a large lavage (15 ml/kg) volume, which the child tolerated satisfactorily.

Regarding a large-volume surfactant lavage, a technology for recovery of lavage fluid from TBT represents a crucial practical issue. In this context, the study by P.A. Dargaville et al. (2008) [60] is of particular interest, which we relied on while deciding to choose a technology to recover return fluid from TBT. MAS was induced experimentally in 2-week-old piglets underwent MV, by administering a 20 % solution of human meconium at a dose of 4.0 ml/kg. Lung lavage with either two 8 ml/kg saline aliquots (n = 5) or a single 15 ml/kg aliquot (n = 6) was performed immediately after meconium instillation. Lavage fluid was recovered by three methods performed in sequence: closed suction via a suction adaptor; open suction with the ventilator disconnected, and open suction with manual vibratory chest squeezing. Closed suction resulted in poor meconium and fluid returns, whereas chest squeeze during suction increased recovery of both meconium and lavage fluid. Overall recovery of instilled meconium was greater with 15 ml/kg lavage (45 ± 17 %) than with two 8.0 ml/kg aliquots (24.0 ± 4.5 %; p = 0.028; ANOVA); the corresponding values for return of lavage fluid were 73 ± 10 % and 49 ± 13 %, respectively (p < 0.01). It turned out that open suction, vibratory chest squeezing and larger aliquot volume (15 ml/kg) each improve the efficacy of lung lavage in MAS [60]. In our clinical observation, the amount of aspirate after lavage administration was about 40–50 % of instillation volume.

In the presented clinical observation, surfactant lung lavage was performed at the patient's age of 12 hours of life (due to extremely unstable central hemodynamics), not contradicting the data for other published studies, where the patient age for performing lavage ranged from 2 to 83 hours of life (**Table 1**) [34].

Thus, numerous studies assessing surfactant lavage in MAS both experimentally and in newborns by using natural (Curosurf, Survanta, Surfactant-BL), semi-synthetic (Neufactan) and synthetic (CHF5633, Lucinoctant or Surfaxin) surfactants, instilled at different volumes of dilute surfactant and applying distinct strategies for its administration, show a consensus that this technology may reduce further progression of respiratory failure (including a need for ECMO); however, the issue of improving morbidity and mortality incidence due to lung diseases remains controversial. For example, P.A. Dargaville et al. [26] and T.E. Wiswell et al. [14] showed no significantly decreased pneumothorax risk developing during lavage. At the same time, H.Y. Chang et al. (2003) [39], M.D. Salvia-Roige´s et al. (2004) [40] and S. Arayici et al. (2019) [29] demonstrated lower pneumothorax incidence, although not clearly describing the timing for pneumothorax development (before or after the lung lavage). Unfortunately, virtually no data about development of serious and extremely rare lung disease for full-term post-MAS newborns such as BPD are available. Such clinical cases were solely described in the work by H.C. Lin et al. (2005) reporting BPD development in 2 (1.0 %) of 198 full-term newborns with MAS born in a single hospital over 9 years [16]. The clinical observation presented by us provides additionally that a mature, even post-term child with MAS subsequently developed a typical BPD, which required proper treatment.

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Conclusion / Заключение

The clinical case presented here has been repeatedly observed in practice, which required to perform tracheobronchial tree lavage with surfactant in an aliquot of 15 ml/kg followed by bolus surfactant instillation after lung lavage. However, the current clinical observation is the first case among Russian medical publications when surfactant replacement therapy (off-label) allowed to avoid ECMO in a patient who had indications for its application. Such respiratory therapy seems to be an effective and fairly safe approach to lower risk of ECMO, air leak syndrome in full-term newborns with severe MAS manifestations. To identify the most effective strategies, it is necessary to prepare and conduct comprehensive multicenter clinical trials.

ARTICLE INFORMATION	ИНФОРМАЦИЯ О СТАТЬЕ
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Author's contribution	**Вклад авторов**
Mostovoi A.V., Karpova A.L. – conceived the study, analyzed the clinical observation data, worked with literature sources, wrote, edited and prepared the manuscript; Popov I.V. – presented the patient case at the neonatal intensive care unit stage; Anikeeva L.A. – presented the patient case at the neonatal pathology unit and premature infants; Karpov N.Yu. – conducted literature search, worked with literature sources, edited the manuscript.	Мостовой А.В., Карпова А.Л. – автор идеи, анализ клинического наблюдения, работа с источниками литературы, написание, редактирование и подготовка статьи к публикации; Попов И.В. – представление информации о пациенте на этапе отделения реанимации и интенсивной терапии новорожденных; Аникеева Л.А. – представление информации о пациенте в отделении патологии новорожденных и недоношенных детей; Карпов Н.Ю. – поиск литературы, работа с источниками литературы, редактирование статьи.
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Patient consent	**Согласие пациента**
The mother signed informed voluntary consent to release the data in anonymized form.	Мать пациента подписала информированное добровольное согласие на разглашение данных в анонимной форме.
Ethics declarations	**Этические аспекты**
Patient management was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (as revised in 2013).	Ведение пациента осуществлялось в полном соответствии с этическими принципами, включая положения Хельсинской декларации Всемирной медицинской ассоциации (пересмотр 2013 г.).
Online content	**Онлайн-контент**
The online version contains supplementary material available at the external sources. Additional file 1: Appendix 1. Video demonstration of surfactant lung lavage for this patient – YouTube. Additional file 2: Appendix 2. Video demonstration of surfactant lung lavage for this patient – VK Video.	Онлайн-версия содержит дополнительные материалы, доступные на внешних первоисточниках. Дополнительный файл 1: Приложение 1. Видеодемонстрация проведения сурфактантного лаважа легких данному пациенту – YouTube. Дополнительный файл 2: Приложение 2. Видеодемонстрация проведения сурфактантного лаважа легких данному пациенту – VK Видео.
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About the authors / Сведения об авторах :
Aleksei V. Mostovoi, MD, PhD / **Мостовой Алексей Валерьевич**, к.м.н. E-mail: valmost@mail.ru. ORCID: https://orcid.org/0000-0002-7040-9683. Scopus Author ID: 57201723894. Wos ResearcherID: AAR-7908-2021.
Anna L. Karpova, MD, PhD / **Карпова Анна Львовна**, к.м.н. ORCID: https://orcid.org/0000-0002-1024-0230.
Igor V. Popov, MD / **Попов Игорь Владимирович**. ORCID: https://orcid.org/0000-0002-0530-2310. Wos ResearcherID: F-7040-2016.
Lubov' A. Anikeeva, MD / **Аникеева Любовь Алексеевна**. ORCID: https://orcid.org/0009-0001-0210-4669.
Nikolai Yu. Karpov, MD / **Карпов Николай Юрьевич**. ORCID: https://orcid.org/0000-0001-6728-726X.

Appendix 1. Video demonstration of surfactant lung lavage for this patient – YouTube (https://youtu.be/bDDTnkt_6Qo?si=jchFi2YjnSpbFXbN). Hyperlink to an external source that is not controlled by the editors of «Obstetrics, Gynecology and Reproduction» Journal.
Приложение 1. Видеодемонстрация проведения сурфактантного лаважа легких данному пациенту – YouTube (https://youtu.be/bDDTnkt_6Qo?si=jchFi2YjnSpbFXbN). Гиперссылка на внешний первоисточник, который не контролируется редакцией журнала «Акушерство, Гинекология и Репродукция».

Appendix 2. Video demonstration of surfactant lung lavage for this patient – VK Video (https://vk.com/video414435049_456239024). Hyperlink to an external source that is not controlled by the editors of «Obstetrics, Gynecology and Reproduction» Journal.
Приложение 2. Видеодемонстрация проведения сурфактантного лаважа легких данному пациенту – VK Видео (https://vk.com/video414435049_456239024). Гиперссылка на внешний первоисточник, который не контролируется редакцией журнала «Акушерство, Гинекология и Репродукция».

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