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# RISK FACTORS ASSOCIATED WITH PROLONGED MECHANICAL VENTILATION IN VERY LOW BIRTH WEIGHT INFANTS

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# Summary

Introduction. Mechanical ventilation (MV) remains a life-saving intervention for the sickest very low birth weight (VLBW) neonates. Despite the widespread use of non-invasive respiratory support, many VLBW neonates require some duration of MV during their initial hospitalization. As prolonged exposure to MV is associated with adverse outcomes in VLBW infants, it is important to identify the factors that influence the duration of this intervention.

The study aimed to determine the factors affecting the duration of MV in VLBW infants.

Material and methods. Data from a prospectively created computerized database were used in a retrospective cohort study. The database included information on 1086 VLBW infants < 32 weeks' gestation who were ventilated at any time during their hospitalization at the tertiary care hospital between January 2010 and December 2020. Factors that potentially influenced the duration of MV were examined.

The research was carried out in compliance with the requirements of bioethics as part of the planned scientific work of the department (state registration number 0117U001083).

The data obtained were analyzed using descriptive and comparative statistics, as well as Spearman's rank correlation coefficient and one-way analysis of covariance (ANCOVA). Measurements with normal distribution are presented as mean (standard deviation). Non-parametric continuous data are presented as median (interquartile range). All values were considered significant when p < 0.05.

The study was carried out as a part of the planned scientific work of the department "Clinical-laboratory and instrumental substantiation of differential approaches to diagnosis, treatment and prevention of childhood diseases" (state registration number 0122U000164) without external sources of funding.

**Results.** According to univariant analysis, bronchopulmonary dysplasia (BPD) (rS=0.32, p<0.05), severe BPD (rS=0.418, p<0.05), pneumothorax (rS=0.06, p=0.05), severe intraventricular hemorrhages (IVH) (rS=0.255, p<0.05), periventricular leukomalacia (PVL) (rS=0.15, p<0.05), sepsis (rS=0.087, p<0.05), necrotizing enterocolitis (rS=0.088, p<0.05), longer duration of antibiotic therapy (rS=0.168, p<0.05), and a lower gestational age (rS=0.118, p<0.05) were associated with longer duration of MV in VLBW infants. At the same time, BPD (rS=18.544, rS=0.0001), severe BPD (rS=109.810, rS=0.0001), severe IVH (rS=23.859, rS=0.0001), PVL (rS=15.031, rS=0.0001), and more days of antibiotic therapy (rS=13.173, rS=0.0001) significantly and independently affected the duration of MV based on the results of one-way ANCOVA.

**Conclusion.** Severe lung and brain injury and prolonged antibiotic exposure were the main risk factors that significantly and independently prolonged MV in VLBW infants.

Keywords: Duration of Mechanical Ventilation; Risk Factors; Very-low-birth-weight Infants.

## Introduction

Mechanical ventilation (MV) is an important intervention to treat respiratory failure and reduce mortality in very low birth weight (VLBW) infants [1]. Severe respiratory failure is a common problem in extremely preterm infants. Most of them may initially require MV to maintain adequate ventilation and oxygenation due to weak respiratory effort, incomplete lung development and surfactant deficiency, or when non-invasive respiratory support fails [2, 3]. Approximately half of extremely preterm neonates require MV due to failure of continuous positive airway pressure after birth [4] or fail their first extubation attempt and require resumption of MV [5]. Despite the important role of MV in reducing mortality in premature infants with severe lung disease, its prolonged use is often associated with complications [6]. The duration of MV exposure determines outcomes in VLBW infants. Immature lungs are more susceptible to damage and MV increases the risk of secondary lung injury [2, 7, 8]. Prolonged MV is associated with an increased incidence of BPD [6, 9] and influences its severity [10]; increases the risk of pulmonary hypertension, of prematurity retinopathy requiring

correction, periventricular leukomalacia (PVL), and is associated with prolonged hospital stay, postnatal growth failure [6], mortality, neurodevelopmental impairment [11, 12], and feeding problems [12]. The use of MV in VLBW infants during the neonatal period was significantly associated with a history of asthma by 12 years of age and a higher incidence of bronchial hyperresponsiveness [13]. Data on risk factors associated with prolonged MV are limited. Very preterm infants may require prolonged MV for a variety of reasons. Given the adverse outcomes associated with prolonged MV, it is important to identify risk factors that influence the duration of MV to improve outcomes in VLBW infants.

**The study aimed** to determine the factors affecting the duration of MV in VLBW infants with GA < 32 weeks.

# Material and methods

Data from a prospectively created computerized database were used in a retrospective cohort study. The database included information on 1086 VLBW infants < 32 weeks' gestation who were treated with MV at

any time during their hospitalization at the tertiary care hospital between January 2010 and December 2020.

The main perinatal characteristics (maternal morbidity and complications of pregnancy and delivery, multiple gestation, antenatal steroid prophylaxis, cesarean section, need for resuscitation, BW and GA), morbidities such as respiratory distress syndrome (RDS), BPD, pneumothorax, intrapartum hemorrhage, and neonatal death were recorded, pneumothorax, intraventricular hemorrhage (IVH), PVL, patent ductus arteriosus (PDA), sepsis, and necrotizing enterocolitis (NEC), as well as medical interventions (surfactant administration, duration of antibiotic therapy) that may affect the duration of MV.

# **Database clinical definitions**

RDS was diagnosed based on the need for supplemental oxygen to maintain pulse oximeter saturation above 90% within the first 24 hours of life and radiographic data consistent with the disease. BPD was diagnosed at 36 weeks of PMA according to the clinical definition after an oxygen reduction test [16, 17]. IVH and PVL were assessed by head ultrasound and at autopsy when appropriate. IVH severity was graded according to Papille [18]. PDA was confirmed by Doppler echocardiography. NEC was diagnosed according to modified Bell's criteria [19].

Standard respiratory support protocols were applied to all neonates with routine monitoring of vital signs and arterial blood gas measurements.

The study was approved by the Ethics Committee of Danylo Halytsky Lviv National Medical University on 3 March 2011 (Act №3).

The data obtained were analyzed using descriptive and comparative statistics, as well as Spearman's rank correlation coefficient and one-way analysis of covariance (ANCOVA). Measurements with normal distribution are presented as mean (standard deviation). Non-parametric continuous data are presented as median (interquartile range). All values are considered significant when p <0.05..

The study was carried out as a part of the planned scientific work of the department "Clinical-laboratory and instrumental substantiation of differential approaches to diagnosis, treatment and prevention of childhood diseases" (state registration number 0122U000164) without external sources of funding.

## Results and discussion

The study included 1086 VLBW infants who received MV at any time during the hospitalization. The mean gestational age of the infants included in the analysis was 27.599 (2.238) weeks. Approximately half of the infants were treated with surfactant. Six hundred seventy-eight (62.43%) of the infants survived to discharge. The median duration of MV was 47 (10-103) hours (Table 1).

It was found that lower GA, higher incidence of severe IVH, periventricular leukomalacia, BPD and especially its severe form, pneumothorax, sepsis, NEC, and more days of antibiotic therapy were significantly associated with longer duration of MV based on the results of univariate analysis (Table 2).

Bronchopulmonary dysplasia (F=18.544, p<0.0001), severe BPD (F=109.810, p<0.0001), severe IVH (F=23.859, p<0.0001), PVL (F=15.031, p<0.0001), and longer duration of antibiotic therapy (F=13.173, p<0.0001) significantly and independently increased the duration of MV based on a one-way analysis of covariance. The largest proportion of this effect was associated with severe BPD ( $\eta$ 2 = 0.093).

Although MV remains a life-saving treatment, especially for extremely preterm infants, prolonged exposure to MV is a significant risk factor for BPD, neurodevelopmental impairment, and other complications in very preterm infants.

In this retrospective cohort study, we describe a cohort of 1086 VLBW infants with GA < 32 weeks who were treated with MV at any time during their hospitalization and the factors influencing the duration of MV.

Table 1

Demographic and clinical characteristics of the cohort

Characteristics	Value
Gestational age, weeks <sup>1</sup>	27.599 (2.238)
Birth weight, g <sup>1</sup>	1007.181 (261.873)
Antenatal steroids <sup>2</sup>	860 (79)
Caesarean section <sup>2</sup>	464 (43)
Multiple pregnancies <sup>2</sup>	277 (26)
Intubation and ventilation at birth <sup>2</sup>	632 (58)
Surfactant administration <sup>2</sup>	534 (49)
Pneumothorax <sup>2</sup>	38 (3)
Bronchopulmonary dysplasia <sup>2</sup>	135 (12)
Severe bronchopulmonary dysplasia <sup>2</sup>	49 (5)
Duration of endotracheal MV, hours <sup>3</sup>	47 (10-103)
Intraventricular hemorrhage, grade 3-42	179 (16)
Periventricular leukomalacia <sup>2</sup>	60 (6)
Necrotizing enterocolitis <sup>2</sup>	41 (4)
Hemodynamically significant patent ductus arteriosus <sup>2</sup>	176 (16)
Sepsis <sup>2</sup>	165 (15)
Antibiotic therapy duration, days	13 (4-38)
Survived until discharge <sup>2</sup>	678 (62)

Table 2

# Factors associated with longer duration of MV in VLBW infants (p<0.05)

Factors	r <sub>s</sub>
Gestational age	-0,118
Intraventricular hemorrhage, grade 3-4	0,255
Periventricular leukomalacia	0,15
Bronchopulmonary dysplasia	0,32
Severe bronchopulmonary dysplasia	0,418
Pneumothorax	0,06
Sepsis	0,087
Necrotizing enterocolitis	0,088
Antibiotic therapy duration, days	0,168

Using correlation analysis, we found that GA, duration of antibiotic therapy, and major neonatal morbidity, especially BPD and severe IVH, were significantly associated with prolonged MV. Based on the results of multivariable analysis, BPD and especially severe form of the disease, severe IVH, PVL, and longer duration of antibiotic treatment remained significant independent determinants of prolonged duration of MV. In another study, the need for higher MV settings and higher respiratory resistance on the first day after birth were identified as risk factors for prolonged ventilation [14]. Both may be associated with more severe acute lung injury - the important factor in the development of BPD that initially determines the need for prolonged MV. At the same time, duration of MV was significantly correlated with increased ventilation/perfusion mismatch at 37 weeks postmenstrual age in preterm infants with BPD [20] and was independently associated with reduced lung volumes and lung growth during infancy [21]. Impaired lung growth and development and more severe lung injury in infants with BPD increase the need for MV. Similarly, the progression of acute lung injury to chronic failure influenced the duration of MV in our study.

Prolonged endotracheal ventilation with an increased likelihood neurodevelopmental impairment [11]. Intraventricular hemorrhage may also complicate the course of severe RDS and determine the need for prolonged ventilation. Yossef et al [15] found a higher incidence of IVH in neonates requiring prolonged IPPV. In our study, both severe IVH and PVL significantly increased the duration of IPPV, but at the same time, it could not be excluded that the development of PVL was a consequence of prolonged IPPV. In any case, severe lung and brain injuries increase the duration of MV, which in turn makes the outcome of infants with these pathologies much worse.

Data describing the possible association between antibiotic treatment and increased incidence of BPD are controversial [22, 23]. It was found that each additional day of antibiotic therapy in the first 2 weeks of life was associated with an increased risk for and severity of BPD [22]. However, in another study, antibiotic exposure in the first week of life without culture-confirmed sepsis was not independently

associated with increased risk of BPD or death in preterm infants [23]. In our study, the longer duration of antibiotic exposure affected the duration of MV, suggesting a possible association of this intervention with acquired infections. At the same time, judicious use of antibiotics is important to improve outcomes in VLBW infants and to avoid the emergence of antibiotic resistance [24].

Several investigators identified lower GA as one of the main factors influencing the duration of MV [14, 15]. According to our data, higher GA was also associated with a shorter duration of this intervention, but lost its protective value after inclusion in the multivariable model.

The implementation of interventions that effectively prevent or reduce the severity of lung and brain injury has been shown to improve outcomes in VLBW infants. The use of antenatal steroid prophylaxis [25], non-invasive support after birth [26], caffeine [27], early surfactant administration with less invasive techniques [28], new modes of ventilation [1], and increased extubation attempts [29] can all reduce lung injury, the need for MV, and improve outcomes in VLBW infants. Also, effective treatment of infections and preventive measures to reduce the incidence of late infections are important to reduce the possibility of brain injury with the development of periventricular leukomalacia [30-32].

The advantage of this study is the cohort design with the inclusion of a large number of infants with a mean gestational age (SD) of 27.599 (2.238) weeks who received standard care in a single tertiary care center. The factors that significantly and independently prolong the duration of mechanical ventilation in very preterm infants have been identified.

This study also has several limitations. It was retrospective and observational by design, using the predetermined computer database data, which limited the possibilities of additional analysis.

# **Conclusions**

Severe lung and brain injury and prolonged antibiotic exposure were the main risk factors that significantly and independently prolonged MV in VLBW infants.

**Financing.** There is no external source of funding. **Conflict of interest:** The authors declare no conflict of interest.

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# ЧИННИКИ РИЗИКУ ТРИВАЛОЇ ШТУЧНОЇ ВЕНТИЛЯЦІЇ ЛЕГЕНЬ У НЕМОВЛЯТ З ДУЖЕ МАЛОЮ МАСОЮ ТІЛА ПРИ НАРОДЖЕННІ

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### Резюме

Вступ. Штучна вентиляція легень (ШВЛ) залишається рятівним утручанням для тяжко хворих новонароджених з дуже малою масою тіла (ДММТ) при народженні. Незважаючи на широке використання методів неінвазивної дихальної підтримки, чимало новонароджених з ДММТ потребують ШВЛ під час їхнього перебування в лікарні. Оскільки тривала ШВЛ пов'язана з несприятливими наслідками, важливо знати чинники, які підвищують ймовірність тривалішої ендотрахеальної вентиляції у цій популяції немовлят. Метою дослідження було визначити чинники ризику, які впливають на тривалість ШВЛ у дітей з ДММТ при народженні.

## Матеріал та методи дослідження.

У ретроспективному когортному дослідженні були використані дані із проспективно створеної комп'ютерної бази даних. Ця база включала інформацію про 1086 немовлят із дуже малою масою тіла та терміном гестації < 32 тижнів, які знаходились на ШВЛ у будь-який час під час перебування в лікарні третинного рівня допомоги в період із січня 2010 р. по грудень 2020 р. Було визначено чинники, які потенційно впливали на тривалість ШВЛ.

Дослідження виконано з дотриманням вимог біоетики у рамках планової наукової роботи кафедри (№ держреєстрації 0122U000164).

Отримані дані аналізували за допомогою описової та порівняльної статистики, а також коефіцієнта рангової кореляції Спірмена й одностороннього коваріантного аналізу (ANCOVA). Дані вимірювань з нормальним розподілом представлено як середнє (стандартне відхилення), а непараметричні дані – як медіану (нижній-верхній квартилі). Усі результати вважали значущими, якщо р <0,05.

Дослідження виконано у рамках планової наукової роботи кафедри «Клініко-лабораторне та інструментальне обґрунтування диференційних підходів до діагностики, лікування та профілактики захворювань дитячого віку» (№ держреєстрації 0122U000164) без зовнішніх джерел фінансування.

**Результати дослідження.** За даними одноваріантного аналізу бронхолегенева дисплазія (БЛД) (rS=0,32; p<0,05), тяжка БЛД (rS=0,418; p<0,05), пневмоторакс (rS=0,06; p=0,05), тяжкі внутрішньошлуночкові крововиливи (ВШК) (rS=0,255; p<0,05), перивентрикулярна лейкомаляція (ПВЛ) (rS=0,15; p<0,05), сепсис (rS=0,087; p<0,05), некротизуючий ентероколіт (rS=0,088; p<0,05), більша тривалість антибіотикотерапії ( rS=0,168; p<0,05) та менший гестаційний вік (rS=-0,118; p<0,05) асоціювались із тривалішою ШВЛ у немовлят з ДММТ при народженні. БЛД (F=18,544; p<0,0001), тяжка БЛД (F=109,810; p<0,0001), тяжкі ВШК (F=23,859; p<0,0001), ПВЛ (F=15,031; p<0,0001) і триваліша антибактеріальна терапія (F=13,173; p<0,0001) достовірно та незалежно впливали на тривалість ШВЛ за результатами одностороннього коваріантного аналізу ANCOVA.

**Висновки:** Тяжкі ураження легень і головного мозку, а також триваліше застосування антибіотиків були основними чинниками ризику, які достовірно і незалежно подовжували тривалість ШВЛ у немовлят з ДММТ при народженні.

**Ключові слова:** тривалість ШВЛ; чинники ризику; новонароджені з дуже малою масою тіла.

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