MECHANICAL VENTILATION AND SUCCESSFUL EXTUBATION AMONG EXTREMELY PREMATURE INFANTS

A population-based study using data from the Norwegian Neonatal Network

Mari Oma Ohnstad RN, NNP, CCN, MNSc

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Abbreviations and terminology

cMV	Cumulative mechanical ventilation
CI	Confidence interval
CRIB	Critical risk index for babies (scoring system)
CRF	Case report form
CV	Conventional ventilation
DPIA	Data Protection Impact Assessment
FRC	Functional residual capacity
HFOV	High-frequency oscillator ventilation
hsPDA	Hemodynamical significant patent ductus arteriosus
MAP	Mean airway pressure
MV	Mechanical ventilation
NAVA	Neurally adjusted ventilatory assist
n-CPAP	Nasal continuous positive airway pressure
NICU	Neonatal intensive care unit
NIPH	Norwegian Institute of Public Health
NIPPV	Nasal intermittent positive pressure ventilation
NIV	Non-invasive ventilation
NNN	Norwegian Neonatal Network
NPR	Nurse–patient ratio
PC–AC	Pressure control–assist control
PDA	Patent ductus arteriosus
PEEP	Positive end-expiratory pressure
PIP	Positive inspiratory pressure
PSV	Pressure support ventilation
REC	Regional Committee for Medical and Health Research Ethics
SIMV	Synchronized intermittent mandatory ventilation
SIPPV	Synchronized intermittent positive pressure ventilation
VG	Volume guarantee
V_T	Tidal volume
V/Q	Ventilation/perfusion

Bronchopulmonary dysplasia (BPD): a chronic lung disease diagnosed in neonates still on oxygen supplementation at a postmenstrual age of 36 weeks (1).

Electronic medical record (EMR): "An electronic record of healthcare information of an individual that is created, gathered, managed, and consulted by authorized clinicians and staff within one healthcare organization" (2).

Extremely premature (EP) infants: According to the World Health Organization (WHO), the definition of EP infants is infants born before 28 weeks of gestational age (GA) (3). The population being explored in this thesis represent a subgroup of EP infants born before 26 weeks of GA. These infants are often referred to as periviable infants, infants born in the gray zone or at the limit of viability. Born at the limit of viability is defined as: "the earliest stage of fetal maturity when there is a reasonable chance, although not a high likelihood, of extrauterine survival" (4). However, the definition has been problematized as the limit of viability is dependent on the social and medical context in which the infant is born (5). Based on uncertainty with the definition of infants born before 26 weeks of GA, the term *EP infants* is used for the population being explored throughout this thesis.

Gestational age (GA): traditionally defined as the time elapsed, in weeks, between the first day of the last menstrual cycle and the day of delivery (6). In Norway, estimated date of term delivery usually is determined on routine ultrasound. GA in preterm birth is calculated based on the date of delivery compared to the estimated date of full term birth at 40 weeks.

Interquartile range (IQR): used to describe variability and is the numerical difference between the 25^{th} and 75^{th} percentiles (7). The values for the 25^{th} and 75^{th} percentiles are used when presenting the IQR.

Respiratory distress syndrome (RDS): diagnosed based on clinical findings of a preterm infant, with the onset of progressive respiratory failure shortly after birth (8).

Patient volume: defined as the total number of newborns staying in the unit on a given day (can also be termed as patient census) (9).

Postnatal age (PNA): the time elapsed after birth (6), described in days or weeks.

Postmenstrual age (PMA): the time between the first day of the last menstrual cycle and birth (GA), plus the time after birth (postnatal age) (6), measured in weeks.

Premature infants: babies born before 37 weeks of GA. The duration of a normal pregnancy is between 38 and 42 weeks of GA (3).

Small for gestational age (SGA): defined as birthweight below the 10^{th} centile according to Norwegian growth charts (10).

Unit acuity: defined as the intensity of nursing care needed by the patients staying at the unit (11).

Z-scores: numerical measurements that describe a value's relationship to the mean of a group of values (can also be termed as normal score). It is measured in terms of standard deviations from the mean. A *Z*-score of 0 indicates that the data's point score is identical to the mean score (7)

Thesis summaries

English

Background
Mechanical ventilation (MV) is necessary for survival in almost all extremely premature (EP) infants born before the gestational age (GA) of 26 weeks. As many as 94% of this population receive MV, either immediately after birth or during their stay in the neonatal intensive care unit (NICU). Nevertheless, long-term MV is associated with a number of negative complications, such as increased mortality, infections, bronchopulmonary dysplasia (BPD), and disturbed neurological development. To reduce the risk of such serious complications, clinicians start weaning from MV and extubate the infant as early as possible. However, knowledge about the optimal time for the EP infant to be disconnected from the ventilator (extubation) is insufficient, and the decision is often based on the subjective opinion of the individual clinician. In approximately half of the infants, it turns out that the MV must be re-introduced (reintubation).

Aim
The aim of the study was to explore MV and extubation outcomes among EP infants born before a GA of 26 weeks. Based on previous research in the field, successful extubation was defined as 72 hours without the infant being reintubated.

Method
The study has a population-based design where we included EP infants born and admitted to all Norwegian neonatal units in the period January 1, 2013 to December 31, 2018. All included infants were identified through the Norwegian Neonatal Network (NNN). The thesis includes three papers. Paper I is a descriptive observational study exclusively based on registry data from the NNN database, where the infants' age at first successful extubation, as well as time on MV, were explored. Descriptive analyses and survival analyses were used to describe the age at first successful extubation. Regression analysis, corrected for gestational age, was used to identify early predictive factors for long-term MV. Papers II and III explore the infants' first extubation attempt and are based on data from NNN, supplemented by data obtained from electronic medical records (EMRs). In paper II, multiple logistic regression analysis is used to identify predictive factors for successful extubation. In paper III, regression analyses are used to identify whether a high unit workload or the day of extubation affect the time on MV before the first extubation attempt or the outcome of the attempt.

Results
A total of 482 EP infants were born and admitted to a Norwegian NICU during the study time period. Of these, 43 (9%) infants were excluded due to unavailability or because the mother chose the opt-out solution. In addition, 23 (5%) infants were excluded as they died before 12 hours of age, and 10 (2%) infants were excluded as they were never intubated and received MV during their stay in the neonatal unit. In paper I, 406 infants were included in the analyses. In papers II and III, infants who died before the first extubation attempt (n = 102) and infants with an identified accidental extubation (n = 11) were excluded. A total of 316 extubation events were included in the final analyses.

The main findings of the study showed that 70% of infants born at gestational week 25 were successfully extubated the first time they were attempted, which was carried out at a median age of five days (interquartile range, 1–10 days). Infants born at gestational weeks 22–23

were receiving MV until a median age of 20 days (interquartile range, 10–32 days) before they were extubated for the first time. The first extubation attempt was successful in 34% of cases.

For the total population, male sex and an Apgar score below 5 at five minutes of age were positively associated with a longer total duration of MV. At the first extubation attempt, 173 (55%) events were identified as successful extubation, while 143 (45%) were unsuccessful. There were more infants who were extubated from conventional ventilator treatment (n = 261, 83%) compared to children who were extubated from high-frequency oscillator ventilation (n = 55, 17%). The findings show higher odds of successful extubation from a conventional ventilator if the pre-oxygen requirement was below 35% prior to the attempt if the infant had an Apgar score above 5 at five minutes of age, the infant had a higher gestational age at birth, if the infant was a girl, and if the infant had a higher postnatal age at the time of the extubation attempt. Furthermore, we found that high unit workload or weekday and season had no association between the number of days on MV before the first extubation attempt or the outcome of the attempt.

Discussion

The study contributes knowledge related to how long infants < 26 weeks GA were treated with MV while they were admitted to the NICU. This is knowledge that can be used by healthcare personnel in dialogues with future EP parents regarding expected trajectories. Furthermore, the results from the present study describe the infants' age at first successful extubation, as well as the proportion of infants who were successfully extubated on the first attempt.

The fact that we found that the smallest EP infants (born at 22–23 weeks GA) were treated with MV longer before the first extubation attempt and that they had a higher proportion of unsuccessful attempts may indicate that we have not found the right clinical criteria for when the most immature infants are ready for extubation. Additionally, in paper II and paper II, all the included infants were clinically judged to be ready for extubation and 45% had to be reintubated before 72 hours had passed. Both prolonged MV treatment and undergoing reintubation can be factors that independently affect respiratory outcomes for the smallest patients.

Furthermore, the study identifies factors that we may not have sufficiently considered in the clinical judgment prior to extubation for EP infants. The fact that we do not find a connection between high unit workload and the number of days on MV before the first extubation attempt, nor the extubation outcome, may indicate that these two outcome measures are resilient despite fluctuations in patient volume and acuity at the unit.

Norwegian

Bakgrunn
Respiratorbehandling er avgjørende for overlevelse hos de fleste barn som fødes før svangerskapsuke 26. Hele 94% av denne pasientgruppen mottar respiratorbehandling, enten rett etter fødselen eller i løpet av oppholdet på nyfødtintensivavdelingen. Langvarig respiratorbehandling er imidlertid forbundet med en rekke negative konsekvenser, som økt dødelighet, infeksjoner, bronkopulmonal dysplasi og forstyrret nevrologisk utvikling. For å redusere risikoen for slike alvorlige konsekvenser, ønsker klinikere å starte avvenning fra respiratorbehandlingen og ekstubere barnet så tidlig som mulig. Kunnskap om det best mulige tidspunktet for å forøke å la barnet puste selv uten hjelp fra respiratoren (ekstubere) er imidlertid mangelfull og baseres på hver enkelt klinikers subjektive vurdering. Hos omtrent halvparten av barna viser det seg at man må starte opp igjen respiratorbehandlingen (reintubering).

Hensikt
Hensikten med studien var å utforske respiratorbehandling og ekstuberingsutfall blant ekstremt premature barn født før svangerskapsuke 26. Basert på resultater fra tidligere forskning på området, ble vellykket ekstubering definert som 72 timer uten at barnet ble reintubert.

Metode
Studien har et populasjonsbasert design hvor vi har inkludert ekstremt premature barn født før svangerskapsuke 26 som var innlagt på alle norske nyfødtavdelinger i tidsperioden 1.1.2013-31.12.2018. Avhandlingen inkluderer tre artikler. Artikkel I presenterer en deskriptiv observasjonsstudie basert utelukkende på registerdata fra Norsk Nyfødtmedisinsk Kvalitetsregister (NNK) hvor barnas alder ved første vellykkede ekstubering, samt tid på respirator utforskes. Det er benyttet deskriptive analyser, samt overlevelseskurver for å beskrive barnas alder ved første vellykkede ekstubering. Regresjonsanalyse hvor det ble korrigert for gestasjonsalder ble benyttet for å identifisere tidlige prediktive faktorer for langvarig respiratorbehandling. Artikkel II og III utforsker barnas første ektuberingsforsøk og er basert på data fra NNK, supplert med data innhentet fra pasientjournaler. I artikkel II er det benyttet multippel logistisk regresjonsanalyse, for å identifisere prediktive faktorer for vellykket ekstubering. I artikkel III er det benyttet regresjonsanalyser for å identifisere hvorvidt travelhet på avdelingen, eller dagen barnet ble ekstubert påvirket tid på respirator før første ekstuberingsforsøk eller utfallet av forsøket.

Resultat
Totalt 482 barn ble identifisert i tidsperioden som aktuelle for inklusjon, 43 (9 %) barn ble ekskludert på grunn av at vi ikke lyktes å få kontakt med mor eller at mor ønsket å reservere sitt/sine barn mot inklusjon. I tillegg ble 23 (5%) barn ekskludert ettersom de døde før 12 timers alder og 10 (2%) barn ble ekskludert da de aldri ble intubert og respiratorbehandlet i løpet av oppholdet på nyfødtavdelingen. I artikkel I er 406 barn inkludert i analysene, mens i artikkel II og III hvor barn som døde før første ekstuberingsforsøk (n=102) og barn med aksidentell ekstubasjon (n=11) ble ekskludert, er 316 hendelser inkludert.

Hovedfunnene i studien viste at 70% av barna født i svangerskapsuke 25 ble vellykket ekstubert første gang de ble forsøkt, som ble gjennomført ved median 5 dagers alder (interkvartilbredde 1-10 dager). Barn født i svangerskapsuke 22-23 ble respiratorbehandlet

frem til median 20 dagers alder (interkvartilbredde 10-32 dager) før de ble forsøkt ekstubert for første gang og 34 % ble da vellykket ekstubert.

Kjønn (gutt) og Apgar score under 5 ved 5 minutters alder ble identifisert som tidlig prediktive faktorer for langvarig respiratorbehandling. Ved første ekstuberingsforsøk ble 173 (55%) hendelser identifisert som vellykkede ekstubasjoner, mens 143 (45%) var ikke-vellykkede. Det var flere barn som ble ekstubert fra konvensjonell respiratorbehandling (n= 261, 83%) i forhold til barn som ble ekstubert fra høyfrekvent ventilering (n= 55, 17%). Funnene viser høyere odds for at ekstuberingsforsøket fra konvensjonell respirator skulle være vellykket dersom oksygentilskuddet var under 35% i forkant av forsøket, om barnet hadde en Apgar score ved 5 minutters alder over 5, barnet hadde høyere gestasjonsalder ved fødselen, om barnet var en jente og dersom barnet hadde en høyere postnatal alder ved forsøket. Videre fant vi at travelhet på avdelingen eller hvilken ukedag barnet ble ekstubert ikke hadde sammenheng mellom antall dager på respirator før første ekstuberingsforsøk eller utfallet av forsøket.

Diskusjon

Funnene fra studien bidrar med viktig kunnskap knyttet til respiratorbehandling og ekstubering av EP barn født før svangerskapsuke 26 i en nasjonal kohort. Kunnskap om total respiratortid kan benyttes av helsepersonell i samtaler med fremtidige foreldre som opplever fødsel før svangerskapsuke 26. I tillegg, beskriver resultatene barnas alder ved første vellykkede ekstubering, samt andel barn som ble vellykket ekstubert på første forsøk.

Funnene knyttet til at de aller minste premature barna (født i svangerskapsuke 22-23) ble behandlet med respirator lengre før de ble forsøkt ekstubert, samt at de hadde høyere andel ikke-vellykkede ekstuberingforsøk kan tyde på at vi ikke har funnet de riktige vurderingskriteriene for når de minste barna er klare for ekstubering. I artikkel II og III var alle de inkluderte barna vurdert som klare for ekstubering av klinikere, likevel var det 45% som ble reintubert før det var gått 72 timer. Både forlenget respiratorbehandling og det å gjennomgå reintubering kan være faktorer som uavhengig kan påvirke respiratoriske utfall for de aller minste pasientene.

Videre identifiserer studien noen faktorer som vi kanskje ikke i tilstrekkelig grad har hensyntatt i den kliniske vurderingen i forkant av ekstubering. At vi ikke finner sammenheng mellom travelhet i avdelingen og antall dager på respirator før første ekstuberingsforsøk og heller ikke ekstuberingsutfallet kan tyde på at de to utfallsmålene vi har utforsket, er resilient til tross for svingninger i pasientbelegg og pasienttyngde på avdelingen.

Articles in the thesis

The thesis is based on the following three papers, which will be referred to by their Roman numerals throughout:

I **Ohnstad M.O., Stensvold H.J., Tvedt C.R., Rønnestad A.E.**
Duration of mechanical ventilation and extubation success among extremely premature infants. Neonatology 2021;118:90-97. https://doi.org/10.1159/000513329

II **Ohnstad M.O., Stensvold H.J., Pripp A.H, Tvedt C.R., Jelsness-Jørgensen L.P., Astrup H., Eriksen B.H., Klingenberg C., Mreihil K., Pedersen T., Rettedal S.I., Selberg T., Solberg R., Støen R., Rønnestad A.E.**
Predictors of extubation success: A population-based study of neonates below a gestational age of 26 weeks. BMJ Paediatrics Open 2022.
http://dx.doi.org/10.1136/bmjpo-2022-001542

III **Ohnstad M.O., Stensvold H.J., Pripp A.H, Tvedt C.R., Jelsness-Jørgensen L.P., Astrup H., Eriksen B.H., Lunnay M.L., Mreihil K., Pedersen T., Rettedal S.I., Selberg T., Solberg R., Støen R., Rønnestad A.E.**
Associations between unit workloads and outcomes of first extubation attempts in extremely premature infants. Submitted to Frontiers in Pediatrics.

1 Introduction

All premature infants born before 26 weeks gestational age (GA) are treated with respiratory support after birth. Most infants are immediately intubated with subsequent mechanical ventilation (MV) treatment (12). Even though MV is required for the infant's survival, the treatment is associated with negative consequences, such as increased risk of chronic lung disease, long-term neurodevelopmental impairment, infections, and prolonged hospital stay (13–16). To prevent such adverse complications, clinicians start weaning from MV as soon as possible. When weaning, the ventilator settings are scaled down so that the infant contributes to the work of breathing to a greater extent. When the infant's respiratory drive and work of breathing are considered adequate, with minimal help from the ventilator, the endotracheal tube is removed in an extubation attempt. However, many extremely premature (EP) infants are back on the ventilator (reintubation) within 1–3 days. Hence, the optimal timing of extubation among EP infants remains uncertain.

Deliveries before a GA of 26 weeks are rare, counting for less than 0.4% of the birth population (17). Consequently, research on the population is characterized by small sample sizes. The most immature infants contribute little to the results published from trials of "extremely premature infants," which includes infants born before a gestational age of 28 weeks (3), resulting in a lack of evidence-based practice for infants born in the lowest GAs (18). This thesis includes papers where we aimed to gain increased knowledge about the duration of MV and extubation outcomes among EP infants born below GA 26 weeks in a population-based cohort.

1.1 Embryology—lung development

Lung development begins when the fetus is four weeks old and continues into childhood. Fetal lung development is classically divided into five overlapping stages: 1) embryonic, 2) pseudoglandular, 3) canalicular, 4) saccular, and 5) alveolar. These stages are pictured in Figure 1.

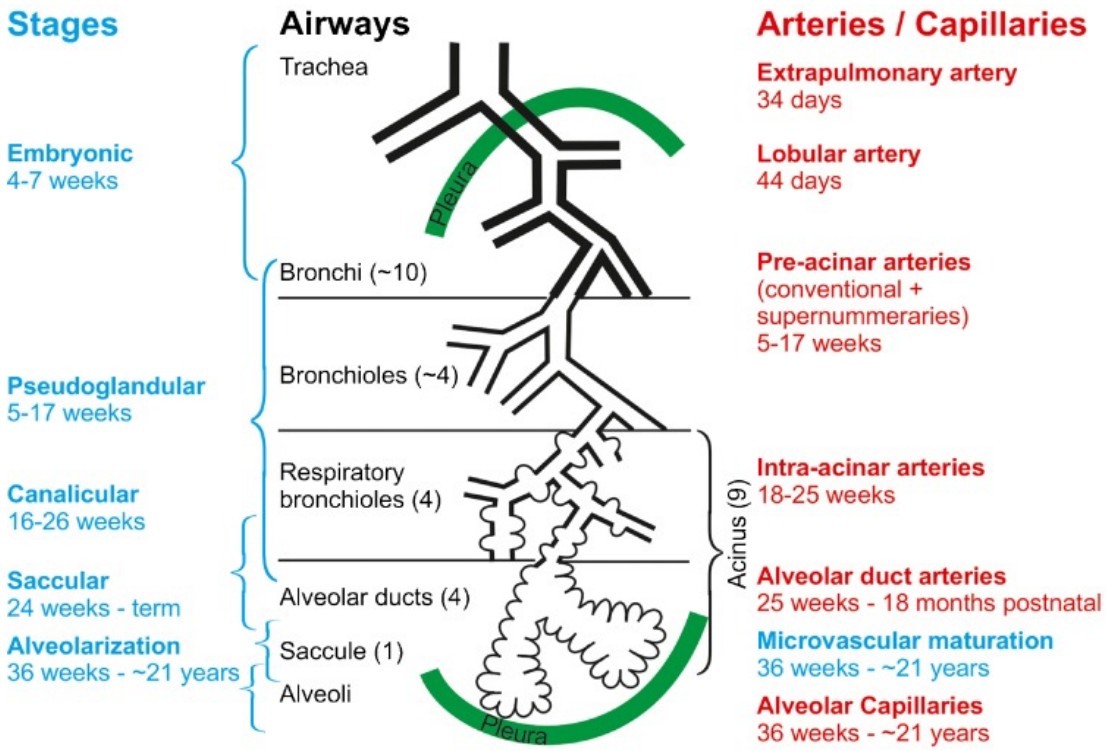


Figure 1. Development of the airways and arteries. The stages of lung development *(blue)*, the development of the airways *(black)*, and the arteries *(red)*. Reuse of image first published by Schittny, J.C., 2017 (CC BY-ND 2.0).

EP infants born before 26 weeks GA are born during the canalicular stage, starting at the 16th week of gestation and ending at the 25th week. At the beginning of this stage, all non-respiratory portions of the tracheobronchial tree exist, and the airway branching pattern has been finished. Through this stage, the terminal bronchiole differentiates to form primitive pulmonary acini. These primitive acini are different from the mature lung as they do not

contain alveoli, only bronchiole, ducts, and sac. Furthermore, the distal lung epithelium becomes thinner, and the capillary network starts to multiply. This results in the formation of a functional air–blood barrier that is thin enough to sustain gas exchange in EP infants (19). Effective respiration is thought to be possible by the end of this period, and the formation of the acinus and the surrounding capillary network is a critical step for providing the gas-exchange surface for the lungs, where there is a transition from the fetal lung to a more potentially viable lung. However, gas exchange is dependent on the degree of an interface between air and blood, for example, the acinus–capillary coupling (19,20).

At the end of the canalicular stage, all the large leading airways are formed and the development of Type II pneumocytes begins. Around 22 weeks of gestation, the Type II cells begin to produce and store surfactant. Surfactant reduces surface tension within the alveoli, enhancing alveolar expansion necessary for optimal gas exchange (21,22). Without sufficient surfactant, filling the alveoli with air requires higher driving pressure (low compliance). In normal lungs, the alveoli are partly filled between breaths (functional residual capacity, FRC) and circulated capillaries are found in near proximity to ventilated alveoli (ventilation-perfusion, V/Q-match) (21).

The driving pressure in spontaneous breathing is generated as negative pressure in the thoracic cage. However, the thoracic cage of these immature infants is particularly compliant, resulting in an affinity to collapse during inspiratory breathing. The immature lung development, the limited surfactant production, and the compliant thoracic cage are factors that together cause reduced lung compliance and may inhibit the establishment of FRC. The low lung volumes could result in atelectasis, which can lead to V/Q-mismatch and hypoventilation, further leading to hypoxemia and hypercapnia. As a consequence, most EP

infants will need positive inspiratory pressure immediately after delivery. Such positive inspiratory pressure facilitates lung expansion and provides a positive end-expiratory pressure (PEEP) to establish an adequate FRC, in addition to oxygen supplementation (23).

1.2 Survival and active treatment

A total of 347,780 infants were liveborn during 2013–2018 in Norway (24), and the incidence of premature deliveries before 26 weeks GA was 1.6 per 1000 total births through the years 2013–2014 (12).

Ethical and economic issues surrounding the decision to provide active perinatal care (such as antenatal care, resuscitation, and neonatal intensive care) for the most immature infants have been widely debated (25–27). Wide variations are found in the treatment of immature infants in Europe (28), and variation in prenatal and neonatal practices between hospitals appears to explain differences in survival rates and outcomes reported (29).

In 1998, the Research Council of Norway organized a national consensus conference where they advocated that treatment before 23 weeks' gestation was considered experimental and should only be initiated according to a research protocol approved by a research ethics committee and after obtaining parental consent, whereas treatment for infants born at 23 to 25 weeks' gestation ought to be based on viability and the individual judgment of the physician. From week 25, intensive care treatment is considered obligatory unless there are other major negative prognostic indicators (30). In recent years, the use of GA as the sole factor in the criteria for whom to provide life support has been criticized both nationally and internationally (27,31,32).

In a meta-analysis aimed at summarizing cohort studies exploring the prognosis of survival and risk of impairment of EP infants, Myrhaug et al. found that the prognosis for survival and survival without impairment was markedly poorer for infants born below 25 weeks GA (33). The overall prognosis for survival and risk of neurodevelopmental impairment are shown in Figure 2. Studies included in the meta-analysis represented results reported from Sweden, Japan, the United States, the United Kingdom, Norway, Belgium, France, Italy, Canada, and Germany. In the last decade, more attention has been paid to the importance of active treatment for the outcome, and centers practicing active management for infants at the limit of viability have reported positive outcomes with no or mild neurodevelopmental impairment at the age of 2.5 years for the majority of the survivors (34,35).

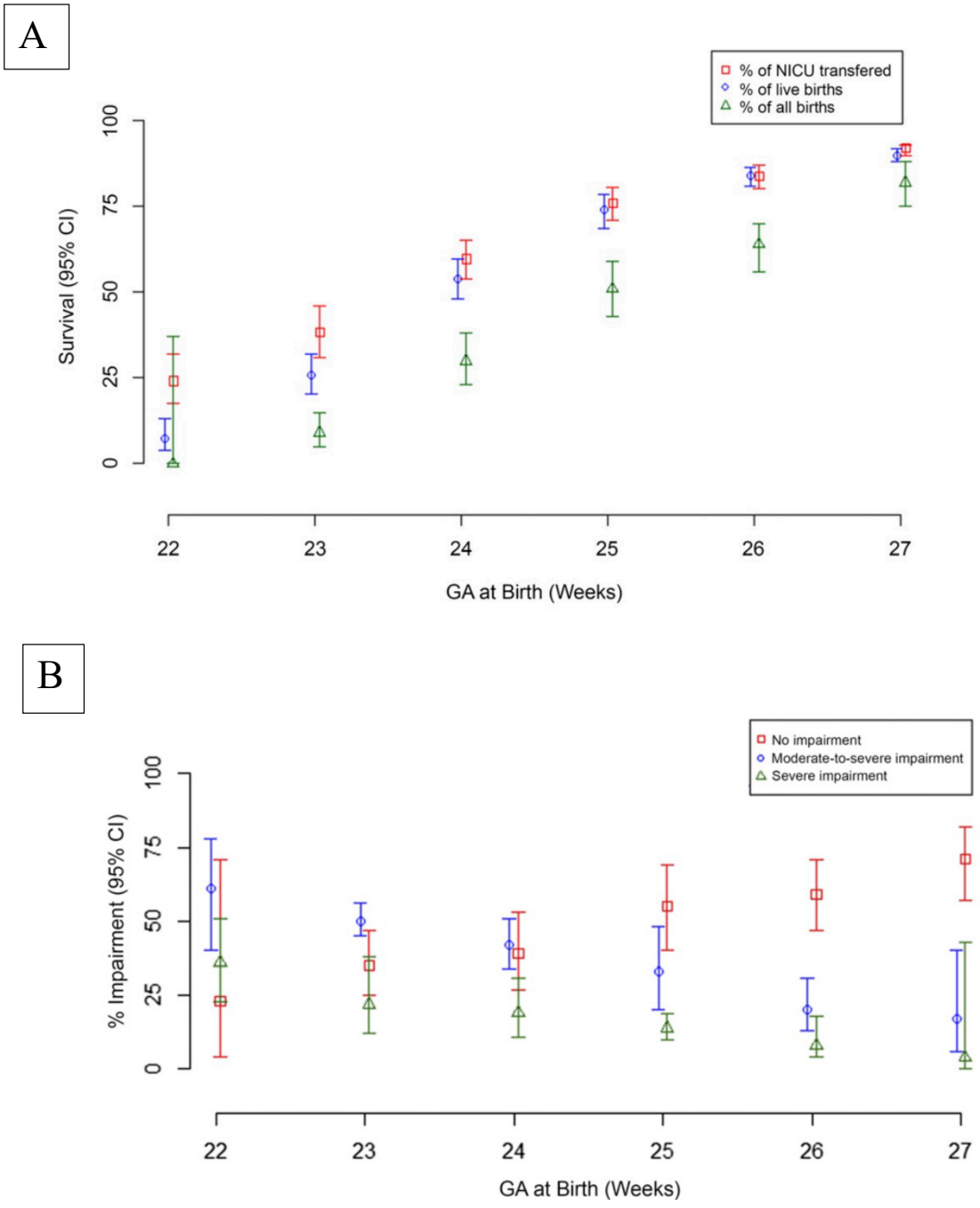


Figure 2. Figures from Myrhaug et al. (2019) illustrate A) the overall prognosis of survival and B) the overall risk of neurodevelopmental impairment among infants born at gestational age 22 to 27 weeks. Reproduced with permission from Journal of Pediatrics, Vol. 143, Page(s) 6-7, © 2022 by the AAP.

Centralization of treatment of EP infants born below a GA of 26 weeks has been recommended, and antepartum referral to tertiary perinatal care is common practice in many countries. In Norway, six regional centers provide perinatal and intensive care immediately after birth for this population (36). The hospitals are presented in Table 1.

Table 1. Tertiary hospitals treating infants below a gestational age of 26 weeks in Norway

Hospital	Health Region in Norway
University Hospital of North Norway, Tromsø	North
Trondheim University Hospital, St. Olavs	Mid
Haukeland University Hospital	West
Stavanger University Hospital	West
Oslo University Hospital, Ullevål	South
Oslo University Hospital, Rikshospitalet	South

When a mother is admitted to a hospital with anticipated premature birth before 26 weeks GA, close cooperation is required between obstetricians, neonatologists, and the parents. Decisions about prenatal interventions such as antenatal steroids, tocolysis, and eventual transportation to a higher-level hospital require active consideration. In addition to the GA, other factors might affect the infant's prognosis of survival and mortality after birth, such as sex, intrauterine growth, plurality, perinatal infection, or another illness in the fetus. The parents are considered as a part of the team treating premature infants and need thorough information. Their wishes related to treatment must be considered in the overall assessment and the parents should be included in shared decision making (36,37).

Antenatal corticosteroids reduce respiratory morbidity. However, presently there is no agreement as to the type of corticosteroid, the recommended dose or frequency, the timing of

when to use them, or the route of administration (38). The Norwegian Society of Gynecology and Obstetrics recommends antenatal steroids to mothers with anticipated premature birth from 23^0 weeks' gestation, and individual deliberation from 22^5 weeks after a consultation between obstetricians and neonatologists where it is determined active ex utero treatment will commence from 23^0 weeks. Their guidelines recommend the use of two doses of betamethasone 12 mg given intramuscularly 24 hours apart (39). However, infants born at GA 22–23 weeks are less exposed to antenatal steroids compared to infants born at higher GA (12,40), probably reflecting variations in active treatment. Sometimes premature birth occurs so rapidly that there is insufficient time for the drug to affect the infant's lung maturation. Tocolytics could be initiated in cases where clinicians want to delay premature delivery until the antenatal steroids take effect or the mother is transported to a regional hospital, but the drugs should be used with caution because of associations with a range of adverse effects (41).

In addition, in cases with preterm prelabor rupture of membranes, Norwegian guidelines recommend antibiotic treatment for the mother for 7–10 days to reduce the risk of neonatal or maternal infection (42).

1.3 Neonatal respiratory morbidity

There are several neonatal morbidities associated with being born EP, such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), infection, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (43). In the further sub-chapters, I will present a short review of the most common respiratory challenges for the EP infant: 1) RDS, 2) the role of a hemodynamical significant patent ductus arteriosus, 3) apnea of prematurity, and 4) BPD.

1.3.1 Respiratory distress syndrome

RDS, previously known as hyaline membrane disease, is a common condition among premature infants. The condition almost exclusively occurs in premature infants and the incidence is inversely related to GA (8). The National Institute of Child Health and Human Development Neonatal Research Network (NRN) reported an incidence of 95–98% (95% Confidence interval [CI] 75–100%) among infants born between 22 and 25 weeks GA during 2003–2007 (40). They defined RDS on the basis of clinical features and oxygen or respiratory support for ≥ 6 of the first 24 hours.

RDS is primarily caused by a deficiency of surfactant, which is a phospholipid mixture that reduces alveolar surface tension. Surfactant deficiency may result in the development of progressive and diffuse atelectasis. Atelectasis develops because the infant is not able to generate the increased inspiratory pressure required to inflate the alveoli (44). Furthermore, surfactant deficiency causes high surface tension in the alveoli. High surface tension may result in difficulties maintaining FRC, low lung volumes, and decreased compliance. The result of these changes in lung function causes hypoxemia (8). RDS is generally clinically manifested by increased work of breathing and increased oxygen requirement. Clinical signs of increased work of breathing include grunting, nasal flaring, and intercostal and subcostal retractions (44). In addition, infants with RDS have typical chest radiographic findings. These show a diffuse, reticulogranular “salt and pepper” appearance with air bronchograms and low lung volume (45). Typical radiographic findings are shown in the images presented in Figure 3.

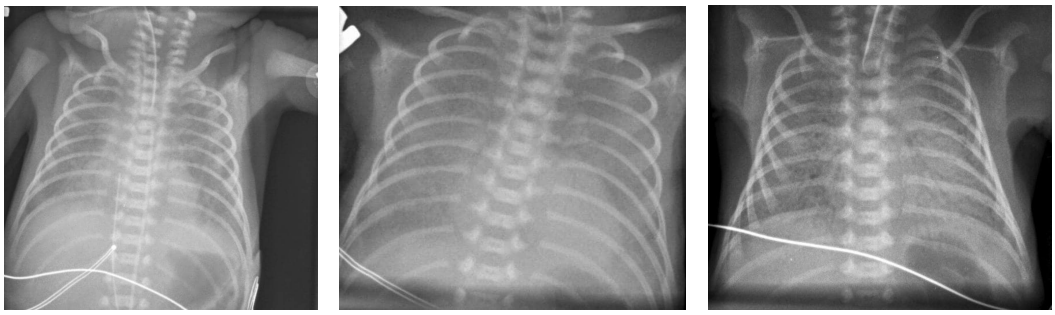


Figure 3. Three radiographs that demonstrate classic (A), moderately severe (B), and severe (C) neonatal respiratory distress syndrome. All three demonstrate the characteristic low lung volumes and diffuse, reticulogranular "salt and pepper" appearance with air bronchograms. Images reproduced with permission from © Medscape Drugs & Diseases (https://emedicine.medscape.com/), Neonatal Respiratory Distress Syndrome (RDS) Imaging, 2022, available at: https://emedicine.medscape.com/article/409409-overview)

1.3.2 The role of a hemodynamical significant patent ductus arteriosus

A patent ductus arteriosus (PDA) is the persistence of the fetal shunt between the aorta and the pulmonary artery after birth (46). The most significant risk factor for PDA is being born premature, and the incidence is inversely related to GA (47). However, the clinical consequence of a PDA is dependent on the degree of left-to-right shunting and ductal steal (48). A hemodynamically significant PDA (hsPDA) has been defined as ≥ 2 mm with major left-to-right shunt on echocardiography (primarily performed at the end of the first postnatal week) in addition to the need for ventilator support (47). Clinical signs of a symptomatic PDA include cardiac murmur, hypotension, widened pulse pressure, or respiratory deterioration. The hemodynamic consequences of a large PDA with a major left-to-right shunt include decreased systemic blood flow to organs and increased pulmonary blood flow. The increased pulmonary blood flow is associated with increased volume load to the left heart and interstitial pulmonary edema. One potential consequence of such left-to-right shunting is the need for prolonged MV (48).

Treatment of a hsPDA includes pharmacological interventions (with ibuprofen, indomethacin, or paracetamol) or surgical/interventional closure. In recent years there has

been a reported decrease in the treatment of PDA among EP infants, and the long-term outcomes remain uncertain. The reason is believed to be partly a result of the adverse consequences of the therapy itself, supplemented by higher spontaneous closure rates (49,50). Consequently, treatment decisions for a diagnosed PDA are based on clinical judgment of the significance and differ among clinicians (51).

1.3.3 Apnea of prematurity

For EP infants, the brainstem respiratory center consists of immature central and peripheral chemoreceptors. In addition, EP infants have poor neuromuscular control of the upper airway patency. The apnea of prematurity is a developmental disorder that demonstrates these infants' immature control of breathing, and the frequency and degree of severity are inversely correlated with GA. A widely used definition for apnea of prematurity is the evidence of prolonged apnea lasting for more than 15–20 seconds or a shorter respiratory pause associated with bradycardia or desaturation (52,53). Apnea can be central, obstructive, or mixed. In central apneas, the inspiratory efforts are absent, whereas in obstructive apnea the inspiratory effort exists but is not effective due to upper airway obstruction. In mixed apneas, there is an upper airway obstruction with inspiratory effort before or following a central apnea (52).

There is no consensus on the treatment of apnea of prematurity, but the first choice of therapy is usually methylxanthine (caffeine), which acts both centrally and peripherally to stimulate respiration. Blood transfusion has been found to temporarily decrease the frequency of apneas; however, the long-term effects are uncertain (53). Clinical interventions include tactile stimulation, an oscillating mattress, providing a thermoneutral environment, and non-invasive and invasive ventilation (51). Other non-pharmacologic nursing interventions such

as body positioning, skin-to-skin care, stress reduction, and sleep protection are thought to be preventive but still have an unknown efficacy in reducing the incidence of apneas (53).

1.3.4 Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is a complex neonatal chronic lung disease associated with multiple risk factors such as prematurity, MV, use of high concentrations of oxygen, and infection (54). It is among the most common and severe morbidities of premature birth and was first described by Northway and colleagues in 1967 as a lung injury subsequent to oxygen therapy and MV (55). Studies on premature baboons have shown that MV and oxygen can affect alveolar and vascular development (56,57).

The first diagnostic criteria were published in the late 1970s, heavily relying on the need for continuous oxygen supplements at 28–30 days of age. However, progress in neonatal care and a change in the population at risk has resulted in the need for improvement of the definition. In recent years, changes in the pathophysiology of BPD have been discovered. Before the 1980s, evident findings in BPD were airway injury, inflammation, and parenchymal fibrosis. These findings were common in more mature infants (GA > 28 weeks) and have been referred to as the “old” BPD. In the modern era of neonatal care, where antenatal steroids and surfactant therapy have become a central part of the treatment of premature infants, the lungs of infants dying from BPD have shown less fibrosis and fewer and larger alveoli, indicating interference with septation. Pathophysiological findings for more immature infants (GA < 28 weeks) are characterized by a disruption of the late canicular or saccular phases of lung development with the occurrence of 1) a reduction in the surface area available for gas exchange due to fewer and larger alveoli, 2) a pulmonary vascular disease resulting in pulmonary hypotension, and 3) tissue deformation. These

pathophysiological findings have been referred to as the "new" BPD (54). Severe BPD expresses pathological features from both "old" and "new" BPD (58). Figure 4 illustrates these different pathological features.

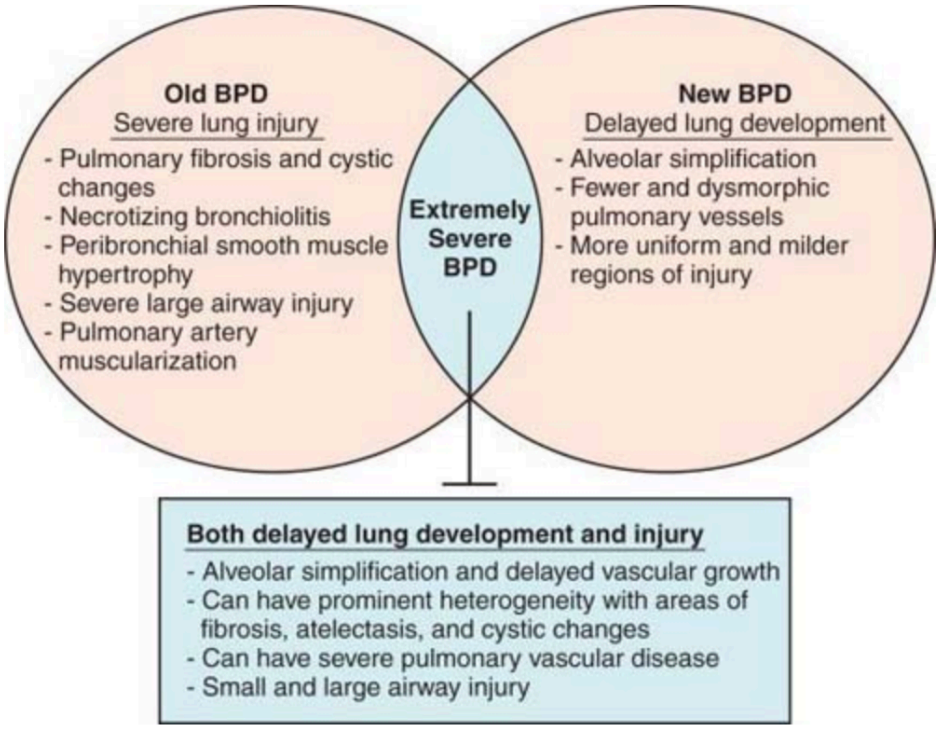


Figure 4. Pathologic features of "old," "new," and severe bronchopulmonary dysplasia (BPD). This figure was published in Management of the Infant with Bronchopulmonary Dysplasia, H.Zhang, N.Bamat, 2022. Red. M.Kezler and K. Gautham in Goldsmith's Assisted Ventilation of the Neonate. An Evidence-Based Approach to Newborn Respiratory Care, 7th ed. © Elsevier, 2022. Reproduced with permission.

A workshop organized by the National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute/Office of Rare Diseases in 2000 reviewed the definition and proposed a new definition that categorized the severity of BPD with different criteria for infants born before or after 32 weeks of GA. Severe BPD is defined as the need for > 30% oxygen and/or positive pressure at 36 weeks postmenstrual age (PMA) or at discharge (1). In recent years, this is found to be the most common definition used (59). However, there is still an ongoing debate regarding the ideal, objective definition of BPD

given the complex multifactorial and clinical presentation of the disease (60). Even though BPD improves with age, the long-term consequences of BPD for older children and adults are not fully described. However, pulmonary artery hypertension is identified as a complication with increased morbidity and mortality. Infants with severe BPD might have need of supplemental respiratory care after hospital discharge, ranging from nasal cannula with supplemental oxygen to tracheostomy with prolonged MV for months/years (61).

1.4 Neonatal care

Optimal neonatal care is considered to be of importance for EP infants' outcomes, consequently also affecting short-term outcomes such as duration of MV and extubation outcomes. The neonatal care of EP infants takes place in a complex intensive care environment, which differs dramatically from the intrauterine life of the fetus in the mother's womb. The immature infant is separated from its mother and placed in an incubator surrounded by high-tech medical equipment and healthcare personnel. Although the design of modern neonatal intensive care units (NICUs) emphasizes family-centered care, many units are still characterized by an intensive care environment with a high level of noise and disturbance for small patients.

In the following sub-chapters, I will present a short review of six neonatal care aspects considered important in the practical management of the EP infant prior to the first extubation attempt: 1) delivery room stabilization and transfer to the NICU, 2) the NICU environment, 3) medical therapy, 4) MV strategies, 5) extubation strategies, and 6) staffing in the NICU.

1.4.1 Delivery room stabilization and transfer to the NICU

The transition from intrauterine to extrauterine life for the EP infant involves extreme physiologic changes in both the respiratory and circulatory systems, requiring stabilization immediately after birth in the delivery room. In the management of EP infants, the term "supporting transition" is therefore preferred rather than "resuscitation" (62). Supporting transition requires a competent healthcare team ensuring immediate, intentional, and systematic interventions aimed at optimizing the EP infant's condition. Martin et al. developed an algorithm for initial management to prevent or reduce the severity of RDS for infants at risk and recommend ventilation including intubation if the infant is apneic, gasping, or has a heart rhythm <100 beats per minute immediately after birth and remains apneic with HR <100 after one minute with adequate bag ventilation (45).

The first 60 minutes of the infant's life play a critical role in the immediate and long-term outcomes for EP infants (63,64), and the concept of the "golden hour" has been adapted into neonatology from the adult trauma setting (65). Care and treatment during the first hour of life should emphasize minimizing complications. Emphasis on respiratory management, thermoregulation, insertion of central lines (both umbilical and venous) to ensure nutrition and prevent hypoglycemia, prevention of sepsis, cardiovascular support, and prevention of intraventricular hemorrhage are identified as key factors for optimizing the golden hour after birth (66,67).

Surfactant therapy is essential in the management of RDS (62). In a Norwegian study of EP infants born between 2013 and 2014, >80% of the infants born below GA 26 weeks received surfactant in the delivery room to prevent the development of RDS (the NEPS2 study) (12). The route of administration is either via an endotracheal tube or via a less invasive surfactant administration (LISA). The LISA method involves the administration of surfactant through a

thin catheter placed in the trachea while the infant is still on continuous positive airway pressure (CPAP). In recent years, there has been a shift from proactive surfactant treatment to a more reserved approach, only treating infants showing clinical signs of RDS (62). However, results from a population-based study in Norway between 2012 and 2018 showed that the LISA method was rarely used for infants born below GA 25 weeks (68). Stabilization in the delivery room and safe transfer to the NICU have been recommended within the infant's first hour of life (66).

1.4.2 The NICU environment

After stabilization in the delivery room, the EP infant is transported to the NICU for further treatment. The NICU environment is often characterized as intensive, stressful, and traumatic for infants (69–71). The still-developing brain and sensory systems of an infant born prematurely are affected by the endless stimuli in the NICU (71). Through the work of Brazelton in the 1970s, the influence of the NICU environment on immature infants' developing brains became apparent to healthcare providers (72). Later, Brazelton's work was advanced by Als in the "synactive theory" (73). Focus on assessing the infant's ability to handle excessive stimulation provides the caregiver with information to adjust the environment and treatment strategies, directed at minimizing unwarranted stimulation that causes physiologic instability (71). Since Als' theory was developed, several models of developmental care have evolved (69,74,75). A common feature in these models is the recognition that fragile premature and sick infants and their families benefit from a healing environment and that care practice should be adjusted to individual and specific developmental needs (71).

The Neonatal Integrative Developmental Care Model by Altimier and Phillips describes seven core measures of neuroprotective family-centered developmental care to support premature infants' development (69) (shown in Figure 5).

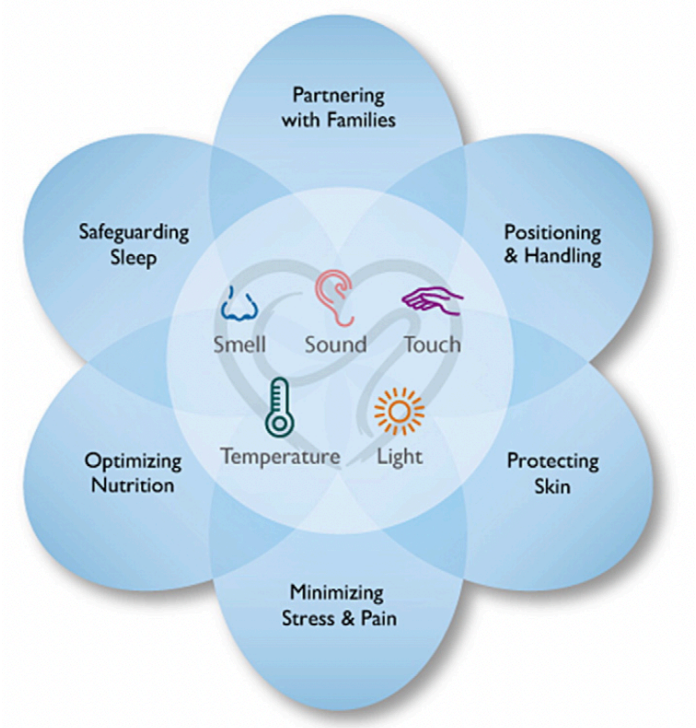


Figure 5. The Neonatal Integrative Developmental Care Model. Reprinted from Newborn and Infant Nursing Reviews, 13 /1, Altimier L, Phillips RM, The Neonatal Integrative Developmental Care Model: Seven Neuroprotective Core Measures for Family-Centered Developmental Care, © (2022), with permission from Elsevier.

For the EP infant, invasive procedures such as intubation, insertion of central and peripheral lines, and gastric tube feeding are common. They require continuous monitoring and thorough documentation of physiologic and invasive or non-invasive ventilatory parameters. All infants should have a minimum of monitoring, such as a continuous electrocardiogram (ECG), pulse oximetry (SpO_2), and blood pressure and temperature monitoring. The necessary apparatus and invasive procedures can result in stress and pain for the immature infant and, in turn, disturb the infant's sleep cycles and quality, further influencing growth and overall health (71). Healthcare personnel must always consider what actions are

necessary based on the infant's condition, and all necessary procedures must be weighed against the infant's need for minimal handling.

1.4.3 Mechanical ventilation strategies

Even though there is growing attention to avoiding endotracheal intubation by increased use of non-invasive ventilation (NIV), the majority of EP infants born below GA < 26 weeks are intubated and treated with MV immediately after birth. In the Norwegian NEPS2 study, 100%, 95%, and 88% were on MV before three days of age at GA 22–23, 24, and 25 weeks, respectively (12). Similar rates have been reported by the Canadian Neonatal Network (CNN) (76). The Swedish EXPRESS study reported that 85% of infants born between 22 and 27 weeks were treated with MV during their initial hospitalization (77).

Regardless of duration, MV with high intrathoracic airway pressures and tidal volumes (V_T) may cause injury to the lungs and other organs due to hemodynamic disturbances and/or inflammatory mediator-induced systemic responses (78,79). Therefore, various lung-protective ventilator strategies have been introduced to minimize lung injuries associated with MV, with the main goal of avoiding volutrauma, atelectotrauma, and oxygen toxicity (80). There are different MV strategies aimed at minimizing lung injuries. However, the choice of ventilator modes may be limited to the actual machine available in the NICU, though most modern ventilators are capable of providing the basic modes of synchronized ventilation. In Norway, the first choice of MV mode when treating EP infants with RDS is usually conventional ventilation (CV), with patient-triggered, synchronized ventilation.

The most common patient-triggered ventilator modes are:

- Pressure control–assist control (PC–AC), similar to synchronized intermittent positive pressure ventilation (SIPPV)
- Pressure support ventilation (PSV)
- Synchronized intermittent mandatory ventilation (SIMV)

Volume guarantee (VG) ventilation may be combined with any of the basic ventilator modes. Applying VG, the clinician chooses a target V_T and sets a pressure limit up to which the ventilator may adjust the pressure needed to achieve the desired V_T. The purpose of using VG is to prevent overdistention of the lungs due to high pressures and volumes. To calculate actual V_T in uncuffed endotracheal tubes with leakage, the ventilator usually uses the expiratory V_T. Suggested initial V_T for premature infants < 700 grams with RDS is 5.5–6 ml/kg (81,82).

Another patient-triggered ventilator mode is the neurally adjusted ventilatory assist (NAVA). This mode uses the electrical activity of the diaphragm detected by transesophageal electromyography to trigger ventilator inflation (81). NAVA is currently only in use by one NICU in Norway.

For infants where CV does not provide sufficient respiratory support, high-frequency oscillator ventilation (HFOV) is commonly used as a rescue treatment (83). HFOV uses small tidal volumes and very rapid ventilator rates. Potential advantages of this technique over CV include the use of lower peak alveolar pressures, the ability to achieve oxygenation and ventilation relatively separately in the recruited lung while using very small V_T, and the

maintenance of normal lung structure even when using high mean airway pressures (MAPs) (84).

1.4.4 Extubation strategies

Due to complications associated with MV, clinicians strive for early extubation. However, many EP infants are extubated prematurely and require reintubation, which also carries potential hazards (85). In addition, for some, endotracheal reintubation is not an easy or gentle process. The procedure is associated with distress to the patient and may result in malposition of the endotracheal tube, airway trauma, and hemodynamic instability (86–89). Therefore, identifying the optimal time for extubation is highly desirable. Currently, the decision to extubate is principally based on the clinical judgment made by the physician and is not always evidence-based (90). Several studies have investigated predictor tests of successful extubation in premature infants (91–95). According to a systematic review and meta-analysis published in 2019, the majority of the studies exploring extubation readiness tests are small, single-center, and with significant risks of bias and applicability concerns (96). The meta-analysis showed that the predictor tests had high sensitivity but low and variable specificity, and the authors stated that "predictors are great at reinforcing the clinician's intent to extubate but add little to no value in detecting failures."

An international survey conducted in level III NICUs in Australia, Canada, Ireland, New Zealand, and the USA (112/162 units responded) on periextubation practices among EP infants reported that extubation readiness was assessed based on ventilator settings, blood gases, and the presence of clinical and hemodynamic stability (90). Nasal continuous airway pressure (n-CPAP) has been found to be the most common type of post-extubation respiratory support, followed by nasal intermittent positive pressure ventilation (NIPPV)

(90,97). In a systematic review and meta-analysis published in 2016 aimed at identifying interventions to improve successful extubation in premature infants, Ferguson et al. concluded that premature infants should be extubated to NIV support with continuous positive airway pressures of at least 5 cm H_2O and caffeine should be routinely used, while corticosteroids should be used cautiously (98).

1.4.5 Medical therapy

Some medications are an essential part of the treatment in the postnatal period for the EP infant and are considered important for the respiratory outcome. These medications include caffeine therapy, postnatal corticosteroids, and antibiotic treatment.

Caffeine therapy

Caffeine therapy is used as a respiratory stimulant. The medication has become standard based on studies showing that early initiation of caffeine is associated with better outcomes (99). Caffeine has been shown to facilitate earlier extubation with a reduction of BPD and better neurodevelopmental outcomes (100,101); therefore, caffeine therapy is initiated early in the course of treatment while the infant is treated with MV. Providing a respiratory stimulant while the infant is treated with MV is probably beneficial regarding spontaneous breathing, facilitating minimal help from the ventilator and potential earlier extubation.

Postnatal corticosteroids

For some of the EP infants who are difficult to wean and remain on MV for a prolonged period of time, the use of a postnatal corticosteroid is considered to facilitate extubation (62). Even though dexamethasone increases the chance of successful extubation and reduces BPD, it has been shown to increase the risk of neurodevelopmental impairment if used in the first

week after birth. Therefore, the use of steroids is often reserved for infants who are ventilator-dependent after the first 7–14 days (102).

Antibiotic treatment

Sepsis during the neonatal period is a common and feared complication for EP infants and is associated with a high risk of mortality and morbidity (103,104). Because immature infants are vulnerable to sepsis, prevention strategies such as strict aseptic precautions when handling central lines and other invasive procedures are necessary. In addition, antibiotic treatment should be initiated in cases with a high risk of infection (e.g., preterm prelabor rupture of membranes). It has been recommended that a blood culture and the first dose of antibiotics should be administered within the golden hour for infants with suspected sepsis (67).

1.4.6 Staffing in the NICU

The care of neonates admitted to a NICU requires timely, safe, effective, efficient, and evidence-based care 24/7, every day of the year. Collaborative teams of healthcare personnel work to meet the critical and complex healthcare needs of these infants and their families. Many NICU provider teams in Norway include neonatologists, registered nurses, nurses with advanced education and training (i.e., neonatal nurses, critical care nurses, and pediatric nurses), physicians, and assistants. In addition, the parents should be empowered (well-informed, competent, and confident) and included as an important part of the infant's team (36).

The patient population in the NICUs represents a heterogenous group, ranging from patients with the need for near maternity care to critically ill patients with the need for high intensive

care and continuous monitoring. EP infants treated with MV need continuous monitoring and advanced nursing care with a nurse–patient ratio (NPR) of 1:1 (36,105,106). NPRs appear to affect patient outcomes in the NICU (107), and previous studies have identified associations between nursing overtime, low staffing level and low ratio of specialist nurses with increased risk of infections and higher mortality among premature infants(108,109).

1.5 Summary and knowledge gaps

EP birth disturbs lung development during a stage with simplification of alveoli, ineffective gas exchange, and surfactant deficiency. The immature lung development must then be completed in an extrauterine intensive care environment. Despite major advances in neonatal care in recent decades, EP infants remain at great risk of respiratory challenges such as RDS, and treatment with MV is required for their survival. Nevertheless, the negative consequences associated with MV treatment result in a desire to extubate the EP infant as early as possible. However, the optimal timing of extubation remains a clinical challenge and many extubation attempts on immature infants fail. For this reason, we aim to provide further knowledge about the respiratory treatment of EP infants and identify possible factors that can strengthen the clinical judgment of extubation readiness. Furthermore, the extubation of EP infants requires close and continuous monitoring and observation from advanced healthcare specialists, and we do not know if a high workload in the NICU affects the duration of MV and extubation outcomes.

2 Thesis aims

General aim: To explore MV and extubation outcomes among EP infants born below a GA of 26 weeks.

2.1 The specific research aims

Aim of paper I: To examine the duration of MV in days until the first successful extubation and the cumulative MV (cMV) until discharge home. We also aimed to explore the associations between cMV and early clinical variables, such as gestational age (GA), growth restriction at birth, illness severity score at birth (Critical Risk Index for Babies, CRIB II), and Apgar score.

Aim of paper II: To investigate infant characteristics and ventilation parameters at the first extubation attempt. In addition, we aimed to explore if there were single or compound clinical factors that, given the clinical decision to extubate, might further predict successful extubation. Successful extubation was defined as no reintubation within 72 hours.

Aim of paper III: To examine the association between unit workload and weekend or seasonal effects with the duration of MV treatment until the first extubation attempt and the outcome of the attempt. In addition, our secondary aim was to assess the association between unit workload and weekends or seasons with indicators of respiratory status before and shortly after reintubation.

3 Materials and methods

3.1 Design

This thesis consists of three observational studies, presented in papers I–III. Prospectively collected data from the Norwegian Neonatal Network (NNN) were the main source for all three studies. In papers II and III, the dataset was supplemented by data extracted from the included patients' electronic medical records (EMRs) in order to provide a richer description of the infant's respiratory state and the respiratory treatment delivered.

The NNN is set up to cover the registration of all neonatal care treatment activity at each of the 20 NICUs in Norway. Every day, treatment for each admitted patient is recorded by dedicated physicians, nurses, or secretaries at the units in the software named "the neonatal program." Figure 6 show a screenshot of the daily registration form with the patient classification system, ranging from level 1 (the lowest patient acuity level) to level 5 (the highest patient acuity level). Every day, all inpatients are classified in this system.

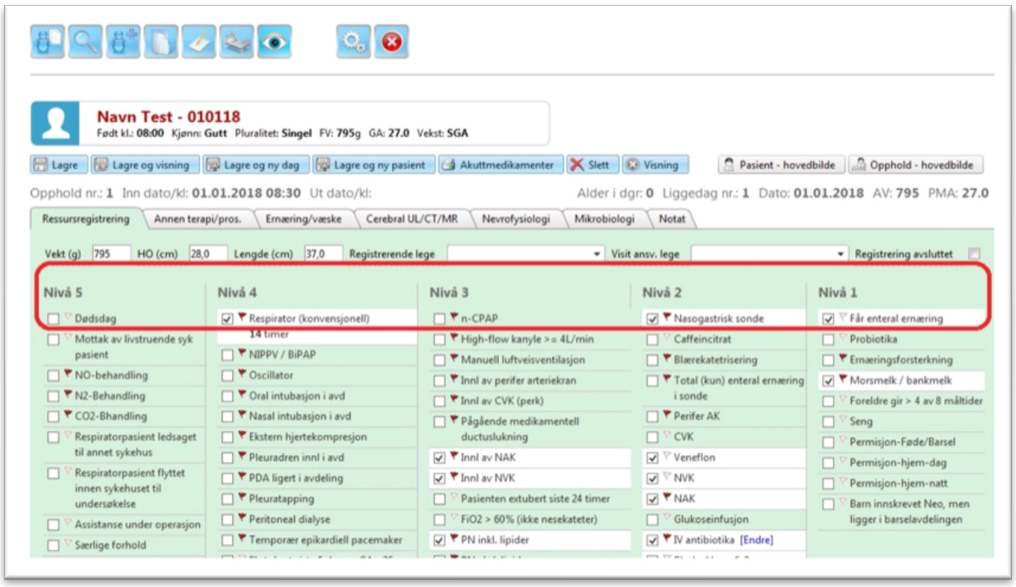


Figure 6. Screenshot of the daily registration form in the Norwegian Neonatal Network database, picturing the patient classification system, level 1–5. Source the NNN annual report 2021.

To ensure the collection of correct and complete data, automated functions have been developed in the software. One example of such an automated function is that the program "follows" different courses of treatment, for example, infection and antibiotic treatment (110).

3.2 Study population

Register records of EP infants born before 26 weeks GA between 2013 and 2018 were screened for eligibility. Infants alive at 12 hours of age who had received MV during admission in the NICU and the mother had not chosen the opt-out alternative were enrolled in the study. In studies II and III, infants who died before the first extubation attempt and infants with an identified accidental extubation were excluded from the analyses. Flowchart of the included infants are shown in Figure 7.

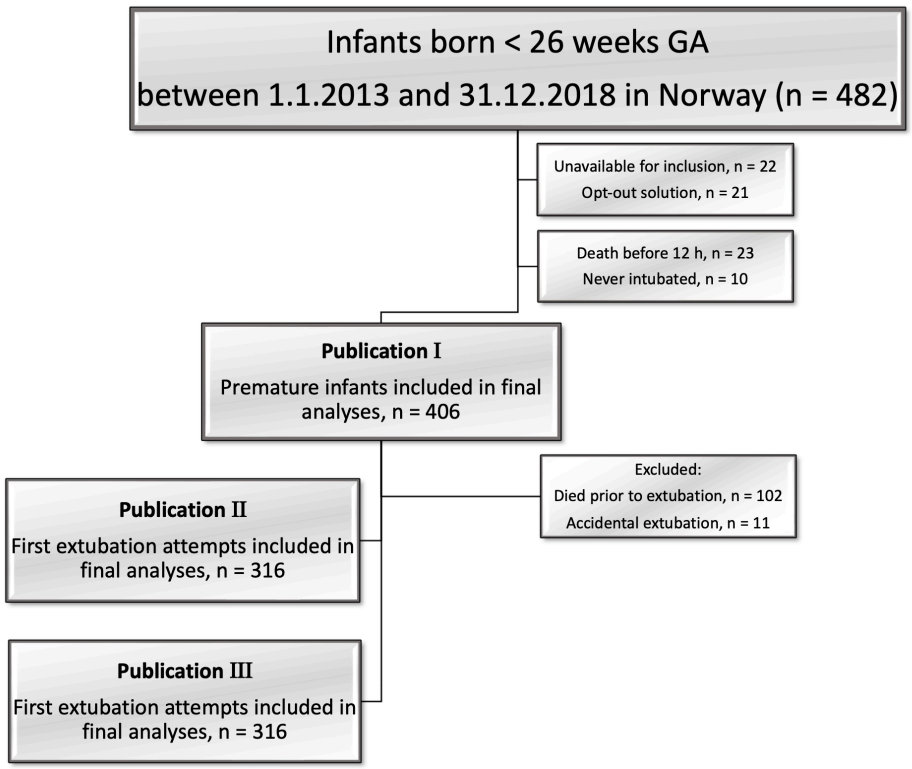


Figure 7. Flowchart of included infants in the three publications.

In paper I, where the duration of MV until first successful extubation and the cMV until discharge home were explored, 406 infants were included in the final analyses. In papers II and III, where only the first extubation attempt was surveyed, 316 infants were included in the final analyses.

3.3 Data collection

Data extraction from the Norwegian Neonatal Network (NNN)

After obtaining consent from the Norwegian Institute of Public Health (NIPH), relevant variables were extracted from the NNN including:

- Relevant variables linked to the patient including anthropometric measurements, gestational age, APGAR score, and CRIB score.
- Relevant variables related to respiratory treatment including time of intubation, time of extubation, CV, HFOV, and medical treatment (postnatal steroids/caffeine).
- Relevant variables related to organizational factors including total number of patients in the unit, and number of patients in categories 1 to 5.

Data collection from EMRs

Variables extracted from the EMRs were determined a priori based on clinical experience and previous research in the field. We extracted variables related the respiratory treatment on the EP infant's day of birth, the identified days of extubation, and the eventual day of reintubation. An overview of the variables extracted from EMRs regarding the days of intubations and extubations are shown in Tables 2 and 3.

Table 2. Variables extracted from patient records at intubation events	
Time in patient record	Description of the variables extracted
Before intubation	**NIV-mode:** Respiratory support registered before the intubation event, i.e nCPAP, BiPAP, NIV-NAVA (only relevant for first intubation if the infant was not immediately intubated)
	PEEP: Last PEEP value registered prior intubation and mean PEEP value for the last 6 hours prior intubation
	Administered oxygen: Last FiO_2 value registered prior intubation and mean FiO_2 value for the last 6 hours prior intubation
	Blood gas variables: pH, pCO_2 and BE (maximum 12 hours prior intubation)
After intubation	**MV- mode:** First registered mode i.e PC AC/SIPPV, PSV, SIMV, NAVA, HFOV, with or without VG
	PIP: First registered PIP value after intubation and mean PIP value for the first 6 hours after intubation
	PEEP: First registered PEEP after intubation and mean PEEP value for the first 6 hours after intubation
	Tidal volume: First registered tidal volume value after intubation and mean tidal volume value for the first 6 hours after intubation
	MAP: First registered MAP value after intubation and mean MAP value for the first 6 hours after intubation
	Administered oxygen: First registered FiO_2 value after intubation and mean FiO_2 value for the first 6 hours after intubation
	Blood gas values: pH, pCO_2 and BE (maximum 12 hours after intubation)
Day of intubation	**Medical therapy:** Methylxanthine, postnatal steroids (generic names and doses)

Abbreviations: NIV, non-invasive ventilation; nCPAP, nasal continuous positive airway pressure; BiPAP, bilevel positive airway pressure; NIV-NAVA, non-invasive neurally adjusted ventilatory assist; PEEP, positive end expiratory pressure; FiO_2, fraction of inspired oxygen; BE, base excess; MV, mechanical ventilation; PC AC, pressure control–assist control; SIPPV, synchronous positive pressure ventilation; PSV, pressure support ventilation; SIMV, synchronized intermittent mandatory ventilation; HFOV, high frequency oscillator ventilation; VG, volume guarantee; MAP, mean airway pressure.

Table 3. Variables extracted from patient records at extubation events	
Time in patient record	Description of the variables extracted
Before extubation	**MV-mode:** Last registered mode, i.e PC-AC/SIPPV, PSV, SIMV, NAVA, HFOV, with or without VG
	PIP: Last registered PIP value before extubation and mean PIP value for the first 6 hours before extubation
	PEEP: Last registered PEEP value before extubation and mean PEEP value for the first 6 hours before extubation
	Tidal volume: Last registered tidal volume value before extubation and mean tidal volume value for the first 6 hours before extubation
	MAP: Last registered MAP value before extubation and mean MAP value for the first 6 hours before extubation
	Administered oxygen: Last registered FiO_2 value before extubation and mean FiO_2 value for the first 6 hours before extubation
	Blood gas values: pH, pCO_2 and BE (maximum 12 hours before extubation)
After extubation	**NIV-mode**: First registered NIV-mode, i.e nCPAP, BiPAP, NIV-NAVA
	PEEP: First registered PEEP after extubation and mean PEEP value for the first 6 hours after extubation
	Administered oxygen: First registered FiO_2 value after extubation and mean FiO_2 value for the first 6 hours after extubation
	Blood gas values: pH, pCO_2 and BE (maximum 12 hours after extubation)
Day of extubation	**Medical therapy:** Methylxanthine, postnatal steroids (generic names and doses)

Abbreviations: MV, mechanical ventilation; PC AC, pressure control–assist control; SIPPV, synchronous positive pressure ventilation; PSV, pressure support ventilation; SIMV, synchronized intermittent mandatory ventilation; NAVA, neurally adjusted ventilatory assist; HFOV, high frequency oscillator ventilation; VG, volume guarantee; PIP, positive inspiratory pressure; PEEP, positive end expiratory pressure; MAP, mean airway pressure; FiO_2, fraction of inspired oxygen; BE, base excess; NIV, non-invasive ventilation; nCPAP, nasal continuous positive airway pressure; BiPAP, bilevel positive airway pressure; NIV-NAVA, non-invasive neurally adjusted ventilatory assist.

3.4 Statistical analyses

The statistical analyses used in the thesis were performed by Mari Oma Ohnstad with support and guidance from statistician Are Hugo Pripp. Supervisors Arild Rønnestad, Christine Raaen Tvedt, and Lars-Petter Jelsness-Jørgensen, and project member Hans Jørgen Stensvold were involved in the analysis process and interpretation of the results.

Descriptive statistics were compiled to describe population characteristics (I, II, III), compare perinatal and extubation characteristics of infants successfully extubated on the first attempt with those who failed (II), and explore unit workload based on z-scores for patient volume and unit acuity (III). Continuous variables were presented as mean with standard deviations (SD) or median with interquartile range (25^{th} and 75^{th} percentiles) dependent on the variable distribution. Normality was assessed with histograms and Q-Q plots. Categorical variables were presented as numbers with percentages. Statistical significance was defined as a *p*-value of $< .05$.

In paper I, analyses were stratified by GA at birth—group 1: GA 22^{0}–23^{6}, group 2: GA $24^{0–6}$, and group 3: GA $25^{0–6}$. Age at successful extubation and cMV were explored for each of these three groups. A multiple linear regression model with cMV as the dependent variable was used to identify early clinical variables associated with longer duration of MV. To build the regression model, all variables associated with a study outcome at $p \leq .20$ in the bivariate testing were evaluated in a stepwise manner for inclusion in the final model. Furthermore, Kaplan–Maier curves with log-rank test were used to compare time-to-event variables, such as postnatal age (PNA) and postmenstrual age (PMA) at the first extubation. The statistical analyses for paper I were performed in SPSS 26.0 (SPSS Inc., Chicago, IL, USA).

In paper II, categorical variables were compared between successful and failed extubations by using the χ^2 or Fisher exact when appropriate, while the Wilcoxon rank sum test was used for continuous variables. The 95th percentiles for successfully extubated infants determined a cut-off point for pre-extubation FiO_2 and the respiratory severity score (RSS). Logistic regression modelling was performed to identify variables predicting extubation success. The models were internally validated by bootstrapping, using 1000 bootstrap replications to assess overfitting, and proven shrinkage factors for adjusting regression coefficients. Stata/MP (2019, Stata statistical software: Release 16. College station, TX: StataCorp, LL) was used for all the descriptive statistics and the comparison tests, while the R package rms was used to perform the internal validation.

As mentioned at the beginning of this chapter, z-scores were calculated for patient volume and unit acuity in paper III. Each day, the workload in the NICU was defined based on these z-score calculations. The day was defined as a day with normal workload if the z-score was ± 1 SD, a day with high workload if the z-score was >+1 SD, and a day with low workload if the z-score was < -1 SD. Dependent on variable distribution, Kruskal–Wallis and logistic regression analysis were used to examine unadjusted associations between the outcomes of interest and the exposure variables. All statistical analyses were performed using Stata/MP (2019, Stata statistical software: Release 16. College station, TX: StataCorp, LL).

4 Results/summary of the papers

The three papers included in this thesis had a common main objective, which was to explore MV and extubation outcomes among EP infants. Each paper, with its own aims, plays an important part in contributing to the overall goal.

In paper I, a total of 406 infants were included in the analyses, where we examined duration of MV and age at first successful extubation. There were 293 (72%) of the included infants who survived until discharge from the NICU (GA 22–23, n = 67, 60%; GA 24, n = 97, 68%; GA 25, n = 129, 85%). For the survivor infants, the incidence of neonatal morbidities such as severe IVH, BPD, NEC (Bell stage 2–3), and ROP was n = 26 (9%), n = 207 (71%), n = 29 (10%), and n = 70 (24%), respectively.

Outcomes of first extubation attempt

The proportion of infants successfully extubated on their first attempt was 34% of infants born at GA 22–23 weeks, 50% at GA 24 weeks, and 70% at GA 25 weeks. Infants born at GA 25 weeks were generally extubated successfully upon their first attempt during the first week of life (median PNA at first extubation attempt was 5 days, IQR 1–10 days). In comparison, the smallest infants (born at GA 22–23 weeks) were kept longer on MV before clinicians decided to extubate (median PNA at first extubation attempt was 20 days, IQR 10–32 days).

Age at first successful extubation

Infants born at GA 22–23 weeks had their first successful extubation at a median of 33 postnatal days (IQR 23–43 days), whereas infants born at GA 24 weeks had a first successful

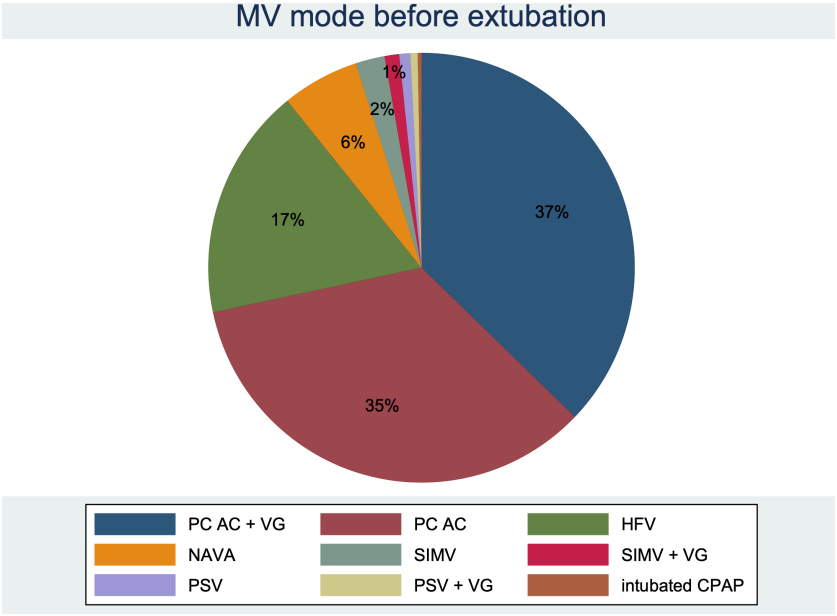
extubation at 21 postnatal days (IQR 7–32 days), and infants born at GA 25 weeks were successfully extubated for the first time at a median of 7 postnatal days (IQR 2–19 days).

Duration of MV and early clinical predictors of prolonged MV

Infants born at the lowest GA received MV to a higher PMA compared to infants born at GA 25 weeks. Male infants, small for gestational age (SGA) infants, infants with a CRIB score > 14, and infants with a five minutes Apgar score < 5 had significantly longer cMV than their counterparts. When corrected for GA in multiple regression analyses, male sex and low five minutes Apgar scores remained strongly associated with prolonged MV.

Extubation characteristics

In paper II, we investigated the infants' first extubation attempt, and 316 infants were included in the final analysis. A total of 173 (55%) infants were successfully extubated, whereas the attempt failed in 143 (45%) infants. The infants were extubated from CV (n = 261, 83%) or HFOV (n = 55, 17%). Distribution of the last documented MV mode before the extubation attempt are shown in Figure 8. The most commonly used MV mode was PC AC/SIPPV with or without VG (72%). There was no difference in MV modes before the extubation attempt between infants with successful and unsuccessful attempts.



Abbreviations: MV, mechanical ventilation; PC AC, pressure control–assist control; VG, volume guarantee; HFV, high frequency oscillatory ventilation; NAVA, neurally adjusted ventilatory assist; SIMV, synchronized intermittent mandatory ventilation; PSV, pressure support ventilation; CPAP, continuous positive pressure airway ventilation

*PC AC includes synchronous positive pressure ventilation (SIPPV) mode

Figure 8. Last documented MV mode before the extubation attempt.

Unadjusted analyses showed significantly higher weight, higher pH, lower oxygen, and lower mean RSS before extubation between successfully extubated infants and those who were not successfully extubated. All infants received either bilevel positive airway pressure (BiPAP) or n-CPAP as respiratory support immediately after extubation, with n-CPAP as the main chosen support regardless of GA (as shown in Figure 9).

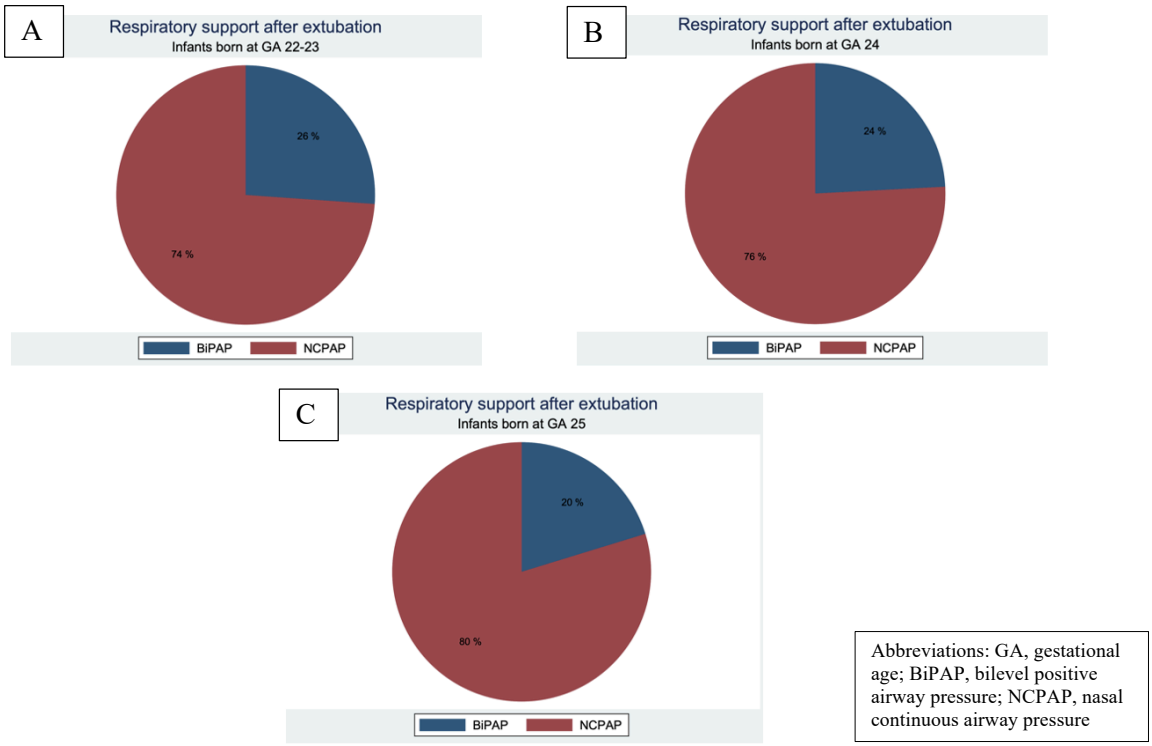


Figure 9. Distribution of the respiratory support provided immediately after extubation. A: Infants born at GA 22–23 weeks, B: Infants born at GA 24 weeks, C: infants born at GA 25 weeks.

In multivariable analysis, a pre-extubation $FiO_2 \leq 0.35$, higher Apgar score, higher gestational age at birth, female sex, and higher postnatal age were identified as important predictors of successful extubation for infants extubated from CV. In extubation from HFOV, a pre-extubation FiO_2 level ≤ 0.35 was a relevant predictor of successful extubation.

Reintubation characteristics

In analysis exploring status for the reintubated infants, 51% were treated with BiPAP immediately before reintubation, whereas 48% were treated with n-CPAP. The frequency distribution of the reported reasons for reintubation are shown in Figure 10, with apnea (48%) as the most commonly reported reason.

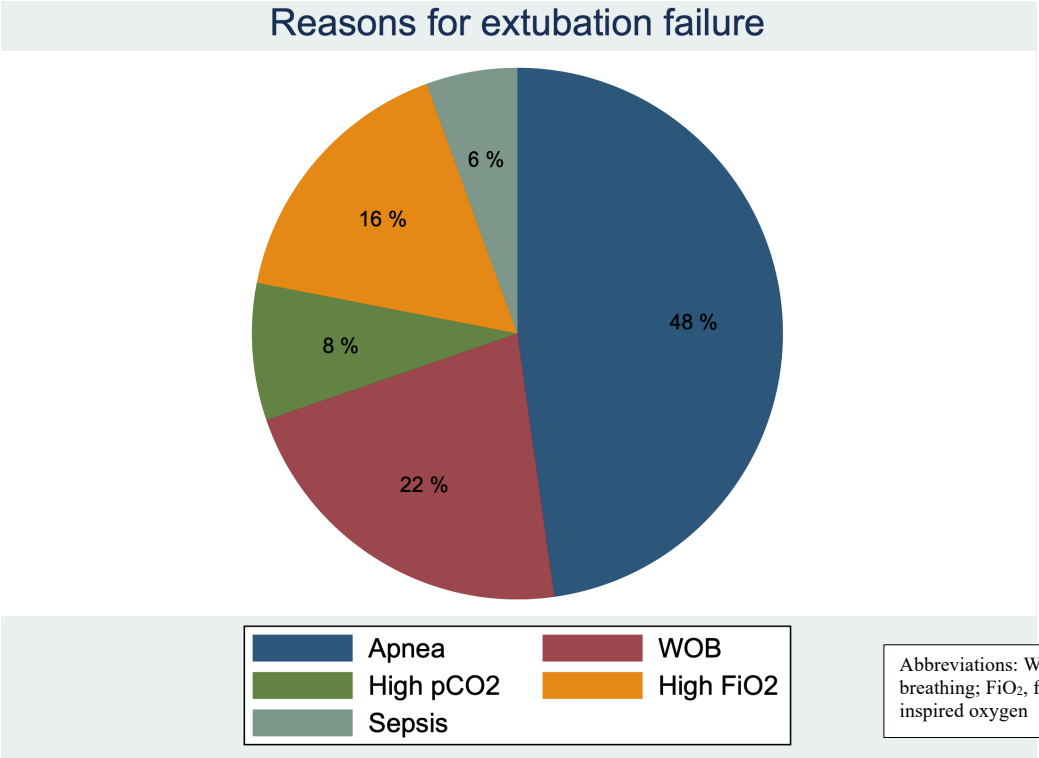


Figure 10. Reasons for extubation failure documented in the EMRs.

Unit workload and the effect of weekend/season

In paper III, we explored whether high workload in the NICU was associated with prolonged MV before the first extubation attempt or the outcome of the attempt. In addition, the weekend and seasonal effects on the outcomes were examined.

Most of the extubation attempts were managed on days categorized as a day with a normal workload at the unit. There was no statistical difference in the duration of MV or incidence of successful extubations if the infant was extubated on a day with a low, normal, or high workload in the NICU. There were 247 (78%) infants who had the first extubation attempt on a weekday, while 69 (22%) had the first attempt during a weekend. There were significantly

more attempts during weekdays compared to Sundays (with a factor of 1.4–1.9, $p = < .01–.03$).

For the reintubated infants, analyses showed no statistical associations between causes for reintubation and unit workload, weekends, or seasons. There was a borderline significant higher pre-reintubation FiO_2 for infants reintubated on days with a high unit workload compared to days with a low unit workload. In addition, there was higher post-reintubation pCO_2 for infants reintubated on days with normal unit workload compared to low unit workload. However, there were no other differences in the pre- and post-reintubation variables explored.

5 Discussion of main findings

Based on the result sections in papers I–III, some of the main findings require a broad discussion in light of previous central research in the area. The main findings that will be discussed throughout this chapter are 1) age at extubation, 2) rates of successful extubation, 3) early clinical predictors of prolonged MV, 4) predictors of successful extubation, 5) the association of unit workload, and 6) the effect of weekend and season.

5.1 Age at extubation

In paper I, we describe both PNA and PMA at the first extubation attempt and at successful extubation. Our results identified delayed first extubation attempts for the infants born at GA 22–23 weeks compared to the infants born at GA 24 and 25 weeks. The most immature infants were extubated for the first time at a median of 20 postnatal days (IQR 10–32 days), whereas half of the infants born at GA 24 weeks (median 7 postnatal days, IQR 3–20 days) and the majority of the infants born at 25 weeks (median 5 postnatal days, IQR 1–10 days) experienced a first extubation attempt during the first week of life.

In our national population, there were higher rates of first extubation attempts during the first week of life for infants born at GA 24 and 25 weeks compared to the results of secondary analyses from the APEX study conducted in five tertiary NICUs in Canada and the US (111). The APEX study presents rates of first extubation attempts in the first week of life of 13% and 30% for the infants born at GA 24 and 25 weeks, respectively. Only a few infants born at GA 23 weeks were extubated during their first week of life, and all the attempts were unsuccessful. That infants born at GA 23 weeks are rarely extubated during their first week of life is comparable to our findings described in paper I. These results might suggest that

clinicians hesitate before they attempt to extubate the smallest infants. There may be various explanations for this phenomenon. It could be explained by the strong associations between low GA and neonatal morbidities with an increased risk of exposure to intensive care treatment such as invasive procedures. However, other factors than immaturity per se may have a significant impact on extubation readiness. In our study, rates of surgical or medical treatment for a PDA were higher among infants born at GA 22–23 weeks and 24 weeks than for infants born at 25 weeks. The presence of a hemodynamically significant PDA could partly explain delayed extubation attempts in the more immature infants.

The timing of the first extubation attempt and respiratory outcomes among EP infants has been studied previously. In a single-center randomized control trial conducted in the early 2000s among EP infants born between 24 through 27 weeks GA, Danan et al. found that delaying extubation by 36 hours after meeting the extubation criteria did not reduce the failure rates nor change the respiratory outcome (112), whereas Berger et al. found that delaying extubation beyond the first three and seven days were associated with increased risk of BPD, even after adjusting for reintubation (113). In a retrospective cohort study including EP infants born at 22^{0}–25^{6} weeks before and after implementing guidelines recommending delayed extubation, Söderström et al. found that the incidence of severe BPD was higher and the duration of MV was longer in babies experiencing delayed extubation (114). Based on these previous findings, a routine approach of postponing extubation among infants conceivably ready for extubation seems to be unjustifiable at present.

5.2 Rates of successful extubation

In paper I, the proportion of successfully extubated infants on their first attempt ranged from 34% of the infants born at GA 22–23 weeks to 70% for the infants born at GA 25 weeks. It is

difficult to compare our results with previous research in the field due to the heterogeneity in the populations being studied as well as varying definitions applied when defining successful extubation. In previous research on extubation outcomes among infants born before GA 28 weeks or ≤ 1250 gram, the rates of successful extubation range between 53% and 77% (97,115–119). These studies report rates of success based on the seven-day or the five-day definition (97,115–119), whereas the recently published paper by He et al. reported rates using the 72 hours definition (120). Of the 359 infants included in the study from He et al., 69% were defined as successfully extubated and 31% failed. However, these rates were based on a more mature population, as all infants < 32 weeks GA were included. An observation window of 48, 72, and 168 h (seven days) without reintubation has previously been identified as the most commonly used definitions (121). A longitudinal study evaluating the prevalence, timing, and causes of reintubations among infants ≤ 1250g reported infrequent reintubations attributable to non-respiratory causes in the first seven days after extubation (122), and Shalish et al. recommend reporting rates at 48–72 hours and at seven days post-extubation to avoid under-reporting true reintubation rates caused by respiratory deficiency (123). In addition, with the focus on avoiding MV as much as possible, the NIV treatment for EP infants has changed and developed in the last decades. Development of NIV treatment includes new devices, such as headgear, masks, and prongs. Perhaps this development may have led to a postponement of reintubation due to respiratory causes. Nevertheless, it is necessary to be aware that expanding the observation window for extubation success among this population could increase the risk of including extubations that failed for non-respiratory reasons.

In paper II, we separated the analysis for infants extubated from CV and HFOV. The rates for successful extubation among the infants extubated from CV were 54%, as opposed to a

success rate of 60% in infants extubated from HFOV. We argue that characteristics in the population extubated from HFOV in our study differs from those extubated from CV, since HFOV is commonly used as a rescue treatment for infants when CV does not provide sufficient respiratory support. Similarly, a prospective observational study conducted at one tertiary NICU in Italy explored 108 EP infants (26 ± 1.4 weeks of GA) directly extubated from HFOV and identified 83% successfully extubated infants using the seven-day definition. However, all infants in this Italian study were managed with elective HFOV, creating difficulty in comparing results.

5.3 Early clinical predictors for prolonged MV

In paper I, we identified that male infants, SGA status, infants with a CRIB score > 14, and infants with five minutes Apgar score < 5 had significantly longer cMV compared to their counterparts. Similar to other investigators, we found that cMV was negatively associated with lower GA, male sex, and low five-minute Apgar scores (15,119). Jensen et al. conducted a retrospective cohort study of infants with birth weight < 1000 g born between 2006 and 2012 and identified lower GA, lower birth weight, and male sex being associated with longer cMV and a greater number of ventilation courses (15). The same researchers showed that longer cMV was of higher importance compared to the experience of a reintubation event when it comes to increased risk of BPD.

The negative association of longer duration of cMV with lower GA is not surprising. Lower GA is strongly associated with severe neonatal morbidities (124), and it is therefore a risk of increased exposure to invasive procedures and intensive care for the most immature infants. Increased exposure to intensive care treatment might negatively affect lung maturation and extubation readiness.

The duration of MV among infants included in paper I was notably lower than the duration reported for comparable infants in the United States of America (124). For EP infants born between 2013 and 2018, they reported cMV (HFOV and/or CV) for the most immature infants born at GA 22 and 23 weeks at 65 median days (IQR 50–81 days) and 51 median days (36–70), respectively, whereas for the infants born at GA 24 and 25 weeks, the cMV were 37 days (IQR 23–57 days) and 23 days (IQR 7–40 days), respectively. Contrary, 75% of the most immature infants in our cohort, infants born at GA 22–23 weeks, were treated with MV for less than 50 days. However, our results are comparable with the duration of MV reported in the Swedish EXPRESS study including EP infants during 2004–2007 (77). Sweden is a country comparable to Norway regarding the approach and management of EP infants born below a GA of 26 weeks (125).

5.4 Predictors for successful extubation

Since there is a high proportion of EP infants experiencing failed extubation with the need for reintubation, there is a demand for well-designed studies identifying predictors of successful extubation. Extubation failure among EP infants has been associated with a significant setback in the respiratory status where infants who fail an extubation attempt may not achieve pre-extubation respiratory status for many days after reintubation (116).

In paper II, we found that successful extubation from CV was associated with pre-extubation $FiO_2 \leq 0.35$, a five-minute Apgar score > 5, higher GA, female sex, and higher PNA, while successful extubation from HFOV was associated with pre-extubation $FiO_2 \leq 0.35$.

We acknowledge that the relationship between lower FiO_2 and extubation success has been well-established in previous studies (117,119,126). However, to our knowledge, no previous studies reporting predictors of extubation success among EP infants have previously specified a cut-off value for FiO_2. We chose to define the cut-off value for "pre-extubation FiO_2" based on the 95th percentile for the successfully extubated infants (0.35). In the results of the adjusted analyses, the odds of successful extubation were 6.3 (95% CI 2.5–16.0) if the pre-extubation administered oxygen was below 35%, indicating a significantly greater risk of failure if the infant is extubated with pre-extubation oxygen above this cut-off.

Surprisingly, we did not identify the CRIB II score as a predictor for extubation success. However, our findings of an odds of three times more likely successful extubation if the infant had an Apgar score above 5 at five minutes of age could suggest that the infant's general condition at birth may be of importance when immature infants are about to be extubated for the first time. The value of the Apgar score to assess the condition of premature infants has been questioned. The Apgar score was originally developed to assess infants born at term in order to be able to carry out a rapid assessment of the newborn immediately after birth. It is normally carried out at one, five, and ten minutes of age and is based on individual scores carried out by either a midwife or a pediatrician. The Apgar score consists of five variables (heart rate, respiration, muscle tone, reflexes, and skin color), which are scored from 0–2 points and summed to a maximum score of 10. It is an expression of the infant's physiological condition immediately after delivery. Nevertheless, there are several factors possibly influencing the score, including maternal drugs before birth, congenital malformations, gestational age, trauma, and interobserver variability (127). However, in a large study using data from the Swedish Medical Birth Register including premature infants (GA 22–37) born from 1992 through 2016, Apgar scores at five minutes were found to

provide prognostic information about neonatal survival (128). In addition, Moreira and colleagues developed and validated a new mortality prediction model for EP infants < GA 28 weeks, where the five minutes Apgar score is one of three components (birth weight, Apgar at five minutes of life, and GA in weeks) that provides a quantitative measure of the probability of death (129). These findings highlight the importance of optimizing prenatal care, as well as neonatal care and treatment in the delivery room, requiring a highly competent and specially trained team.

In our cohort, pre-extubation positive inspiratory pressure (PIP) and/or MAP were not identified as predictors of successful extubation. This result contradicts previous results reported by Kidman et al., which identified MAP as a predictor for successful extubation in a cohort of EP infants born < GA 28 weeks (97). Based on clinical relevance, in our multivariable analyses, we included both pre-extubation PIP and pre-extubation MAP variables, despite the non-significant difference between successful and failed extubations in univariate analysis. We believe that one important reason for the differences in identified predictors between studies may be the influence of the clinical judgment made prior to the extubation attempts. Consequently, results from retrospective cohort studies should be interpreted with this aspect in mind. It is challenging to develop prediction models constructed on results from studies including infants already clinically considered extubation-ready if one cannot clearly account precisely for the clinical assessment made of each individual infant. Among the participating units in our study, similar extubation criteria were reported. Still, we have not been able to control if these reported criteria were followed by the individual clinicians in the events explored. Results from retrospective study designs can be used to identify factors that possibly need additional clinical emphasis. Hence, we conclude in paper II that “our results suggest that additional emphasis on oxygen requirement, sex, and

general condition at birth may further increase extubation success when clinicians are about to extubate EP infants for the first time."

5.5 The association of unit workload

In paper III, we hypothesized that the ability to provide optimal respiratory care might be influenced by the unit workload. Higher nursing provision ratios have been associated with a reduction in the incidence of BPD among very premature infants (130). Conversely, our results showed no association between high workload in the unit and the duration of MV before the first extubation attempt or the outcome of the attempt. We provide two possible explanations for this finding. The first explanation is that Norwegian NICUs have a sufficient number of nurses and physicians to provide optimal respiratory care for EP infants regardless of whether there is a high workload in the unit or not. However, the outcome variables explored are short-term based, illustrating that nurses and physicians might prioritize airway (A) and breathing (B) and perhaps also circulation (C) on days with high unit workload. The no association observation might reflect that the outcomes explored in our study are resilient to variations in workload in the unit. Our results must be interpreted in light of the study's limitations. We were not able to include the actual number of healthcare professionals on call at each participating unit on each day. In addition, we considered two measures of unit workload based on available variables in the NNN: patient volume and unit acuity. In paper III, we argue that unit acuity may be a more meaningful measure of workload compared with patient volume, because a higher patient volume with few infants at the highest patient levels requests different unit resources compared with lower patient volumes with a high number of infants demanding high intensive care treatment. There may also be restrictions in the patient classification system to capture the existent workload in the unit. It is known that extra resources are needed for families with special needs, for example families with a foreign

language background with the need for an interpreter. Such factors are not captured in the daily resource registration in the NNN.

5.6 The effect of weekend and season

In paper III, we examined the effect of weekends or seasons on the duration of MV until the first extubation attempt and the outcome of the first extubation attempt, because weekends and holidays have been identified as times when staffing in hospitals tends to be lower. Additionally, several researchers have noted associations between weekend admissions and worse patient outcomes (109,131,132). Our results identified no effect of weekend or season on the duration of MV before the first extubation attempt or on the outcome of the attempt. However, we identified that the first extubation was more often attempted on weekdays compared with weekends. Based on this finding, we speculate that clinicians postpone the extubation attempt on weekends and that considerations of available staffing at the weekends may be part of the clinical assessment. If this is the case, such assessments might result in a prolonged duration of MV for the extubation-ready infant.

6 Methodological considerations

6.1 General considerations

All three papers included in this thesis had an observational design. We chose an observational study design based on our acquaintance with the unique data material prospectively collected in the NNN and what opportunities this created regarding an investigation of MV and extubation success for the total EP population in Norway. In addition, the scarce knowledge about indicators of successful extubation among the EP population caused ethical difficulties to initiate a randomized controlled trial. Some areas in epidemiological research are not advisable to be investigated by randomized control trials, and the observational study design can therefore be a good alternative to obtain more knowledge. Conducting a study exploring already collected data does not affect the infants' treatment. In addition, observational designs are relatively cheap and easy to carry out within a relatively short time frame (7). Data from national quality registers and EMRs are increasingly used to study health in specific populations, develop prediction models, identify best practices, and simulate randomized clinical trials (by using propensity score analyses) (133). Still, such designs have some limitations one should be aware of. It is impossible to identify causal relationships; however, an observed association may be used for the development and specification of hypotheses. In observational studies, it is essential to be aware of confounding variables as most individuals are subject to various exposures during their hospital stay. Still, there is a risk of not being able to capture all the variables that can influence the outcome of interest. In addition, the variables collected to create the dataset were originally not recorded for the study purpose. This can provide concerns about how variables are subsequently interpreted and analyzed (134).

6.2 Selection of the population being explored

We chose to explore a population of infants born before 26 weeks GA. The rationale for choosing 22 through 26 weeks was based on the reported use of MV in the Norwegian NEPS2 study. In this cohort, 96% of the infants born at 25 weeks GA were treated with MV (any) and 88% were on MV before three days of age. For infants born in GA 22, 23, and 24 weeks, 100% were treated with MV (any), and 100% of the infants born in GA 22 and 23 were treated with MV before three days of age, while 95% of the infants born in GA 24 were treated with MV (12). We did not include infants > 26 weeks GA because the proportion of infants treated with MV (any or before three days) was below 80% (76% and 63%, respectively). The first choice of immediate respiratory support for more mature infants is non-invasive respiratory support. Some centers providing active treatment for the most immature infants have reported almost universal use of early intubation (34,135). This is in line with the NEPS2 study reporting that of infants admitted to NICU, 100% of infants born at GA 22 and 23 were intubated in the delivery room, while among infants born at GA 24 and 25 weeks, 97% and 75%, respectively, were intubated immediately after birth (12). However, as the findings in paper I illustrate, lung maturation and respiratory trajectory differ between infants born at GA 25 weeks from the more immature infants born at GA 22–24 weeks. The smallest EP infants are treated with MV to a higher PNA and PMA compared to infants born at GA 25 weeks. There was also a higher proportion of infants born at GA 22–24 weeks who received medical or surgical treatment for PDA compared to infants born at GA 25 weeks.

Even though the total population of infants born < 26 weeks GA are all born during the canicular stage in fetal lung development, our results confirm variations between gestational ages as the most immature infants were exposed to MV for considerably longer than infants born at GA 24 and 25 weeks.

6.3 Deciding the outcome measure: definition of extubation success

There is heterogeneity regarding the reported definition of extubation success in premature infants, ranging from 12 hours to seven days (121). We chose a definition of successful extubation as 72 hours without the need for reintubation to prevent the inclusion of non-respiratory-related failed extubation. However, recent studies have recommended reporting rates at both 48–72 hours and 7 days (122,123). In paper I, we show that the rate of first successful extubation matches over 80% of the events regardless of whether a 72-hour or a seven-day window is chosen. In paper II, we show that the rate of first extubation success using the 72-hour definition is 55%, while using the seven-day window the success rate decreases to 44%. In paper III, we explored the reasons for reintubations at 72 hours. However, exploring the reasons for reintubations while using the seven-day definition revealed similar results, indicating that among this population the reasons for reintubations within seven days are also predominately respiratory-related. This finding is consistent with the results reported from a longitudinal study conducted by Shalish and colleagues (122) .

6.4 Prediction modeling based on infants clinically judged ready for extubation

In paper II, we built a prediction model, internally validated by bootstrapping. Developing valid prediction models can be challenging and faces various challenges in providing reliable predictions (136). An example of probability providing no certainty can be illustrated by the insecurity of the extubation calculator developed by Gupta et al. (117). Their calculator has been problematized based on the sensitivity and specificity of the prediction model. In the prediction model, the sensitivity and specificity of the prediction alternate with the results of the calculated probability of successful extubation. The authors report that the model had a

sensitivity/specificity of 87%/53% if the calculator predicts a 60% probability of success, whereas, if the calculator predicts an 80% chance of success, the sensitivity falls to 54% and the specificity increases to 81%, suggesting that the ability to predict failures improves. The uncertainty associated with the predictive value of the extubation calculator has been compared with the uncertainty we already find in individual clinical judgment. Shay and Wright raise questions about whether this uncertainty potentially may result in unanticipated harm as poor predictive calculations could postpone extubation attempts, resulting in an increased duration of MV and lung injuries (137). Furthermore, they question whether a tool developed retrospectively could be transferred prospectively. In paper II, we highlight the aspect that all infants in our cohort were already judged extubation-ready. This is an important aspect in developing prediction models based on retrospective cohort analyses. Although all the included NICUs in our study reported similar extubation criteria, we do not have a complete overview of the exact criteria used when the individual infant was extubated.

When developing a prediction model for extubation success, we are interested in the validity of the prediction outside the study sample for new EP infants. One main concern about the validity of a prediction model is overfitting. Overfitting causes optimism for the model performance in future patients (136). We were not able to externally validate our prediction models. However, we internally validated the models by bootstrapping using 1000 bootstrap samples to assess overfitting. In the book *Clinical Prediction Models*, Steyerberg presents bootstrap resampling as a central technique to correct overfitting and quantify optimism in model performance (136). In paper II, the two prediction models we developed are presented. One model was developed for infants extubated from CV, and another model was developed for infants extubated from HFOV. There was a higher model uncertainty for the infants

extubated from HFOV because of relatively high overfitting caused by many variables in relation to the small number of patients (n = 55).

6.5 Exploring data material using register variables

In 2004, the NNN database was established as a national medical quality register by the Ministry of Social Affairs and Health (138). It contains registered data on all patients admitted to and who receive treatment in the Norwegian NICUs. The mandate of the register follows the same associated laws and regulations as the Norwegian Medical Birth Registry. The register can obtain relevant personal identifiers and health information without the hindrance of confidentiality and without the requirement of consent. The purpose of the NNN is to compare treatment activity, patient progress, and results in order to contribute to offering NICU patients in Norway the same high-quality treatment regardless of geographical affiliation (110).

As mentioned under general considerations in Chapter 6.1, the NNN was not initially constructed with the aim of identifying a cohort to investigate MV and extubation attempts among EP infants. However, the database collects several relevant variables for each infant regarding respiratory treatment if the infant receives MV or NIV. Based on the variables recorded in the NNN, it is possible to explore the duration of MV and age at extubation, as presented in paper I. The uniqueness of the database, containing such a large amount of already captured data, facilitates national cohort studies that span over several years and offers the opportunity to compare Norwegian results with international comparable results (110). Quoting Professor J. Olsen: “Register-based research can be done without risk of unwanted disclosure of personal data, and it involves no invasive procedures. It is a valuable gift given by the people to be used for the people” (139). This highlights the importance of

our responsibility to manage the collected data so that it profits future NICU patients. Exploring data from national registers, researchers are able to include large population-based sample sizes. Large sample sizes are beneficial when considering transferability and may increase the statistical power when conducting subgroup analyses and reduce the risk of type II errors (133). In addition, exploring already collected data material can reduce administrative efforts, costs, and sample selection bias.

6.6 Exploring data collected from electronic medical records

In papers II and III, we supplemented the dataset with variables extracted from EMRs. The extracted variables were determined a priori based on clinical experience and previous research. EMRs are intended for patient care, and the data are not systematically recorded for research purposes. Using guidelines for data collection may enhance the quality of the research data (140). Still, errors are difficult to avoid when conducting research on data from EMRs. Possible limitations in our data collection are errors at two different levels: 1) errors in the registration made by healthcare personnel when entering the variables into the medical form, and 2) errors in the registration made by the data collector when extracting variables from the EMR.

Errors at level 1: The variables collected were documented in medical forms by nurses or physicians in charge of the patients. Possible errors that might have been made when these registrations were performed bedside with the patient include entering the wrong value or entering the wrong value at the wrong place, or failing to record the value. Documentation of variables might be subjective, but it can also be a result of procedures and training in the individual unit. For example, there were differences in how the value V_T was documented.

Some documented V_T per kilo body weight, while others documented total V_T. In addition, one unit routinely disconnected the flow sensor for some of the infants, resulting in missing V_T values. This inconsistency in registration led to a high degree of uncertainty for the V_T-variable, and we were not able to use the variable in the analysis. Furthermore, in paper III, we extracted reasons for reintubation from written documentation in the EMRs. This information is not standardized and is prone to subjectivity.

Errors at level 2: Incorrect registration of data from the EMRs is a problem in large studies, and interobserver variability poses a threat to the quality of the data collected (140). Several considerations were taken to prevent and reduce such errors. Firstly, we designed a case report form (CRF) to use in the data collection process. The CRF was created in the computer database program Microsoft Access® (2016, ©Microsoft Corporation), as this was considered an easy-to-use database with which we were familiar. Automatic limit values were inserted in the CRF to prevent typing errors in connection with the registration. Secondly, the coding must be performed accurately and consistently, or the validity of the data may be compromised. Therefore, the final CRF was pilot tested on ten patients and adjusted for weaknesses. A handbook of standards for each variable was made to attain uniformity of data and avoid misinterpretation. We performed a double registration on 10% of 100 completed forms in order to control the accuracy of the registrations. Prior to analyses, we performed consistency checks on the dataset to reveal outlier results. Thirdly, all registration of data into the CRF was performed by Mari Oma Ohnstad to ensure that the data was obtained in the same way for all patients. However, in large studies, it is recommended that the data collection is performed by teams of specially trained data collectors experienced in dealing with large volumes of data (140). Even though the size of the dataset was perceived as

manageable for one person, we recognize this as a limitation and that there might be a possibility of errors in the registration.

Another methodological challenge was that the data collection was performed at 11 different NICUs, and the electronic patient systems were not similar at the hospitals. While the majority of the units used “Distribuert Informasjons- og Pasientdatasystem i Sykehus” (DIPS), two units used DocuLive. However, the data collector had clinical experience with both patient systems, which was an advantage when navigating through the EMRs. There were similarities in the documentation forms when it came to the set of variables that were to be registered for infants receiving MV or NIV, as well as how often the variables were registered. The values were commonly registered once per hour. However, there were differences in format design and how many medical forms the units used for documentation. Some units documented set and measured MV and NIV variables, blood gas values, and prescribed and administered medication on the same medical form, while others had separate forms: one form for set and measured MV and NIV variables, a second form for blood gas variables, and a third form for medications.

Further challenges arose when extracting variables from handwritten documents that had been scanned into the EMRs (see example in Figure 11). Sometimes the entire document was not scanned, it was scanned upside down, or it was systematized on the wrong date. Misinterpretations of handwritten values might be present, and the reason for some of the missing values in the dataset are that it was impossible to interpret the written value.

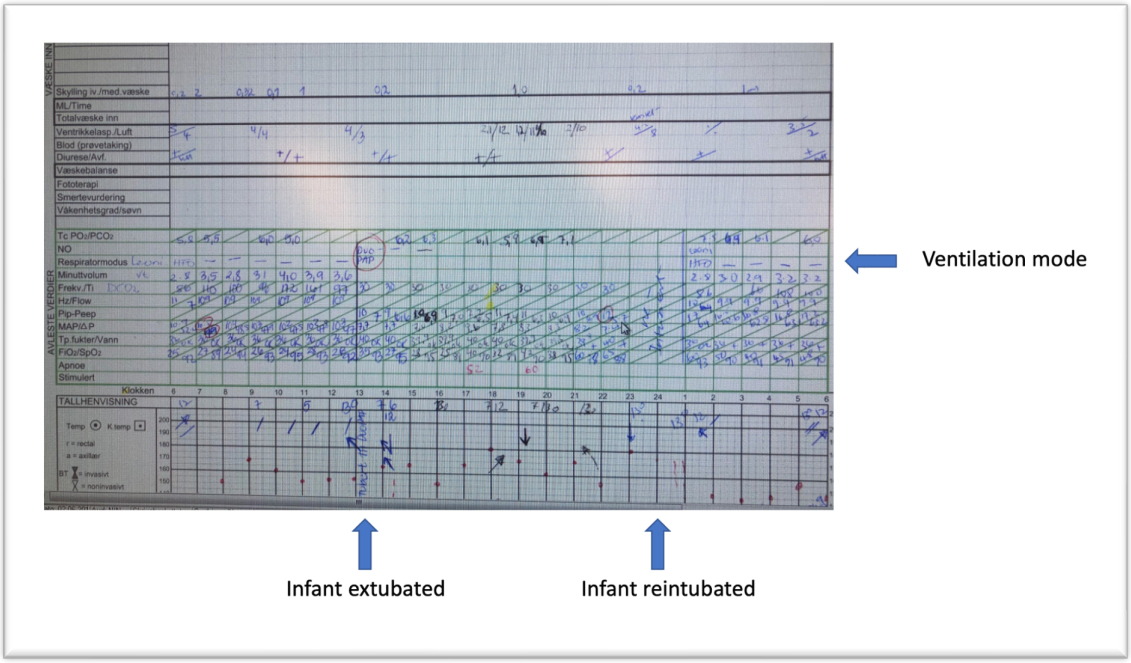


Figure 11. Example of handwritten documentation in the medical record. © Private photo.

The main part of data extraction was conducted from handwritten medical forms, with the exception of patients treated at Trondheim University Hospital after March 2017. In March 2017 the hospital converted from paper-based medical forms to a patient management software system called PICIS. PICIS automatically transfers data from technical equipment to the patient's medical record. Such automatic electronic transfer of data is believed to improve documentation and is perceived to contribute to a higher proportion of completeness in variables and less uncertainty compared with handwritten documentation forms (141). However, our data collection revealed some challenges with the automatic electronic documentation, which we had not anticipated. There were missing values for some of the infants, for example, due to cables from the medical technical equipment not being inserted, resulting in values not being transferred into the patient's EMR. In a healthcare setting, one might forget to insert a cable in situations that are perceived as acute and demanding. Since

we explored extubation and reintubation events, this could possibly explain why it had happened in some of the cases in our population.

However, there was high completeness on several of the collected variables. For example, there was 100% completeness in the "pre-extubation oxygen" variable and 98% in the "pre-extubation MAP" variable. For infants extubated from CV, in the variable "pre-extubation PIP" there were 1.5% (n = 4/261) values missing, while the "pre-extubation set frequency" variable was missing in 6% (n = 15/261) of cases. For all infants, there was 12% (n = 39/316) missing in the pre-extubation blood gas variables (pH, pCO_2, and BE), whereas there were 17% (n = 53) missing in the post-extubation blood gas variables. A higher proportion of missing blood gas values after extubation might be caused by clinicians prioritizing minimal handling after extubation where they follow transcutaneous values instead of performing a potentially painful blood test sampling. In paper II and paper III, we handled missing values by including only observations with complete data (complete data analyses) into the regression analyses, where we accepted a proportion of missing values under 5%.

7 Ethical considerations

The PhD project was approved by the Regional Committee for Medical and Health Research Ethics (REC, north) in Norway, with reference number 2018/1346. Additionally, the NIPH, acting as the data processing officers for the NNN, approved data extraction from the register (reference number 19/11623). Furthermore, the data protection representative at Oslo University Hospital approved the project (reference number 4558653). In accordance with guidelines at the Oslo University Hospital, a self-declaration form was filled out and considered adequate for the Data Protection Impact Assessment (DPIA) of the project (142).

Initially, we applied to REC for an exemption from the need for consent, based on our plans of investigating already captured data material and the fact that a large number of the parents had experienced losing their infant during hospitalization. The initial REC application was approved, but with a requirement of distributing an information letter about the study to the infants' mothers with an opt-out alternative. According to the Guidelines for Research Ethics in the Social Sciences and the Humanities provided by the National Committee for Research Ethics in the Social Sciences and the Humanities in 2021, obtaining passive consent may be appropriate, specifying that the demand for information and the right to reservation have been secured (143).

The information letter was distributed to eligible infant mothers for whom we were able to identify their listed address. Cases where we were unable to identify the mother's address were excluded (n = 22). Infants were automatically enrolled in the study if the mothers did not respond to the letter within four weeks to decline participation. Mothers of 21 infants

chose the opt-out alternative. Two mothers expressed that receiving the information letter had been a painful reminder of a very difficult time in their lives when they lost their newborn.

The thesis investigates intensive care treatment of some of the most vulnerable patients in hospitals. Furthermore, the existing body of evidence for this population is limited due to restrictions on enrolment and eligibility criteria in previous randomized trials, eliminating high-risk infants (18). Our study design enabled the inclusion of all treated EP infants born before a GA of 26 weeks in Norway during a six-year time period. It entails an ethical responsibility to communicate the findings, aiming at contributing to the optimization of advanced intensive care treatment for the most immature infants.

8 Conclusion and implications/future perspectives

This thesis provides additional knowledge about MV treatment and extubation attempts in a national cohort of EP infants born below a GA of 26 weeks. Our results identify some clinical indicators associated with successful extubation. Based on our findings, we suggest that in supplement to the clinical judgment of extubation readiness, additional emphasis on pre-extubation oxygen requirement, sex, and five-minute Apgar score may contribute to reduced duration of MV and reduced numbers of stressful reintubations. We have provided further knowledge about differences between infants born at GA 25 weeks compared to infants born at GA 22–23 weeks regarding the duration of MV and age at extubation success. This finding indicates a gap in the knowledge of the optimal timing of extubation, especially for the most immature infants.

Extubation readiness is a complex, multifactorial topic with important clinical implications. There is a need for further studies exploring how to optimize the intensive care treatment for this vulnerable population avoiding severe complications affecting neurological development and quality of life. Such studies may contribute to socioeconomic gains, benefiting society. Prospective follow-up studies with a focus on MV and extubation attempts among EP infants could be initiated based on the knowledge obtained in previous studies and ours. In addition, exploring these outcomes in relation to minimal handling versus frequent interruptions/manipulations could contribute to a broader understanding of extubation readiness.

In conclusion, the results presented in this thesis might have a possible effect on the treatment of the future EP infant. Dissemination of our findings might lead to increased awareness among clinicians of the importance of optimal MV treatment and extubation success, with the possibility of a change in practice.

9 References

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Reprint of papers I-III

I **Ohnstad M.O., Stensvold H.J., Tvedt C.R., Rønnestad A.E.**
Duration of mechanical ventilation and extubation success among extremely premature infants. Neonatology 2021;118:90-97. https://doi.org/10.1159/000513329

II **Ohnstad M.O., Stensvold H.J., Pripp A.H, Tvedt C.R., Jelsness-Jørgensen L.P., Astrup H., Eriksen B.H., Klingenberg C., Mreihil K., Pedersen T., Rettedal S.I., Selberg T., Solberg R., Støen R., Rønnestad A.E.**
Predictors of extubation success: A population-based study of neonates below a gestational age of 26 weeks. BMJ Paediatrics Open 2022. http://dx.doi.org/10.1136/bmjpo-2022-001542

III **Ohnstad M.O., Stensvold H.J., Pripp A.H, Tvedt C.R., Jelsness-Jørgensen L.P., Astrup H., Eriksen B.H., Lunnay M.L., Mreihil K., Pedersen T., Rettedal S.I., Selberg T., Solberg R., Støen R., Rønnestad A.E.**
Associations between unit workloads and outcomes of first extubation attempts in extremely premature infants. Submitted to Frontiers in Pediatrics.

Original papers

Paper I

Paper II

BMJ Paediatrics Open

Predictors of extubation success: a population-based study of neonates below a gestational age of 26 weeks

Mari Oma Ohnstad ,[1,2] Hans Jørgen Stensvold,[3,4] Are Hugo Pripp,[5,6] Christine Raaen Tvedt,[1] Lars-Petter Jelsness-Jørgensen,[1,7,8] Henriette Astrup,[9] Beate Horsberg Eriksen,[10,11] Claus Klingenberg,[12,13] Khalaf Mreihil,[14] Tanja Pedersen,[15] Siren Rettedal ,[16,17] Terje Reidar Selberg,[18] Rønnaug Solberg,[19,20] Ragnhild Støen,[21,22] Arild E Rønnestad,[2,3,4,23] On behalf of the Norwegian Neonatal Network

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For numbered affiliations see end of article.

Correspondence to
Dr Mari Oma Ohnstad; mari.oma.ohnstad@ldh.no

ABSTRACT

Objective The aim of the study was to investigate first extubation attempts among extremely premature (EP) infants and to explore factors that may increase the quality of clinical judgement of extubation readiness.

Design and method A population-based study was conducted to explore first extubation attempts for EP infants born before a gestational age (GA) of 26 weeks in Norway between 1 January 2013 and 31 December 2018. Eligible infants were identified via the Norwegian Neonatal Network database. The primary outcome was successful extubation, defined as no reintubation within 72 hours after extubation.

Results Among 482 eligible infants, 316 first extubation attempts were identified. Overall, 173 (55%) infants were successfully extubated, whereas the first attempt failed in 143 (45%) infants. A total of 261 (83%) infants were extubated from conventional ventilation (CV), and 55 (17%) infants were extubated from high-frequency oscillatory ventilation (HFOV). In extubation from CV, pre-extubation fraction of inspired oxygen (FiO_2) ≤0.35, higher Apgar score, higher GA, female sex and higher postnatal age were important predictors of successful extubation. In extubation from HFOV, a pre-extubation FiO_2 level ≤0.35 was a relevant predictor of successful extubation.

Conclusions The correct timing of extubation in EP infants is important. In this national cohort, 55% of the first extubation attempts were successful. Our results suggest that additional emphasis on oxygen requirement, sex and general condition at birth may further increase extubation success when clinicians are about to extubate EP infants for the first time.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Identifying the optimal time for the first extubation of extremely preterm infants is complex and clinically challenging.

⇒ A large proportion of infants born before 26 weeks' gestational age are reintubated after their first extubation attempt.

WHAT THIS STUDY ADDS

⇒ This study identifies factors that predict whether extubation of extremely premature infants, clinically considered ready for extubation, will succeed in the first attempt.

⇒ Pre-extubation fraction of inspired oxygen (FiO_2) ≤0.35, higher 5 min Apgar scores, higher gestational age, female sex and higher postnatal age at extubation are associated with successful first extubation attempts.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We suggest pre-extubation FiO_2 at 0.35 as a cut-off level predictive for extubation outcome.

⇒ Inclusion of sex and general condition at birth may improve clinical judgement of extubation readiness for the most immature infants.

INTRODUCTION

Most extremely premature (EP) infants born before a gestational age (GA) of 26 weeks receive mechanical ventilation (MV).[1 2] Although MV may be life-saving, ventilator-induced lung injury increases the risk of chronic respiratory morbidity.[3 4] Therefore, clinicians strive for extubation as soon as possible. Extubation failure is common, and associated with longer duration of MV, increased length of hospital stay and increased risk of nosocomial infections and death.[5–9] Clinical assessment of the ideal timing of extubation for EP infants is complex, including identification of optimal pre-extubation, periextubation and postextubation management.[10] Consequently, studies that can help predict successful extubation in EP infants are warranted and of clinical importance.[11]

Several studies have investigated extubation readiness in premature infants.[12–14] A systematic review and meta-analysis of predictors of extubation readiness found insufficient

evidence to support the use of any predictors over clinical judgement alone.[15] Although various prediction models have been developed, none have been widely accepted in clinical practice.[16–18] Gupta *et al* developed a prediction model for extubation success and proposed an extubation calculator for use in clinical practice.[18] A recent study conducted at two tertiary perinatal centres in Australia suggested that the extubation outcome is associated with the mean airway pressure (MAP) and GA.[19] However, these previous studies have examined populations of EP infants with a mean GA of 26–27 weeks, potentially limiting the applicability to the most immature infants. Hence, the primary aim of our study was to investigate infant characteristics and ventilation parameters at first extubation attempt in a national cohort of EP infants below 26 weeks GA, and second to explore factors that may increase the quality of clinical judgement of extubation readiness.

METHODS

We conducted an analysis of prospectively registered data from the Norwegian Neonatal Network (NNN), supplemented by data extracted from patient records, to explore the first extubation events among premature infants <26 weeks GA born in Norway between 1 January 2013 and 31 December 2018. Eligible infants were identified in the NNN database. An information letter describing the purpose of the study was distributed to the infants' mothers, including an opt-out alternative. Infants were automatically enrolled in the study if the mother did not respond to the letter within 4 weeks to decline participation.

Demographic and clinical factors with a potential predictive effect on extubation success were determined a priori by the study investigators and were based on clinical experience and prior research in the field. Data regarding MV settings and blood gas samples related to the extubation events were extracted from patients' medical records at the 10 neonatal intensive care units (NICUs) where the infants had been treated. A senior clinician at each participating NICU reported the unit's clinical extubation strategy during the study period.

Variables and definitions

The primary outcome was a successful first extubation attempt, defined as no reintubation event within 72 hours. We also explored success rates within 7 days with no reintubation. Prenatal variables included antenatal steroids, mode of delivery and plurality. Demographic variables included GA, sex, birth weight (BW) and weight for GA. Apgar score at 5 min and Clinical Risk Index for Babies (CRIB II) score were included as variables describing general condition at birth and illness severity score. Delivery room variables included endotracheal intubation and surfactant administration.

Pre-extubation variables extracted from medical records included the last registered ventilator mode prior to extubation. For infants extubated from conventional ventilation (CV), we extracted fraction of inspired oxygen (FiO_2), peak inflation pressure (PIP; set for infants receiving pressure-limited ventilation and measured for those receiving volume-targeted ventilation-VTV), MAP and the ventilator set rate. For infants extubated from high-frequency oscillatory ventilation (HFOV), FiO_2 and MAP values were extracted. For all variables, both the last registered value and mean values for the last 6 hours prior to the extubation attempt were extracted.

For all included infants, weight at extubation and blood gas variables measured a maximum of 12 hours prior to extubation were extracted. The Ventilation Index (VI) and Respiratory Severity Score (RSS) were calculated and applied as objective measures of respiratory illness. VI was calculated as partial pressure of carbon dioxide (pCO_2) in arterial, venous or capillary blood multiplied by the ventilator set rate multiplied by the difference between PIP and positive end expiratory pressure, all divided by 1000.[20] RSS was calculated as a product of MAP and FiO_2.[21] Growth throughout the MV course was calculated based on the difference between the infants' weight on the day of intubation and the day of extubation. Information regarding caffeine and postnatal corticosteroid therapy on the day of extubation was recorded. Postextubation variables included the mode of non-invasive respiratory support delivered immediately after extubation. Accidental extubation events were identified by screening of notes written by the physician and nurses in charge on the day of extubation.

Statistical analyses

Demographic data were expressed as numbers with proportions (%), means with SD, or medians with 25th and 75th percentiles (IQR). We compared the perinatal and peri-extubation characteristics of infants successfully extubated at the first attempt with those who failed. Extubations from CV and HFOV were explored separately.

Categorical variables were compared between successful and failed extubations by using the χ^2 test or Fisher's exact test when appropriate. Continuous variables were analysed using a Wilcoxon rank-sum test. The pre-extubation variables, FiO_2 and RSS were examined for cut-off points at the 95th percentiles for successfully extubated infants.

Logistic regression modelling to identify variables predicting extubation success was applied separately for the extubations from CV and HFOV. Relevant variables based on clinical significance were included in the logistic regression models. All multivariable logistic regression models were internally validated by bootstrapping, using 1000 bootstrap samples to assess overfitting and provide shrinkage factors for adjusting regression coefficients. We assessed the model performance in terms of the Nagelkerke R-squared (R^2) from logistic regression, calibration slope and area under the curve before and after internal validation with optimism corrected estimates, please

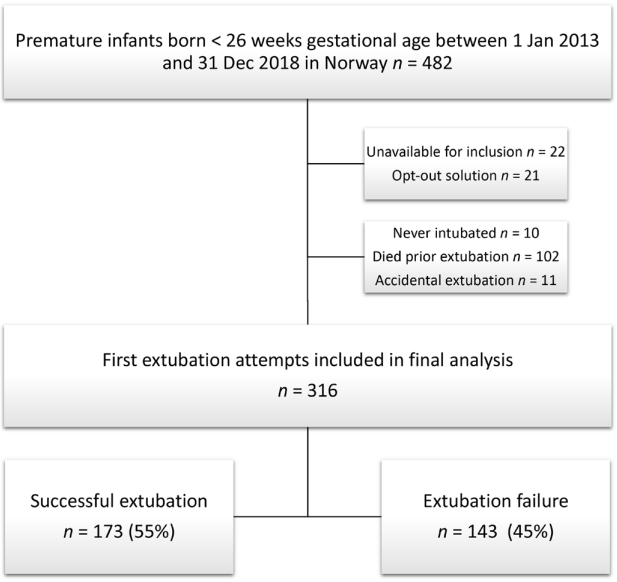

Figure 1 Flowchart of infants in the study.

see[22 23] for a through statistical explanation of internal validation with bootstrapping.

The threshold for statistical significance was set at p<0.05. Initial summary statistics and comparison tests were performed using Stata/MP V.16.1 and internal validation was conducted using the R package rms.[24]

RESULTS

During the 6-year study period, 482 EP infants of <26 weeks GA received treatment in Norwegian NICUs (figure 1). Of these, 43 (9%) infants were excluded because the mothers' address could not be verified or the mother chose to opt out. There were no statistical differences in GA, BW or mortality before discharge between infants who were included versus excluded (data not shown). Furthermore, 10 (2%) infants were excluded because they only received non-invasive respiratory support, 102 (21%) died prior to the first extubation attempt and 11 (2%) infants had an identified accidental extubation. In the final analysis, 316 infants with first extubation attempts were included, 173 (55%) were successfully extubated and 143 (45%) failed. While exploring success rates using the 7-day definition, 138 (44%) infants were successfully extubated.

Clinical extubation criteria and ventilator mode at extubation

Similar extubation criteria were reported in all participating units. Infants treated with CV were generally considered ready for extubation with a sufficient respiratory drive, PIP <20 cm H_2O and FiO_2 <0.3–0.4. Two NICUs reported clinical considerations for extubation readiness in infants treated with HFOV, that is, MAP at 7–8 cm H_2O and a FiO_2 requirement <0.3–0.4.

Overall, a total of 261 (83%) and 55 (17%) infants were extubated from the CV and HFOV, respectively.

Characteristics at birth

Characteristics at birth in infants with successful and failed first extubation attempts are presented in table 1. Antenatal steroids were given to 298 (94%) infants, and 183 (61%) infants received a complete course. There was no association between receiving antenatal steroids and extubation outcomes.

Successful extubation from CV was associated with GA, BW, delivery method, sex, 5 min Apgar score and CRIB II score. For the infants extubated from HFOV, there was no significant difference in characteristics at birth between those with successful and unsuccessful attempts.

Extubation characteristics

Extubation characteristics of infants with successful or failed first extubation attempts are presented in table 2. Among extubations from CV, 11 (4%) infants received synchronised intermitted mandatory ventilation, 230 (89%) received synchronised positive pressure ventilation or pressure support ventilation and 18 (7%) infants received neurally adjusted ventilatory assist prior to the extubation attempt. A total of 123 (47%) infants received VTV.

Unadjusted analyses showed significantly higher weight, higher pH, lower oxygen and lower mean RSS before extubation but no other differences in objective measures of respiratory illness or medical treatment between successfully extubated infants and those who failed. All infants received either bilevel positive airway pressure or nasal continuous positive airway pressure (NCPAP) immediately after extubation, with NCPAP as the foremost chosen respiratory support.

Adjusted analyses

In a multivariable analysis of extubation from CV, pre-extubation FiO_2 ≤0.35, 5 min Apgar score >5, higher GA, female sex and higher postnatal age at the extubation day remained predictive of successful extubation (table 3). The OR of successful extubation was 6.3 (95% CI 2.5 to 16.0) if the received pre-extubation FiO_2 ≤0.35 prior to the attempt. In multivariable analysis of extubation from HFOV, pre-extubation FiO_2 ≤0.35 remained predictive of successful extubation.

The predictors of successful extubation were combined in a model to construct a receiver operating characteristic curve for the two prediction models. Internal validation of the model for extubation from CV showed the optimism corrected (a measure of model performance after internal validation) R^2 at 0.28, corrected area under the curve at 0.77 and calibration slope at 0.89. The internal validation of the model for extubation from HFOV identified large model overfitting (R^2=0.23, area under the curve=0.76, calibration slope=0.76). Multivariable analyses performed separately for female and male infants, as well as for infants with late first extubation attempt (>14 days postnatal age) are shown in online supplemental tables 1 and 2, respectively.

Table 1 Characteristics at birth of infants extubated from conventional ventilation and high-frequency ventilation at first extubation attempt, n=316

	Extubated from CV			Extubated from HFOV		
Variable	Successful, n=140	Failed, n=121	P value	Successful, n=33	Failed, n=22	P value
GA, weeks, median (IQR)	25.1 (24.4–25.5)	24.4 (23.5–25.1)	<0.001*	24.4 (23.5–25.1)	24.1 (23.5–24.4)	0.13*
Birth weight g, mean (SD)	695 (147)	651 (124)	0.01	641 (127)	628 (118)	0.69
Complete ANS course†, n (%)	84/133 (63)	69/116 (59)	0.60	20/31 (65)	10/20(50)	0.39
Vaginal delivery, n (%)	86 (61)	91 (75)	0.02*	20 (61)	16 (73)	0.40*
Male sex, n (%)	64 (46)	77 (64)	0.004*	9 (27)	10 (45)	0.25*
Female sex, n (%)	76 (54)	44 (36)		24 (73)	12 (55)	
Multiple birth, n (%)	32 (23)	33 (27)	0.48	10 (30)	6 (27)	1.0
SGA, n (%)	29 (21)	21 (17)	0.35*	6 (18)	4 (18)	1.0
RSS at birth‡, median (IQR)	2.1 (1.7–2.9)	2.3 (1.9–2.9)	0.14	2.6 (1.9–4.0)	3.1 (2.0–4.6)	0.39
Apgar <5 at 5 min, n (%)	15 (11)	29 (24)	0.01*	9 (27)	7 (32)	0.77*
CRIB II>14, n (%)	64 (48)	74 (64)	0.02*	20 (61)	14 (67)	0.78*
Surfactant <first 30 min of life, n (%)	137/139 (99)	119/120 (99)	1.0	31 (94)	22 (100)	0.51
LISA, n (%)	19 (14)	9 (7)	0.16	0 (0)	2 (9)	0.16

*Variables included in multivariable analysis.
†A complete ANS course was defined as when the first dose was administered at least 24 hours before birth. Time of first dose was not registered in 16 (4.9%) infants.
‡RSS was calculated as a product of MAP and fraction of inspired oxygen. Mean RSS at birth was calculated for each infant's first 6 hour of life.
ANS, antenatal steroids; CRIB, Clinical Risk Index for Babies; CV, conventional ventilation; GA, gestational age; HFOV, high frequency oscillatory ventilation; LISA, less invasive surfactant administration; MAP, mean airway pressure; RSS, Respiratory Severity Score; SGA, small for gestational age.

DISCUSSION

In this population-based study of EP infants clinically judged ready for extubation, we found that successful extubation from CV was associated with pre-extubation FiO_2 ≤0.35, a 5 min Apgar score >5, higher GA, female sex and higher postnatal age. Successful extubation from HFOV was associated with pre-extubation FiO_2 ≤0.35. It is important to note that associations between these factors and the results of extubation attempts may be an addition to, not replacement for, clinical judgement.

Our results align with Gupta *et al*, with a higher GA, higher postnatal age, and lower pre-extubation FiO_2 being predictive of successful extubation.[18] In contrast, pre-extubation pH, weight at extubation and RSS at birth did not independently predict extubation success in our cohort. The differences in the findings may be related to differences in the populations explored. Our population only included EP infants <26 weeks GA in a national cohort, whereas the Gupta study was not population based and included more mature infants. In contrast to the results of Kidman *et al*,[19] we did not identify associations with successful extubation and MAP, a finding that probably reflects the clinical evaluation prior to the extubation attempt because all the participating units reported PIP (to achieve normal tidal volume) and oxygen requirement as clinical considerations for extubation readiness.

In several previous studies, low pre-extubation FiO_2 has been reported as predictive of extubation success.[9 18 25] We suggest that a cut-off for pre-extubation FiO_2 at ≥0.35 is a clinically relevant predictor indicating a high risk for extubation failure. In addition to oxygen requirement, clinicians consider blood gas measurements including pCO_2 prior to extubation. Earlier studies have identified lower pre-extubation pCO_2 as an important predictor of successful extubation,[8] as hypercapnia could be an indication of insufficient respiratory drive or low lung compliance. In this study, the pre-extubation pCO_2 was not significantly lower in infants with extubation success compared with those who failed. These results may indicate that clinicians attempt extubation when infants' blood gas measurements are within the normal range.

Similar to previous studies, a 5 min Apgar score >5 was associated with extubation success in the present research.[9 26] The value of the Apgar score in EP infants has been questioned because the frequency of low Apgar scores increases with decreasing GA and may reflect immaturity in general.[27] The relevance of the Apgar score in clinical practice regarding the evaluation of extubation readiness is also questionable. We find the association

Table 2 Characteristics at first extubation attempt, n=316

	Extubated from CV			Extubated from HFOV		
Variable	**Successful, n=140**	**Failed, n=121**	**P value**	**Successful, n=33**	**Failed, n=22**	**P value**
PNA in days, median (IQR)	5 (2–19)	7 (3–16)	0.14*	18 (9–32)	15 (8–25)	0.46*
PMA in weeks, median (IQR)	25.9 (25.4–27.1)	25.6 (24–9–26.7)	0.004	27.3 (25.8–28.2)	25.9 (25.1–28.0)	0.13
Weight g, median (IQR)	740 (620–864)	675 (607–780)	0.02	792 (653–924)	800 (653–1000)	0.97
Growth course g†, median (IQR)	0 (-41–129)	1 (-31–112)	0.87*	118 (37–305)	148 (43–300)	0.87*
Pre-extubation VI‡, median (IQR)	1.9 (1.2–2.4)	1.9 (1.3–2.7)	0.32	NA	NA	NA
Pre-extubation pH§, median (IQR)	7.30 (7.26–7.34)	7.28 (7.23–7.33)	0.04	7.27 (7.19–7.35)	7.26 (7.20–7.33)	0.73
Pre-extubation pCO_2§¶ median (IQR)	6.2 (5.5–7.0)	6.3 (5.7–7.5)	0.06	6.6 (6.3–7.5)	6.6 (5.4–8.0)	0.67
Pre-extubation BE‡, median (IQR)	–3.6 (-6.3 to -1.1)	–5.1 (-6.8 to -1.6)	0.18	–2.5 (-7.0–1.5)	–2.6 (-8.2–0.6)	0.51
Pre-extubation FiO_2, median (IQR)	0.23 (0.21–0.28)	0.25 (0.21–0.33)	0.006*	0.28 (0.24–0.31)	0.33 (0.29–0.44)	0.001*
Pre-extubation RSS**, median (IQR)	1.9 (1.7–2.3)	2.1 (1.7–2.9)	0.005	2.8 (2.2–3.4)	3.3 (2.8–4.0)	0.02
Pre-extubation set ventilation rate, median (IQR)	35 (30–40)	35 (30–45)	0.03	NA	NA	NA
Pre-extubation MAP††, mean (SD)	8.1 (0.13)	8.4 (0.11)	0.07*	9.7 (0.30)	10.2 (0.44)	0.40*
Pre-extubation PIP‡‡, median (IQR)	15 (12–17)	15 (13–16)	0.95	NA	NA	NA
Caffein administration at the day of extubation, n (%)	137 (98)	120 (99)	0.63	32 (97)	22 (100)	1.0
Caffein mg/kg/day, median (IQR),	9.3 (6.0–10.8)	9.8 (7.1–12.4)	0.10	7.5 (6.2–9.8)	8.5 (5.9–16.3)	0.42
Steroid administration at the day of extubation, n (%)	37 (26)	30 (25)	0.78	21 (64)	11 (50)	0.41

*Variables included in multivariable analysis.
†Growth course is the calculated difference between weight at the intubation day and the day of extubation.
‡VI was calculated as partial pressure of carbon dioxide (pCO_2) in arterial, venous or capillary blood multiplied by the ventilator set rate multiplied by the difference between PIP and positive end expiratory pressure, all divided by 1000.
§Measured in arterial, capillary or venous blood samples.
¶The pCO_2 values are given in kilopascal (multiplication by 7.50062 provide values in milimetres of mercury).
**RSS was calculated as a product of MAP and FiO_2. Pre-extubation RSS was calculated based on the last 6 hours before extubation.
††Presented as mean MAP last 6 hours before extubation, missing values in 4 (7%) infants extubated from HFOV.
‡‡PIP derived by a set pressure for infants on pressure limited ventilation, and measured PIP for infants on volume target ventilation.
BE, base excess; CV, conventional ventilation; FiO_2, fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation; MAP, mean airway pressure; NA, not applicable; pH, potential of hydrogen; PIP, peak inspiratory pressure; PMA, postmenstrual age; PNA, postnatal age; RSS, Respiratory Severity Score; VI, ventilation index.

between Apgar score and the lack of association between CRIB II and extubation outcome surprising. Notably, our findings indicate that the association between the general condition at birth and extubation outcome may be reserved for female infants.

The relationship between extubation success and increased GA is well established.[8 21 28–30] A likelihood of extubation success for infants born at higher GA could be explained by advanced lung maturity with increasing GA. However, GA was not independently predictive of extubation success for infants extubated from HFOV in our study. HFOV is commonly used as a rescue treatment for infants where CV does not provide sufficient respiratory support. In our cohort, infants extubated from HFOV had a significantly higher postnatal age when clinicians first attempted extubation. In addition, the proportion of infants who received corticosteroids on the extubation day was higher among infants extubated from HFOV compared with infants extubated from CV. These findings may indicate that infants extubated from HFOV had more severe pulmonary morbidity compared with infants extubated from CV, because in Norwegian NICUs

Table 3 Adjusted markers of successful extubation for infants extubated from conventional ventilation (CV) and for infants extubated from HFOV

Effect	OR	95% CI	P value	Coef.	Adj. coef.
Extubation from CV, n=261					
GA, weeks	3.1	2.03 to 4.58	<0.001	1.19	1.05
Female sex	2.4	1.34 to 4.16	0.003	0.87	0.77
Apgar >5 at 5 min of age	3.3	1.46 to 7.25	0.004	1.18	1.05
Age at extubation, days	1.1	1.02 to 1.08	<0.001	0.06	0.05
Pre-extubation FiO_2 ≤0.35	6.3	2.51 to 16.00	<0.001	1.92	1.70
MAP at extubation	0.8	0.66 to 1.06	0.135	−0.18	−0.16
Extubation from HFOV, n=55					
Female sex	2.6	0.71 to 9.71	0.15	0.97	0.73
Age at extubation, days	1.1	1.00 to 1.13	0.08	0.06	0.05
Pre-extubation FiO_2 ≤0.35	8.6	1.76 to 42.19	0.008	2.15	1.63
MAP at extubation	0.6	0.38 to 1.00	0.05	−0.49	−0.37

Coef, coefficient; FiO_2, fraction of inspired oxygen; GA, gestational age; HFOV, high-frequency oscillatory ventilation; MAP, mean airway pressure.

postnatal corticosteroid therapy are usually reserved infants considered in high risk of bronchopulmonary pulmonary disease and prolonged MV treatment after 10–14 days of age.

We found that females were more often successfully extubated than males. Male sex has previously been identified as a risk factor for longer hospital stay, higher postmenstrual age at discharge and lower survival.[31] In addition, we previously reported that males had significantly longer cumulative MV compared with females.[32]

Our study has limitations. We relied on retrospective data retrieved from medical records when infants were considered extubation ready. Some potentially useful variables (eg, blood gas values and tidal values) were missing and not included. Furthermore, information on maternal health and infant infection status at birth which could affect the respiratory trajectory and first extubation outcome were not available.

The strength of our study is the inclusion of a complete national cohort of premature infants born at <26 weeks GA were we provide descriptions of extubation outcomes for infants extubated from CV and HFOV. In addition to the already established clinical evaluation of lung compliance, respiratory drive and oxygen demand, clinicians may also consider the infants' GA, postnatal age, sex and general condition at birth in the evaluation before first extubation of the smallest EP infants.

CONCLUSION

In this population-based study exploring first extubation attempts among EP infants <26 weeks GA, 55% remained successfully extubated within the first 72 hours. Our results suggest that additional emphasis on oxygen requirement, sex and general condition at birth may further increase extubation success when clinicians are about to extubate the most immature infants for the first time.

Author affiliations
[1]Department for Postgraduate Studies, Lovisenberg Diaconal University College, Oslo, Norway
[2]Institute of Clinical Medicine, Medical Faculty, University of Oslo, Oslo, Norway
[3]Department of Neonatal Intensive Care, Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
[4]Norwegian Neonatal Network, Oslo University Hospital, Oslo, Norway
[5]Oslo Centre of Biostatistics and Epidemiology, Research Support Services, Oslo, Norway
[6]Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway
[7]Department of Health and Welfare, Østfold University College, Halden, Norway
[8]Department of Internal Medicine, Østfold Hospital Trust, Kalnes, Norway
[9]Department of Pediatric and Adolescent Medicine, Sorlandet Hospital Trust, Kristiansand, Norway
[10]Department of Paediatrics, Møre og Romsdal Hospital Trust, Alesund, Norway
[11]Clinical Research Unit, Norwegian University of Science and Technology, Trondheim, Norway
[12]Faculty of Health Sciences, University of Tromsø, Tromso, Norway
[13]Department of Pediatrics, University Hospital of North Norway, Tromso, Norway
[14]Department of Pediatric and Adolescent Medicine, Akershus University Hospital, Lorenskog, Norway
[15]Neonatal Intensive Care Unit, Department of Pediatrics, Haukeland University Hospital, Bergen, Norway
[16]Department of Paediatrics, Stavanger University Hospital, Stavanger, Norway
[17]Faculty of Health Sciences, University of Stavanger, Stavanger, Norway
[18]Department of Pediatric and Adolescent Medicine, Ostfold County Hospital, Gralum, Norway
[19]Department of Paediatrics, Vestfold Hospital Trust, Tonsberg, Norway
[20]Department of Paediatric Research, Oslo University Hospital, Oslo, Norway
[21]Department of Paediatrics, St Olavs Hospital Trondheim University Hospital, Trondheim, Norway
[22]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[23]Research group for clinical neonatal medicine and epidemiology, Institute of clinical medicine, Oslo, Norway

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ORCID iDs
Mari Oma Ohnstad http://orcid.org/0000-0002-5904-1347
Siren Rettedal http://orcid.org/0000-0002-0462-0659

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Supplementary Table 1 Adjusted markers of successful extubation for the groups of female and male infants extubated from conventional ventilation. Area under the curve (AUC) for the female group 0.79, AUC for the male group 0.80

Effect	Odds Ratio	95% Confidence Interval	*p*-value
Female infants, n = 120			
GA, weeks	3.6	1.96–6.74	<0.001
Apgar > 5 at 5 min of age	5.3	1.46–19.6	0.01
Age at extubation, days	1.0	1.00–1.09	0.05
Pre-extubation $FiO_2 \leq 0.35$	5.2	1.36–19.8	0.02
Male infants, n = 138[1]			
GA, weeks	3.9	2.01–7.71	<0.001
SGA	2.5	0.92–6.88	0.07
Age at extubation, days	1.0	1.00–1.09	0.05
Pre-extubation $FiO_2 \leq 0.35$	17.6	3.14–98.48	0.001
MAP at extubation	0.7	0.53–0.9	0.006

GA, gestational age; *FiO_2,* fraction of inspired oxygen*; SGA*, small for gestational age; *MAP,* mean airway pressure

[1]Missing pre-extubation MAP for 3 (2%) infants

Supplementary Table 2 Adjusted markers of successful extubation for the group of infants first extubated at postnatal age >14 days. Area under the curve (AUC) 0.79.

Effect	Odds Ratio	95% Confidence Interval	*p*-value
Extubation from both CV and HFOV, n=108			
GA, weeks	1.6	0.91–2.85	0.10
Female sex	2.9	1.17–7.42	0.02
Apgar > 5 at 5 min of age	2.6	0.80–8.72	0.11
Age at extubation, days	1.1	1.01–1.12	0.01
Pre-extubation $FiO_2 \leq 0.35$	4.4	1.57–12.51	0.005
Steroid treatment at the day of extubation	2.3	0.70–7.26	0.17

CV, Conventional ventilation; *HFOV*, high-frequency oscillatory ventilation; *GA,* gestational age; *FiO_2*, fraction of inspired oxygen*;*

Paper III

Associations between unit workloads and outcomes of first extubation attempts in extremely premature infants

Mari Oma Ohnstad[1,2*], Hans Jørgen Stensvold[3], Are Hugo Pripp[4,5], Christine Raaen Tvedt[1], Lars-Petter Jelsness-Jørgensen[1,6,7], Henriette Astrup[8], Beate Horsberg Eriksen[9,10], Mai Linn Lunnay[11], Khalaf Mreihil[12], Tanja Pedersen[13], Siren Irene Rettedal[14,15], Terje Selberg[16], Rønnaug Solberg[17,18], Ragnhild Støen[19,20], Arild Rønnestad [2,3,21]

[1] Department of Master and Postgraduate Education, Lovisenberg Diaconal University College, Oslo, Norway

[2] Faculty of Medicine, University of Oslo, Oslo, Norway

[3] Department of Neonatal Intensive Care, Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

[4] Oslo Centre of Biostatistics and Epidemiology, Research Support Services, Oslo, Norway

[5] Faculty of Health Sciences, OsloMet – Oslo Metropolitan University, Oslo, Norway

[6] Department of Health and Welfare, Østfold University College, Halden, Norway

[7] Department of Internal Medicine, Østfold Hospital Trust, Kalnes, Norway

[8] Department of Pediatric and Adolescent Medicine, Sorlandet Hospital Trust, Kristiansand, Norway

[9] Department of Pediatrics, Møre and Romsdal Hospital Trust, Ålesund, Norway

[10] Clinical Research Unit, Norwegian University of Science and Technology, Trondheim, Norway

[11] Department of Pediatrics and Adolescence Medicine, University Hospital of North Norway, Tromsø, Norway

[12] Department of Pediatrics and Adolescence Medicine, Akershus University Hospital, Lørenskog, Norway.

[13] Neonatal Intensive Care Unit, Department of Pediatrics, Haukeland University Hospital, Bergen, Norway

[14] Department of Pediatrics, Stavanger University Hospital, Stavanger, Norway

[15] Faculty of Health Sciences, University of Stavanger, Stavanger, Norway

[16] Department of Pediatrics and Adolescence Medicine, Østfold Hospital Trust, Kalnes, Norway

[17] Department of Pediatrics, Vestfold Hospital Trust, Tønsberg, Norway

[18] Department of Pediatric Research, Oslo University Hospital, Oslo, Norway

[19] Department of Neonatology, St Olavs – Trondheim University Hospital, Trondheim, Norway

[20] Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[21] Research group for clinical neonatal medicine and epidemiology. Department of Neonatal Intensive Care, Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

*** Correspondence:**
Mari Oma Ohnstad
mari.oma.ohnstad@ldh.no

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Abstract

Objective: The objective was to explore whether high workloads in neonatal intensive care units were associated with short-term respiratory outcomes of extremely premature (EP) infants born < 26 weeks of gestational age.

Methods: This was a population-based study using data from the Norwegian Neonatal Network supplemented by data extracted from the medical records of EP infants born from 2013–2018.

Results: We analyzed 316 first extubation attempts. There were no associations between unit workloads and the duration of mechanical ventilation until each infant's first extubation or the outcomes of these attempts. Additionally, there were no weekend or seasonal effects on the outcomes explored. Workloads did not affect the causes of reintubation for infants who failed their first extubation attempt.

Conclusion: Our finding that there was no association between the organizational factors explored and short-term respiratory outcomes can be interpreted as indicating resilience in Norwegian neonatal intensive care units.

1 Introduction

Neonatal intensive care units (NICUs) provide care for some of the most vulnerable patients admitted to hospitals, and all admissions to Norwegian NICUs are essentially emergencies (1).

In Norway, the vast majority of extremely premature (EP) infants who are born alive between 23 and 26 weeks of gestational age (GA) receive transitional assistance, mainly with respiratory support. Those who respond positively are admitted to a NICU immediately after birth. Survival rates decrease with decreasing GA, and the smallest babies require treatment in the NICU for weeks or months (2).

The risk of neonatal mortality and morbidity has been shown to increase with increased workloads and decreased staff ratios (3–5). Moreover, NICUs differ from adult and pediatric intensive care units, which exclusively treat intensive care patients, as NICUs treat patients with varied resource needs, from highly intensive care to nearly normal maternity care (6). This creates challenges regarding unit staffing (7). Synnes et al. linked intraventricular hemorrhage to unit characteristics, suggesting that practices in NICUs with higher patient volumes and those with higher neonatologist-to-house staff ratios result in a lower incidence of severe intraventricular hemorrhage (8). In a study from Canada, greater resource use in the unit at the time of admission was associated with a higher risk of neonatal morbidity in very premature infants (9). Furthermore, weekends and holidays have been identified as times when staffing in hospitals tends to be lower, and several researchers have noted associations between weekend admissions and worse patient outcomes (10–12).

For most EP infants < 26 weeks GA, mechanical ventilation (MV) is required for survival (13,14). However, MV itself is associated with complications (15,16), and the optimal timing of extubation is one of many challenges for clinicians (17). Close and continuous observation and monitoring, as well as clinical assessment, are essential to deciding whether and why MV is needed and to prevent prolonged MV treatment or failure of an extubation attempt (18). Moreover, the post-extubation period is considered a time during which the EP infant requires special attention and management to prevent reintubation. In the current study, we hypothesize that the ability to provide optimal respiratory care may be influenced by the unit workload.

It is unknown whether a high unit workload affects the duration of MV until the first extubation attempt and the first extubation outcome. The main objective of this study was to explore whether high workloads in NICUs were associated with adverse short-term respiratory outcomes of EP infants born < 26 weeks of GA. We examined the association of unit workloads and the effects of weekends or seasons with the duration of MV until the first extubation attempt and the outcome of the first extubation attempt. As many EP infants < 26 weeks GA are reintubated after their first extubation attempt (19), our secondary objective was to assess the association of unit workloads and the effects of weekends or seasons with indicators of respiratory morbidity before and shortly after reintubation.

2 Methods

2.1 Setting

This population-based cross-sectional study included infants born at 22^0 through 25^6 weeks GA and admitted to a Norwegian NICU between January 1, 2013, and December 31, 2018. Eligible infants were identified in the Norwegian Neonatal Network (NNN) database. An informational letter describing the purpose of the study was distributed to the infants' mothers and included an opt-out alternative. Infants were enrolled in the study if the mother did not indicate a desire to opt out within four weeks.

2.2 Data collection

We examined data from the NNN supplemented by data extracted from medical records. Data on all patients admitted to any Norwegian NICU (n = 20) are collected daily by trained staff and entered into the NNN's electronic registration platform. The NNN contains anthropometric and demographic data and detailed data on resuscitation, treatment modalities, treatment procedures, diagnoses, outcome parameters, and status at discharge.

From the NNN, we extracted perinatal variables, which included antenatal steroids, delivery method and plurality, and demographic variables, such as GA, sex, birth weight, and weight at GA. In addition, the Clinical Risk Index for Babies (CRIB II) and Apgar scores at 5 minutes were included as variables describing illness severity and general condition at birth. Furthermore, we extracted delivery room variables, which included endotracheal intubation and surfactant administration. From the medical records, we extracted data on MV settings and blood gas samples.

2.3 Exposure: unit workload

Unit workloads were calculated based on variables extracted from the NNN database for each day during the six years studied. To describe the workloads, measurements of daily patient volume and unit acuity at each participating NICU were derived and used as follows.

The patient volume of a given NICU on a given day was defined as "the number of all infants staying in the unit," not only those born below 26 weeks GA and included in our study. Unit acuity was defined as the "intensity of nursing care needed by the patients" in a given NICU on a given day and was calculated based on daily resource registration in the NNN (shown in Figure 1). Each day, patient care and individual treatment procedures are recorded in the NNN database. Patients are classified into five levels, similar to the Vermont Oxford Network researcher's classification (20). Levels 1 and 2 represent patients with low acuity who require basic monitoring and care. Level 3 represents patients receiving breathing assistance with nasal continuous airway pressure and often drug therapy. These infants require frequent monitoring. Level 4 typically represents patients on MV requiring continuous monitoring, and Level 5 represents patients requiring the highest level of intensive care treatment and surveillance. The coding accuracy for the patient classification variable is considered high, as each hospitalized newborn is registered in the NNN each day, and there is little room for individual interpretation of each newborn's clinical condition. The total acuity in one NICU for each day was calculated based on an estimation of the need for nursing, as described elsewhere (7). Patient volume and unit acuity were calculated for each day in the study period and defined as a low, normal, or high unit workload based on standard deviations. We also extracted the number of patients admitted and discharged each day, as these patients often require more resources. Furthermore, unit workloads were explored at three time points that are considered important in an EP infant's course of treatment:

i) the infant's day of birth,

ii) the day of the first extubation attempt, and

iii) the week after the first extubation attempt.

Moreover, if the infant was reintubated, the workload on the day of reintubation was explored. We chose to explore the unit workload on the infant's day of birth, as this day was considered important based on prior research and clinical experience, suggesting that interventions performed in the first minutes after birth may have long-term consequences in addition to short-term effects on the rate and quality of survival of EP infants (21,22).

2.4 Exposure: weekdays and seasons

To distinguish weekdays from weekends, weekends were defined as Saturdays and Sundays, as this is the most common weekend definition in "off-shift" research (23). Summer days were defined from July to August, as this is the most common period for annual leave among Norwegian healthcare professionals.

2.5 Outcomes

The primary outcomes were the duration of MV until the first extubation attempt and the first successful extubation attempt. Extubation success was defined as no reintubation within 72 hours.

Secondary outcomes were causes of reintubation and short-term respiratory states of the infants reintubated within 72 hours. The causes of reintubation and variables relevant to the ventilation treatment provided six hours before and after the reintubation event were extracted from the medical records to enable a description of short-term respiratory states. The pre-reintubation variables extracted included the mode of non-invasive ventilation, such as positive end-expiratory pressure, and fraction of inspired oxygen (FiO_2) administered. The post-reintubation variables included

ventilator modes and settings, such as peak inspiratory pressure, mean positive airway pressure, and FiO_2. In addition, blood gas variables before and after reintubation were extracted.

2.6 Statistical analysis

Data were expressed as means with 95% confidence intervals or standard deviations (SDs), medians with 25th and 75th percentiles (the interquartile range), or numbers with proportions (%). For patient volume and unit acuity, *z*-scores were calculated for the total of the six years studied because stratified analyses for each hospital did not show a distinctive change in patient volume or unit acuity over these years. *Z*-scores were calculated as the association between each day's patient volume and unit acuity as measured by standard deviations from the mean. According to this, each day was defined as normal if the *z*-score was ± 1 SD, high if the *z*-score was > +1 SD, and low if the *z*-score was < -1 SD. Depending on the variable distribution, we examined unadjusted associations between the outcome and exposure variables using Kruskal–Wallis and logistic regression analyses with unit workloads as independent variables. In the regression analysis, days with low patient volume or low unit acuity were used as the reference groups. All statistical analyses were performed using Stata/MP (2019, Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). The threshold for statistical significance was set at $p < 0.05$.

3 RESULTS

Of 482 infants with GA < 26 weeks admitted to a NICU during the study period, 43 (9%) infants were excluded, as the mother's address could not be verified or the mother chose to opt out. Additionally, 10 (2%) infants were excluded because they had never been intubated during admission. Furthermore, 102 (21%) infants died prior to the first extubation attempt, and 11 (2%) had an identified accidental extubation. In the final analysis, 316 first extubation attempts were included (Figure 2). The first extubation attempts were performed in 11 different Norwegian NICUs. Table 1 presents the characteristics of the study population.

The associations between the exposure variables and primary outcomes are presented in Table 2. Most of the infants had their first extubation attempt on a day categorized by normal patient volume and normal unit acuity. There was no statistical difference in the outcomes if the infant was extubated on a day with low, normal, or high patient volume or unit acuity. Additionally, there was no association between patient volume and unit acuity in the week after the first extubation attempt with the duration of MV or extubation success (data not shown).

There were 247 (78%) infants who had their first extubation attempt on a weekday, while 69 (22%) experienced their first attempt on a weekend. Extubation was more often attempted on weekdays compared to Sundays (with a factor of 1.4–1.9, $p = < 0.01–0.03$). Moreover, 51 (16%) infants had their first extubation attempt on a day categorized as a summer holiday. There was no statistical difference in the duration of MV or extubation success between weekdays and weekends, and no statistical difference in these outcomes if it was a summer holiday compared with other days during the year.

A total of 143 (45%) infants experienced reintubation within 72 hours after the first extubation attempt, as described elsewhere (24). The documented causes of reintubation are presented in Table 3. The analyses showed no statistical associations between causes of reintubation and weekends, seasons, or unit workloads. For the reintubated infants, the short-term respiratory states and associations with the unit workloads are presented in Table 4. There were borderline significant higher pre-reintubation FiO_2 between days with a high patient volume and days with a low patient

volume, and higher post-reintubation pCO_2 on days with a normal patient volume compared with those with a low patient volume. No other differences in the pre- and post-reintubation variables were found. Analyses of differences in unit acuity on the day of reintubation revealed similar results.

The results from all pre- and post-reintubation variables explored are provided in Supplementary Tables 1 (patient volume) and 2 (unit acuity).

4 DISCUSSION

In this national cohort of EP infants, unit workloads, weekdays, or seasons did not affect the duration of MV until the first extubation attempt or the outcome of the extubation attempt. In addition, for infants reintubated within 72 hours, the organizational factors explored did not affect the causes of reintubation or the indicators of respiratory morbidity before or after reintubation. To our knowledge, this is the first study exploring NICU characteristics and outcomes related to the first extubation attempt among EP infants.

Our results may have two potential interpretations. First, the results could suggest that the level of staffing in Norwegian NICUs is sufficient, regardless of fluctuations in patient volume, unit acuity, weekends, and holiday seasons. Alternatively, one might speculate that tight and continuous observation and monitoring of EP infants on MV is resilient to fluctuations in workloads in the NICU. Resilience in healthcare has been defined as "the capacity to adapt to challenges and changes at different system levels, to maintain high quality care" (25). Our database did not include the actual number of healthcare professionals on call in each participating unit on each day. It also did not include the hours actually worked by physicians and nurses. For instance, individual healthcare personnel might make an extra effort to compensate for the higher unit workload and work overtime if needed. The nursing overtime ratio and unit occupancy have been associated with medical incidents, nosocomial infections, and unplanned extubation events (26–28).

The results of our study indicate that healthcare personnel in Norwegian NICUs were able to deliver high-quality short-term respiratory care independent of unit workloads. However, we speculate whether resources used to maintain high quality in fundamental short-term outcomes aimed at airways and breathing could have come at the expense of attention to other important assignments. Tubbs-Cooley et al. determined that high workloads of NICU nurses were significantly associated with missed nursing care, e.g., missed hourly intravenous site assessments, oral feedings, and parental involvement (29). Hence, the long-term consequences of higher workloads and missed care for infants, parents, and healthcare professionals are uncertain.

Our finding that there was no weekend or seasonal association is comparable to the results of a large cohort study from the National Institute of Child Health and Human Development Neonatal Research Network database. They found little effect on the risks of death and morbidity among very low birth weight infants born on weekends or during the months of July and August (30). However, our study identified fewer extubation attempts on weekends compared to weekdays. This finding may indicate that extubation attempts were postponed from the weekends and that available staffing on weekends might influence judgments related to the timing of extubation. A lower tendency to extubate on weekends could be a contributing factor to prolonged duration of MV. Over the last decades, the weekend effect has been analyzed and discussed in several studies in both adult and maternal-neonatal settings (31–35). Still, the weekend phenomenon is not yet fully understood, emphasizing the need for further studies exploring actual weekend staffing in relation to respiratory neonatal outcomes.

Our study has certain limitations. First, we included patients treated in 11 different NICUs in Norway and were unable to collect the existing staffing levels, seniority, and experience levels of staff present in the unit on each day. Second, we were unable to describe fluctuations in workloads during the day. Previous studies have identified higher odds of mortality for infants admitted to the NICU at night compared to the daytime (36). However, a recent study examining overnight extubation was not able to identify differences in success rates between day and night shifts (37). Future studies investigating unit workloads in relation to actual staffing levels and healthcare experiences are needed to further explore the complex contexts of the first extubation events among EP infants. Still, there is a lack of a standard method for modeling unit workloads, and the description of a workload effect depends on several factors, including its measure and definition. We considered two measures of unit workload: patient volume and unit acuity. Our calculations were based on *z*-scores for the total of six years examined. Furthermore, unit acuity may be a more meaningful measure of workloads, as a higher patient volume with relatively few infants at the highest patient levels places different requests on a unit compared with lower patient volumes with a relatively high number of infants demanding intensive care treatment.

The strength of this study is the prospective collection of data on a daily basis by the NNN and the inclusion of a large population-based sample of EP infants. The completeness of the variables allowed us to explore unit workloads on days perceived as critical in these vulnerable infants' courses of treatment in the NICU. Several neonatal networks (e.g., the Vermont Oxford Network, Neonatal Research Network, Italian Neonatal Network, and others) collect data on an individual infant level, and research into the treatment and outcomes of premature infants has expanded, partially due to these large multicenter databases (38). However, few studies using data from neonatal databases address features of the environment where neonatal care takes place, e.g., the unit workload.

In conclusion, we found that there was no association between unit workloads and weekday/season with the duration of MV until the first extubation attempt and the result of the attempt. This can be interpreted as an indicator of resilience in Norwegian NICUs. Our results may suggest that the potential threat to short-term respiratory morbidity associated with total patient burden is alleviated by clinical resilience.

5 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6 Author Contributions

MOO. conceptualized and designed the study; contributed to the data acquisition, database preparation, statistical analyses, and interpretation of the results; and wrote the initial and subsequent drafts of the manuscript. HJS. contributed to the study design, data acquisition, statistical analyses, interpretation of the results, and drafting of the manuscript. AHP., CRT. and LPJJ. co-supervised the study and contributed to the study design, statistical analyses, interpretation of the results, and critical revision of the manuscript. HA., BHE., MLL., KM., TP., SIR., TRS., RSo., and RSt. contributed to the data acquisition, interpretation of the results, and critical revision of the manuscript. AER. conceptualized, designed, and supervised the study; contributed to data acquisition, statistical analyses, and interpretation of the results; and drafted the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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9 Data Availability Statement

The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants, but they are available from the corresponding author (MOO) upon reasonable request.

10 Ethics approval and consent to participate

The study design and procedures were approved by the Regional Committee for Medical and Health Research Ethics (REC North) (approval number: 2018/1346) and performed in accordance with the Declaration of Helsinki (1964) and its later amendments.

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Figure captions

Figure 1. Screenshot of part of the daily resource registration form in the Norwegian Neonatal Network database (the patient classification system, with levels 1–5). This form was translated into English from Norwegian

Figure 2. Flowchart of included infants

Name Test - 010118

Time born: **08.00** Sex: **Boy** Plurarity: **Singel** Birthweight: **795g** Growth: **SGA**

Save | Save and display | Save and new day | Save and new patient | Emergency medications | Delete | Display | Patient - main page | Admission - main page

Admission number: 1 Admission date/time: 01.01.2018 0830 Discharged date/time: Age in days: 0 Number of days hospitalized: 1 Date: 01.01.2018 Actual weight: 795 Postmenstrual age: 27.0

Resource registration | Other treatment | Nutrition/fluid | Cerebral ultrasound/CT/MRI | Neurophysiology | Microbiology | Notes

Weight (g) 795 Head circumference (cm) 28.0 Lenght (cm) 37.0 Registrating physician Attending physician Registration completed

Level 5	Level 4	Level 3	Level 2	Level 1
☐ Day of death	☑ Mechanical ventilation (conventional)	☐ n-CPAP	☑ Nasogastic feedingtube	☑ Recieving enteral feeding
☐ Admission of life-threatning patient	☐ NIPPV/BiPAP	☐ High-flow cannulae >= 4 L/min	☐ Caffeine citrate	☐ Probiotics
☐ NO-treatment	☐ High frequency oscillator ventilation	☐ Manual airway ventilation	☐ Bladder catheterization	☐ Feeding fortifier
☐ N2-treatment	☐ Oral intubation in the unit	☐ Insertion of a peripheral arterial line	☐ Totally enteral nutrition in feeding	☑ Maternal milk/donor milk
☐ CO2-treatment	☐ Nasal intubation in the unit	☐ Insertion of a central venous catheter	☐ Pheripheral arterial line	☐ Parents provide > 4 of 8 meals
☐ Inter-hospital transportation of patient on mechanical ventilation	☐ External cardiac compressions	☐ Ongoing medical treatment of Persistent Ductus Arteriosus	☐ Central venous catheter	☐ Bed
☐ Intra-hospital transportation of patient on mechanical ventilation	☐ Pleural tube insertion in the unit	☑ Insertion of an umbilical arterial catheter	☑ Peripheral venous catheter	☐ Admitted, but may be in the maternity ward
☐ Assistance during operation	☐ PDA ligation in the unit	☑ Insertion of an umbilical venous catheter	☑ Umbilical arterial line	☐ Admitted, but may be at home during daytime
☐ Special conditions	☐ Pleural fluid drainage	☐ Patient extubated last 24 hours	☑ Umbilical venous line	☐ Admitted, but may be at home (also during the night)
	☐ Peritoneal dialysis	☐ FiO2 > 60% (not nasal cannulae)	☐ Dextrose infusion	☐ Admitted, but is in the maternity ward
	☐ Temporary epicardial pacemaker	☑ Parenteral nutrition including lipids	☑ Intravenous antibiotics	

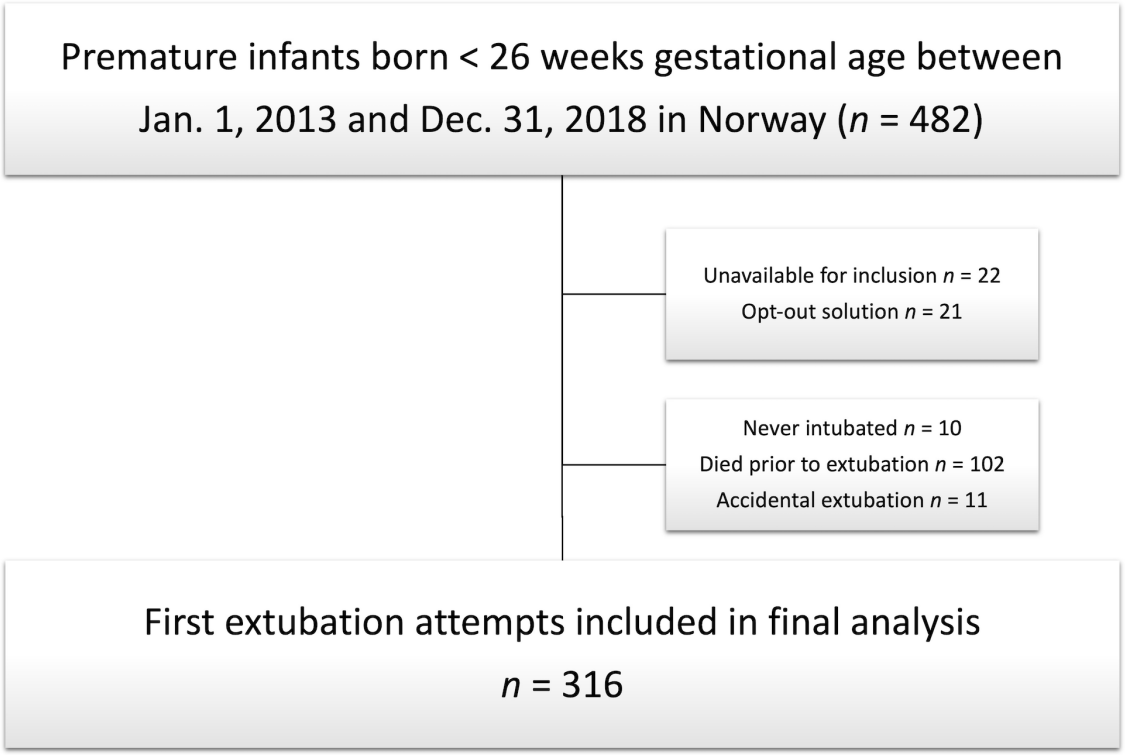
Premature infants born < 26 weeks gestational age between Jan. 1, 2013 and Dec. 31, 2018 in Norway (n = 482)
Unavailable for inclusion n = 22
Opt-out solution n = 21
Never intubated n = 10
Died prior to extubation n = 102
Accidental extubation n = 11
First extubation attempts included in final analysis n = 316

Table 1. Characteristics of the study population

Variable	Value
No. of infants	316
GA, weeks, mean (SD)	24.5 (0.8)
Birth weight, mean (SD)	667.8 (136)
Male, *n* (%)	160 (51)
Small for GA, *n* (%)	60 (19)
Caesarean delivery, *n* (%)	103 (33)
Apgar < 5 at 5 minutes of age, *n* (%)	60 (19)
CRIB II score > 14, *n* (%)[1]	172/304 (57)
ANS any exposure, *n* (%)[2]	298 (94)
ANS complete course, *n* (%)	183/300 (61)
Surfactant administered prior to 30 minutes of age, *n* (%)[3]	309/314 (98)
Transport prior to extubation attempt, *n* (%)	20 (6)

GA, gestational age; *SD*, standard deviation; *CRIB*, Clinical Risk Index for Babies; *ANS*, antenatal steroid; *NICU*, neonatal intensive care unit.

[1] CRIB II scores were not registered in 12 infants (3.8%).
[2] ANS complete course: defined as when the first dose was administered at least 24 hours before birth. The time of the first dose was not registered in 16 (5%) infants.
[3] The time of surfactant administration was not registered in two (0.6%) infants.

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Table 2. The association of patient volume, unit acuity, and weekdays with duration of mechanical ventilation and extubation success, *n* = 316

Variable	Median days with MV until first extubation attempt (IQR)	*P*	Extubation success, *n/N* (%)	*P*
Patient volume on day of birth*				
Low[1]	5 (2–17)		17/27 (63)	
Normal	6 (3–19)		113/203 (56)	0.48
High	6 (2–16)	0.75	43/86 (50)	0.24
Patient volume on day of first extubation attempt*				
Low[1]	6 (3–22)		22/37 (59)	
Normal	6 (2–17)		116/214 (54)	0.56
High	6 (2–17)	0.95	35/65 (54)	0.59
Unit acuity on day of birth*				
Low[1]	6 (2–21)		14/20 (70)	
Normal	6 (3–19)		108/193 (56)	0.23
High	6 (3–16)	0.92	51/103 (50)	0.09
Unit acuity on day of first extubation attempt*				
Low[1]	7 (3–23)		19/32 (59)	
Normal	6 (3–17)		107/198 (54)	0.58
High	6 (2–17)	0.88	47/86 (55)	0.65
Weekday/month of first extubation attempt				
Monday–Friday	6 (2–18)		129/247 (52)	
Saturday–Sunday	5 (3–17)	0.78	44/69 (64)	0.14
September–June	6 (2–17)		148/265 (56)	
July–August	5 (3–21)	0.67	25/51 (49)	0.44

MV, Mechanical ventilation; *IQR,* interquartile range

*Based on z-scores for each unit in the study period (1.1.2013–31.12.2018). Normal if the z-score was +-1 SD, high if the z-score was > +1 SD, and low if the z-score was < -1 SD.
[1]Used as a reference group in the regression analysis.

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Table 3. Causes of reintubation and associations with patient volume, unit acuity, and the weekday the infant was reintubated

Variable	Causes of reintubations (within 72 hours), *n* = 142[1]									
	Apnea		WOB		High pCO_2		High FiO_2		Sepsis	
	n	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Causes of reintubation (all)	68	48	31	22	12	8	23	16	8	6
Patient volume on the day of reintubation*										
Low	6	35 (17–60)	7	41 (21–65)	1	6 (1–32)	1	6 (1–32)	2	11 (3–37)
Normal	55	53 (43–62)	17	16 (10–25)	10	10 (5–17)	16	15 (9–24)	6	6 (3–12)
High	7	33 (17–55)	7	33 (17–56)	1	5 (1–27)	6	28 (13–50)	0	0 (0)
Unit acuity on the day of reintubation*										
Low	6	46 (22–72)	5	38 (17–66)	1	8 (1–39)	1	8 (1–39)	0	0 (0)
Normal	49	50 (40–60)	17	17 (11–26)	9	9 (5–17)	16	16 (10–25)	7	7 (3–14)
High	13	42 (26–60)	9	29 (16–47)	2	6 (2–23)	6	19 (9–37)	1	3 (0–20)
Weekday/month when reintubated										
Monday–Friday	45	46 (37–56)	20	20 (14–30)	9	9 (5–17)	17	17 (11–26)	6	6 (3–13)
Saturday–Sunday	23	51 (37–65)	11	24 (14–39)	3	7 (2–19)	6	13 (3–13)	2	4 (1–16)
September–June	52	45 (36–54)	26	22 (16–31)	11	9 (5–16)	21	18 (12–26)	6	5 (2–11)
July–August	16	62 (42–78)	5	19 (8–39)	1	4 (1–23)	2	8 (2–26)	2	8 (2–26)

WOB, Work of breathing; *O2,* need for a high percentage of oxygen %; *CI*, confidence interval

[1]Missing the cause of reintubation for one (0.7%) infant.

*Based on z-scores for each unit in the study period (1.1.2013–31.12.2018). Normal if the z-score was +-1 SD, high if the z-score was > +1 SD, and low if the z-score was < -1 SD.

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Table 4. Indicators of short-term respiratory morbidity for infants reintubated and associations with patient volume, *n* = 143

Variable	Patient volume on the day of reintubation*			P-value	
	Low	Normal	High	Normal vs. low patient volume	High vs. low patient volume
Pre-reintubation variable					
PEEP[1], mean (SD)	7.1 (0.8)	7.0 (1.0)	6.5 (0.6)	0.49	0.07
Oxygen[1,2], median (IQR)	44 (32–48)	42 (32–52)	52 (42–68)	0.90	0.05
pH, median (IQR)	7.23 (7.20–7.30)	7.19 (7.14–7.25)	7.23 (7.15–7.27)	0.14	0.62
pCO_2[4], median (IQR)	7.4 (7.0–8.9)	8.4 (7.3–9.9)	8.8 (7.9–10.2)	0.24	0.24
BE, median (IQR)	-3.4 (-7.1–0.7)	-4.4 (-6.9– -0.8)	-1.6 (-6–2)	0.69	0.42
Post-reintubation variable					
MAP[3], median (IQR)	9 (9–10)	9 (8–10)	10 (9–12)	0.80	0.19
Oxygen[2,3], median (IQR)	34 (28–38)	30 (24–37)	33 (27–42)	0.66	0.43
pH, median (IQR)	7.30 (7.18–7.37)	7.25 (7.18–7.31)	7.30 (7.19–7.35)	0.19	0.55
pCO_2[4], mean (SD)	6.7 (1.4)	7.6 (1.7)	7.3 (1.8)	0.05	0.29
BE, mean (SD)	-3.8 (4.9)	-3.4 (5.6)	-2.8 (7.0)	0.84	0.64
RSS[3], median (IQR)	3.0 (2.5–3.7)	2.8 (2.1–3.6)	2.9 (2.5–5.0)	0.71	0.25
MV days after reintubation, median (IQR)	9 (4–15)	9 (5–16)	8 (5–14)	0.54	0.78

PEEP, positive end expiratory pressure; *SD*, standard deviation; *IQR*, interquartile range; *BE*, base excess; *MAP*, mean airway pressure; *RSS*, respiratory severity score; *MV*, mechanical ventilation

*Based on z-scores for each unit in the study period (1.1.2013–31.12.2018). Normal if the z-score was +-1 SD, high if the z-score was > +1 SD, and low if the z-score was < -1 SD.

[1]Mean values for the last 6 h before reintubation.

[2]Administered oxygen as a percentage.

[3]Mean values in the first 6 h after reintubation.

[4] Values in kPa, kilopascals.

Supplementary Table 1. Respiratory treatment before and after reintubation and association with patient volume on the day of reintubation, *n* = 143

Variable	Patient volume*			*P*-value	
	Low	Normal	High	Normal vs. low	High vs. low
Pre-reintubation variable					
BiPAP, *n* (%)	8 (47)	51(50)	14 (67)	0.85	0.23
NCPAP, *n* (%)	9 (53)	52 (50)	7 (33)		
Last registered PEEP, mean (SD)	7.1 (1.1)	7.0 (0.9)	6.6 (0.7)	0.75	0.12
Mean PEEP last 6 h, mean (SD)	7.1 (0.8)	7.0 (1.0)	6.5 (0.6)	0.49	0.07
Last registered FiO_2, median (IQR)	50 (33–60)	49 (37–70)	59 (40–81)	0.43	0.17
Mean FiO_2 last 6 h, median (IQR)	44 (32–48)	42 (32–52)	52 (42–68)	0.90	0.05
pH, median (IQR)[1]	7.23 (7.20–7.30)	7.19 (7.14–7.25)	7.23 (7.15–7.27)	0.14	0.62
pCO2, median (IQR)[1,2]	7.4 (7.0–8.9)	8.4 (7.3–9.9)	8.8 (7.9–10.2)	0.24	0.24
BE, median (IQR)[1]	-3.4 (-7.1–0.7)	-4.4 (-6.9– -0.8)	-1.6 (-6–2)	0.69	0.42
Post-reintubation variable					
CV, *n* (%)	16 (94)	93 (89)	13 (62)	0.60	0.004
HFOV, *n* (%)	1 (6)	11 (11)	8 (38)		
First registered PIP, mean (SD)	19 (2.3)	19 (4.1)	19 (3.6)	0.94	0.88
Mean PIP first 6 h, mean (SD)	18 (2.1)	19 (3.3)	18 (2.8)	0.79	0.71
First registered PEEP, mean (SD)	5.8 (0.8)	5.7 (0.7)	5.8 (0.8)	0.98	0.73
Mean PEEP first 6 h, mean (SD)	5.8 (0.8)	5.7 (0.7)	5.8 (0.7)	0.91	0.71
First registered MAP, median (IQR)	9 (9–10)	9 (8–10)	10 (9–12)	0.48	0.23
Mean MAP first 6 h, median (IQR)	9 (9–10)	9 (8–10)	10 (9–12)	0.80	0.19
First registered FiO_2, median (IQR)	35 (29–50)	32 (24–45)	36 (26–55)	0.63	0.56
Mean FiO_2 first 6 h, median (IQR)	34 (28–38)	30 (24–37)	33 (27–42)	0.66	0.43
pH, median (IQR)[1]	7.30 (7.18–7.37)	7.25 (7.18–7.31)	7.30 (7.19–7.35)	0.19	0.55
pCO2, mean (SD)[1,2]	6.7 (1.4)	7.6 (1.7)	7.3 (1.8)	0.05	0.29
BE, mean (SD)[1]	-3.8 (4.9)	-3.4 (5.6)	-2.8 (7.0)	0.84	0.64
RSS, median (IQR)[3]	3.0 (2.5–3.7)	2.8 (2.1–3.6)	2.9 (2.5–5.0)	0.71	0.25
MV course, median (IQR), days	9 (4–15)	9 (5–16)	8 (5–14)	0.54	0.78

BIPAP, bi-level positive airway pressure; *NCPAP*, nasal continuous positive airway pressure; *SD*, standard deviation; *PEEP*, positive end expiratory pressure; *FiO_2*, fraction of inspired oxygen; *IQR*, interquartile range; *BE*, base excess; *CV*, conventional ventilation; *HFOV*, high-frequency oscillator ventilation; *PIP*, positive inspiratory pressure; *MAP*, mean airway pressure; *RSS*, respiratory severity score; *MV*, mechanical ventilation

*Based on z-scores for each unit in the study period (1.1.2013–31.12-2018). Normal if the z-score was +-1 SD, high if the z-score was > +1 SD, and low if the z-score was < -1 SD.
[1]Measured in arterial, capillary, or venous blood samples.
[2]pCO2 values in kilopascals (*7.50062 provides values in millimeters of mercury).
[3]RSS was calculated as a product of MAP and a fraction of inspired oxygen. RSS was calculated based on the last 6 h after reintubation.

Supplementary Table 2. Respiratory treatment before and after reintubation and association with unit acuity on the day of reintubation, *n* = 143

Variable	Unit acuity*			*P*-value	
	Low	Normal	High	Normal vs. low	High vs. low
Pre-reintubation variable					
BiPAP, *n* (%)	8 (62)	49 (50)	16 (53)	0.44	0.63
NCPAP, *n* (%)	5 (38)	49 (50)	14 (47)		
Last registered PEEP, mean (SD)	7.2 (0.8)	6.9 (0.9)	6.8 (1.0)	0.29	0.13
Mean PEEP last 6 h, mean (SD)	7.2 (0.8)	6.9 (1.0)	6.8 (0.8)	0.41	0.25
Last registered FiO_2, median (IQR)	40 (38–50)	50 (37–70)	55 (33–85)	0.28	0.15
Mean FiO_2 last 6 h, median (IQR)	42 (36–46)	43 (33–51)	52 (34–62)	0.77	0.18
pH, median (IQR)	7.20 (7.10–7.31)	7.21 (7.14–7.25)	7.21 (7.15–7.26)	1.0	0.64
pCO2, median (IQR)	8.9 (7.0–10.1)	8.4 (7.4–9.9)	8.6 (6.6–9.4)	0.69	0.93
BE, median (IQR)	-6.0 (-8.0–0.6)	-4.0 (-6.3–-0.3)	-4.4 (-7.0–0.0)	0.94	0.94
Post-reintubation variable					
CV, *n* (%)	13 (100)	88 (90)	21 (68)	0.31	0.004
HFOV, *n* (%)	0 (0)	10 (10)	10 (32)		
First registered PIP, mean (SD)	18.8 (1.8)	18.6 (4.1)	18.3 (3.8)	0.85	0.67
Mean PIP first 6 h, mean (SD)	18.3 (1.6)	18.7 (3.1)	18.2 (3.6)	0.72	0.88
First registered PEEP, mean (SD)	5.5 (0.5)	5.8 (0.8)	5.8 (0.8)	0.14	0.21
Mean PEEP first 6 h, mean (SD)	5.5 (0.5)	5.7 (0.7)	5.9 (0.8)	0.24	0.12
First registered MAP, median (IQR)	9 (8–10)	9 (8–10)	10 (9–12)	0.35	0.03
Mean MAP first 6 h, median (IQR)	9 (8–9)	9 (9–10)	10 (9–12)	0.17	0.02
First registered FiO_2, median (IQR)	30 (21–40)	35 (25–47)	32 (25–48)	0.13	0.29
Mean FiO_2 first 6 h, median (IQR)	28 (23–34)	31 (24–38)	33 (25–40)	0.28	0.25
pH, median (IQR)	7.26 (7.21–7.31)	7.25 (7.18–7.31)	7.29 (7.20–7.32)	0.49	0.68
pCO2, mean (SD)	6.8 (1.5)	7.6 (1.7)	7.2 (2.0)	0.13	0.46
BE, mean (SD)	-4.3 (4.0)	-3.1 (5.9)	-3.8 (5.7)	0.49	0.79
RSS, median (IQR)	2.5 (1.9–3.0)	2.8 (2.2–3.8)	2.9 (2.5–4.4)	0.19	0.10
MV course, median (IQR), days	8 (3–11)	9 (5–16)	11 (5–16)	0.47	0.57

BIPAP, bi-level positive airway pressure; *NCPAP*, nasal continuous positive airway pressure; *SD*, standard deviation; *PEEP*, positive end expiratory pressure; *FiO_2*, fraction of inspired oxygen; *IQR*, interquartile range; *BE*, base excess; *CV*, conventional ventilation; *HFOV*, high-frequency oscillator ventilation; *PIP*, positive inspiratory pressure; *MAP*, mean airway pressure; *RSS*, respiratory severity score; *MV*, mechanical ventilation

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