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Respiratory outcomes and survival after unplanned extubation in the NICU: a prospective cohort study from the SEPREVEN trial

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ABSTRACT

Objective To compare reintubation rates after planned extubation and unplanned extubation (UE) in patients in neonatal intensive care units (NICUs), to analyse risk factors for reintubation after UE and to compare outcomes in patients with and without UE.

Design Prospective, observational study nested in a randomised controlled trial (SEPREVEN/Study on Epidemiology and PRevention of adverse EVEnts in Neonates). Outcomes were expected to be independent of the intervention tested.

Setting 12 NICUs in France with a 20-month follow-up, starting November 2015.

Patients n=2280 patients with a NICU stay >2 days, postmenstrual age ≤42 weeks on admission.

Interventions/exposure Characteristics of UE (context, timing, sedative administration in the preceding 6 hours, weaning from ventilation at time of UE) and patients.

Main outcome measures Healthcare professional-reported UE rates, reintubation/timing after extubation, duration of mechanical ventilation, mortality and bronchopulmonary dysplasia (BPD).

Results There were 162 episodes of UE (139 patients, median gestational age (IQR) 27.3 (25.6–31.7) weeks). Cumulative reintubation rates within 24 hours and 7 days of UE were, respectively, 50.0% and 57.5%, compared with 5.5% and 12.3% after a planned extubation. Independent risk factors for reintubation within 7 days included absence of weaning at the time of UE (HR, 95% CI) and sedatives in the preceding 6 hours (HR 1.93, 95% CI 1.04 to 3.60). Mortality at discharge did not differ between patients with planned extubation or UE. UE was associated with a higher risk of BPD.

Conclusion In the SEPREVEN trial, reintubation followed UE in 58% of the cases, compared with 12% after planned extubation.

Trial registration number NCT02598609.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Unplanned extubation (UE) is a frequent and severe adverse event in the neonatal intensive care unit. Outcome has rarely been studied in large prospective cohorts and has not been compared with outcome after only planned extubation.

WHAT THIS STUDY ADDS

⇒ In this study nested in the SEPREVEN (Study on Epidemiology and PRevention of adverse EVEnts in Neonates) trial, reintubation rate after UE was 57.5% compared with 12.3% after planned extubation, due to higher reintubation need in the 30 min and 24 hours but not afterwards. In-hospital mortality did not differ. Reintubation was not systematic after UE with 42% of neonates not reintubated at 7 days. Severe bradycardia occurred in 21.2% and cardiopulmonary resuscitation was performed in 4.4% of UE cases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study confirms severity of UE as an adverse event and encourages prevention. It also suggests a failure in identifying infants ready to be extubated and the relevance of research protocols to neonatal extubation criteria.

INTRODUCTION

Endotracheal intubation is a common life-saving procedure in critically ill or preterm neonates in neonatal intensive care units (NICUs). Unplanned extubation (UE), defined as unintentional removal of an endotracheal tube (ETT) in a mechanically ventilated patient, is a frequent and severe adverse event in NICUs.[1 2] According to a trigger tool-based North American NICU study, UE requiring reintubation was the fourth most common adverse event after nosocomial infection, catheter infiltration and abnormal cranial imaging.[2] The UE incidence rate in the NICU is higher (0.14–5.3/100 intubation days)[1] than among either adults (0.58/100 intubation days)[3] or older children (0.61/100 intubation days).[4] UE rates are monitored in many NICUs as a quality of care metric, with a goal of one UE/100 days of ventilation in most NICU studies designed to reduce its incidence.[5–9]

UE, in contrast to planned extubation, is a potentially life-threatening and costly event.[10] The crucial elements determining its severity are the need for reintubation, which ranges from 8% to 100% in the NICUs,[1] and/or the occurrence of short-term hypoxic complications (bradycardia,

cardiopulmonary resuscitation (CPR)). UE often leads to emergency and thus less-controlled endotracheal reintubation.[11 12] Repeated intubations, especially those performed on an emergency basis, increase the risk of laryngeal or tracheal injury and scarring, pulmonary injury from excessive ventilation and ventilator-associated pneumonia.[11] Known long-term complications of UE are longer lengths of stay, increased duration of mechanical ventilation (MV) and potential increased respiratory morbidity.[1 13–17] Note that this duration is both a cause and a consequence of UE.[1 13]

The main objective of this study was to compare cumulative reintubation rates after planned extubation and UE. The other objectives were to identify factors associated with reintubation after UE, to compare outcomes between patients with and without a history of UE (mortality, length of stay) and for the extremely low gestational age neonates' (ELGANs) respiratory outcomes.

METHODS

Study design

This was an ancillary prospective multicentre observational study nested in the SEPREVEN (Study on Epidemiology and PRevention of adverse EVEnts in Neonates) stepped-wedge randomised controlled trial (RCT), which assessed the efficacy of an intervention—education about root-cause analysis (RCA) and care bundles—to reduce adverse events in NICUs.[18 19] No specific prevention of UE was included, although centres could choose to perform an RCA on this topic.

Participating units and patients

The participating NICUs included six units from Ile-de-France (greater Paris metropolitan area) and six units from six other regions in France, all exclusively dedicated to newborn care and nine with surgery. Mean number of beds (±SD) was 23±7.8.[19] Eligible neonates were inpatients for more than 2 days during the study period in a participating NICU, with a postmenstrual age of 42 weeks or less on admission, whose parents, after information, did not oppose use of their data. This study included all the enrolled intubated patients, except those with severe congenital malformations who were excluded.

Data collection and endpoint definitions

The SEPREVEN trial formalised a prospective collection of adverse events, based on multiprofessional voluntary anonymous reporting.[18–20] A UE was defined as any removal of the ETT that was not planned by the medical team, including ETT removed inadvertently by a professional or patient, or voluntarily in life-threatening situations potentially related to ETT obstruction or position. Confirmation by end-tidal carbon dioxide (CO_2) detector or laryngoscopy was not required. In case of UE, the physician responsible for the infant's care completed prospectively a form with questions on its context: ongoing weaning of MV, sedatives in the 6 previous hours, complications (severe bradycardia, defined as <80 beats/min for at least 3 min, CPR, type of ventilation at different time points after extubation) (see page 3 of the online supplemental file for the English version of the questionnaire).

For the global study population (all intubated neonates), we collected intubation and extubation dates and hours, length of NICU stay and mortality at discharge, and for deceased patients, date and cause/context of death including palliative care with decisions to extubate and/or not to reintubate. For the ELGANs subpopulation, we collected dates of non-invasive ventilation and bronchopulmonary dysplasia (BPD) defined as the need for oxygen and/or ventilation at a corrected gestational age (GA) of 36 weeks.

Statistical analysis

Descriptive results were expressed as medians (IQR) or means±SDs for quantitative variables and as numbers (percentages) for qualitative variables.

Patient characteristics were compared between the groups with and without a UE using the Student's t-test or the Mann-Whitney rank-sum test for continuous variables and the X^2 or Fisher's exact tests for categorical variables. UE incidence rates were expressed per 100 intubation days. The computation of cumulative reintubation proportions used all episodes of intubation—after planned extubation and UE. Planned extubation and UE episodes in palliative care patients involving no reintubation decisions were excluded from cumulative reintubation rates and from analysis of characteristics associated with reintubation after UE. Rates of reintubation after extubation at 30 min, 24 hours, 72 hours and 7 days were assessed and compared between planned extubation and UE episodes. For exploratory purposes, cumulative reintubation rates were analysed in the subgroup of ELGANs.

The analysis of characteristics associated with reintubation after the first UE between 0 and 24 hours, between 0 and 72 hours, and between 0 and 7 days was performed using the frailty regression model with a random intercept to account for the effect of centre-level factor. The centre effect was tested using likelihood ratio tests comparing the frailty null model and the classic Cox regression model. For the outcomes reintubation 0–24 hours and 0–72 hours, there was no statistically significant random effect of the centre ($p=0.31$ and $p=0.12$, respectively), in contrast to reintubation between 0 and 7 days for which a tendency was found ($p=0.052$). Cox regression models were thus used to identify factors associated with reintubation between 0–24 hours and 0–72 hours, and frailty model was used to identify factors associated with reintubation 0–7 days. The univariable analysis of characteristics on reintubation computed the unadjusted HRs along with their 95% CIs using frailty models and Cox regression models. The final model was determined in a multivariable analysis by entering all variables associated with the outcome at a p value of <0.20 in the univariable analysis and applying a backward stepwise approach to retain factors significant at a p value of <0.05. The association between UE and mortality was examined with a Cox proportional-hazards regression model, with UE exposure modelled as a time-dependent covariate to account for its occurrence during follow-up. 'No UE' was coded as 0 (UE, 0); patients experiencing a UE during follow-up switched from 0 ('no UE') to 1 ('with UE') at the date of the first UE. The associations between binary outcomes at discharge and UE were studied by using a mixed-effects logistic regression model with centre level as a random effect, because the likelihood ratio test comparing the mixed-effects logistic regression null model and the classic logistic regression model was statistically significant ($p<0.001$). Normality of the random effect was checked. Associations between binary outcomes at discharge and UE were assessed without and with adjustment for GA, small for GA, sex and total duration of MV at the time of the event, in the total population and in ELGANs. A detailed description of statistical analyses is given in pages 4–5 of the online supplemental file. Statistical analyses used Stata V.17.0 (Stata-Corp, College Station, Texas, USA), and p values of <0.05 were considered statistically significant.

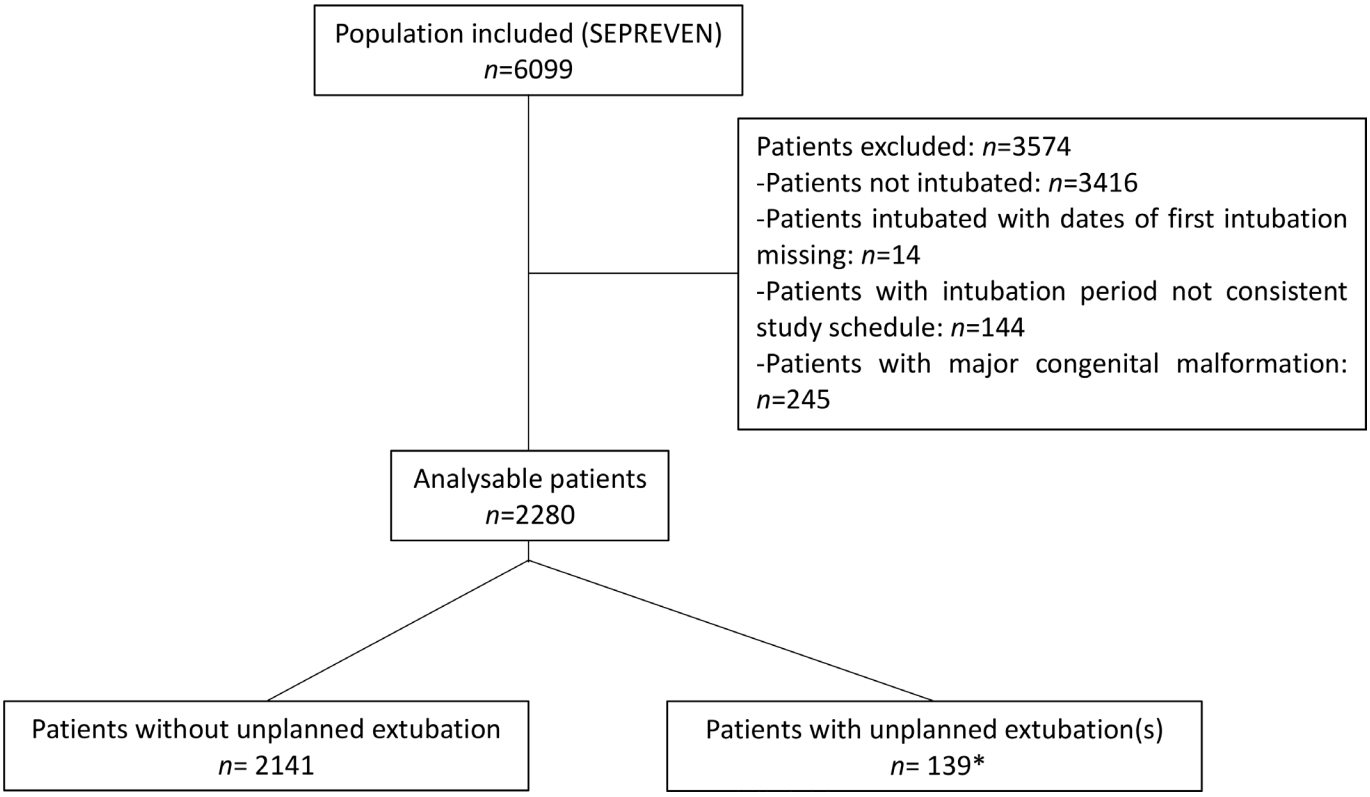

Figure 1 Flow chart. *One unique unplanned extubation (UE) in 122 patients (87.8%), two UEs in 11 patients (7.9%) and three UEs in 6 patients (4.3%). SEPREVEN, Study on Epidemiology and PRevention of adverse EVEnts in Neonates.

RESULTS

Study population and UE incidence rate

Among the 6099 patients included in the SEPREVEN trial, 2280 (37.4%) were intubated and included (figure 1); 139 (6.1%) had at least one UE, with 162 UE events collected. The UE incidence rate was 1.28/100 intubation days. Table 1 presents patient characteristics by the absence/presence of at least one UE. Online supplemental table 1 shows the proportions of UE patients according to the centres.

Cumulative reintubation rates after planned extubation and UE

In the whole population, 483 extubated patients were reintubated. Figure 2 shows the cumulative reintubation rates over time after planned extubation and UE. Online supplemental table 2 describes the concomitant possible non-respiratory causes for reintubation.

Immediate outcomes and risk factors for reintubation after UE

Severe bradycardia was reported in 32 of 151 cases (21.2%), and CPR in 7 of 161 (4.4%). No patient died of a UE complication.

After the first UE, 108 patients were reintubated. The proportion of reintubated UE patients is shown in online supplemental table 3. Risk factors associated with reintubation within 24 hours, 72 hours and 7 days after the first UE are reported in table 2 and online supplemental tables 4 and 5, respectively. Independent risk factors associated with reintubation within 72 hours after UE were the absence of ongoing weaning from ventilation at time of UE, lower GA at birth, having a small birth weight for GA, within 7 days, the absence of ongoing weaning from ventilation at time of UE, having a small birth weight for GA and sedatives in the 6 hours before UE.

The context and reported reasons of UE

Online supplemental table 6 shows the context of UEs: sedatives were administered in the 6 hours before UE in 96 of 134 (71.6%) cases and weaning from MV was ongoing at the time of UE in 40 of 134 (29.9%) cases. The most frequent causes reported were agitation (n=63 of 144, 43.8%), self-extubation (n=37 of 144, 25.7%) and poor tube fixation (n=32 of 144, 22.2%) (online supplemental table 7).

Outcomes at discharge from NICU

Online supplemental table 8 shows the proportion of deaths according to the centres. Comparison of outcomes between patients with planned extubation(s) only (n=2141) and those with UE (n=139) (table 3) showed, for the overall population and for the ELGANs, no difference in mortality and a significantly shorter median NICU stay in patients with only planned extubation. In ELGANs, BPD was significantly less frequent in the subgroup without UE; this was not found after adjustment for the duration of MV. A sensitivity analysis in the ELGANs showed a similar risk of BPD between patients without UE and patients with UE but not reintubated, while reintubation after a UE was associated with a higher risk of BPD, compared with no reintubation (online supplemental table 9).

DISCUSSION

In our global NICU population and in the ELGANs subgroup, cumulative reintubation rates over time after extubation showed reintubation was much more frequent after UEs than after

Table 1 Characteristics of patients, according to the absence/presence of unplanned extubation (UE) anytime during NICU stay (for any intubation period)

Characteristics	Category	All intubated patients (n=2280)	No UE (n=2141)	With UE (n=139)	P value
Gestational age, weeks, median (IQR)		30.6 (27.4–35.7)	30.7 (27.6–36.0)	27.3 (25.6–31.7)	**<0.001**
Gestational age, weeks, n (%)	<26	276 (12.1)	234 (10.9)	42 (30.2)	**<0.001**
	≥26–<28	399 (17.5)	363 (16.9)	36 (25.9)	
	≥28–<32	648 (28.4)	620 (29.0)	28 (20.1)	
	≥32–<37	491 (21.5)	476 (22.2)	15 (10.8)	
	≥37	466 (20.4)	448 (20.9)	18 (13.0)	
Corrected age at 1st intubation, weeks, n (%)	<26	238 (10.4)	204 (9.5)	34 (24.5)	**<0.001**
	≥26–<28	352 (15.4)	318 (14.9)	34 (24.5)	
	≥28–<32	672 (29.5)	641 (29.9)	31 (22.3)	
	≥32–<37	517 (22.7)	500 (23.4)	17 (12.2)	
	≥37	501 (22.0)	478 (22.3)	23 (16.5)	
Corrected age at 1st intubation, weeks, n (%)	<26 ≥26–<28 ≥28–<32 ≥32–<37 ≥37	238 (10.4) 352 (15.4) 672 (29.5) 517 (22.7) 501 (22.0)	204 (9.5) 318 (14.9) 641 (29.9) 500 (23.4) 478 (22.3)	34 (24.5) 34 (24.5) 31 (22.3) 17 (12.2) 23 (16.5)	**<0.001**
Birth weight, g, n (%)	≤1000	730 (32.0)	642 (30.00)	88 (63.3)	**<0.001**
	1001–2499	1006 (44.1)	979 (45.7)	27 (19.4)	
	≥2500	544 (23.9)	520 (24.3)	24 (17.3)	
SGA*, n (%)		440 (19.3)	417 (19.5)	23 (16.6)	0.396
Gender, n (%)	Male	1229 (53.9)	1161 (54.2)	68 (48.9)	0.224
	Female	1051 (46.1)	980 (45.8)	71 (51.1)	
Number of mechanical ventilation periods during NICU stay, n (%)	1	1790 (78.5)	1760 (82.2)	30 (21.6)	**<0.001**
	2	336 (14.7)	288 (13.5)	48 (34.5)	
	>2	154 (6.8)	93 (4.3)	61 (43.9)	
Number of mechanical ventilation days during the stay, days, median (IQR)		2.6 (0.8–6.0)	2.4 (0.7–5.5)	10.0 (3.8–22.8)	**<0.001**

*SGA, as defined by ZS Ohlsen <−1.
NICU, neonatal intensive care unit; SGA, small for gestational age.

planned extubations. Reintubation took place within the first 30 min and 24 hours after only 1.6% and 5.5% of planned extubations but in 38% and 50% of UEs. This striking difference was seen only in these first 24 hours; afterwards, the reintubation rates were very similar. Cumulative reintubation rates were described with a 7-day cut-off after extubation to differentiate failed extubation due to both prematurity from other causes and to avoid the underestimation of the reintubation rate in ELGANs.[1 21–23]

This study is, to our knowledge, the largest cohort comparing outcomes after planned extubation and UE in the NICU. As in other studies, the smallest infants were at the highest risk of UE.[23–25] Considering only the UE cases, approximately 60% were followed by reintubation in the 7 days afterwards—two-thirds of them within 30 min. Our cumulative reintubation rates are consistent with the recent NICU literature: a large 2021 study (588 UEs, median GA: 26.7 weeks) found immediate reintubations for 60%[11] and a 2019 study (134 UEs, median GA: 27 weeks) for 51% and within 48 hours for 68%.[14] An international study including 1167 UEs reported immediate reintubation rates ranging from 49% to 82% of the UE cases.[26]

The UE contexts reported were similar to those in the literature.[1 13 16 17 27] Procedures related to holding the baby or skin-to-skin care were rarely reported, while in nearly half the cases, agitation was reported. Sedation as a method for specifically minimising agitation has not been studied, and its role in preventing UE remains controversial.[7 13 16] No consensus governs sedation management in NICUs. Long-term sedation is known to be associated with tolerance and subsequent opioid weaning symptoms, which include agitation.

In our study, 30% of UE cases occurred during ventilation weaning, 22 of 40 (55%) with sedatives and 18 of 40 (45%) without. Weaning is usually associated with a reduction or interruption of sedation. Weaning from ventilation at the time of the UE reduced the risk of reintubation. This is consistent with practice: weaning generally starts when clinical assessment suggests sufficient breathing capacity. This suggests that one possible strategy to reduce the duration of MV would be to extubate patients earlier in their weaning process. Early identification of infants ready for extubation might have a positive impact on reducing UE without increasing the extubation failure rate. Weaning from ventilation to optimise and predict the success of extubation appears to require a protocol,[28] but studies on this topic are rare. A systematic review of weaning studies in 2020 found only one retrospective study, which suggested a shorter mean weaning time when using a protocol.[28]

Sedation is also involved in MV management. Sedation and analgesia, notably with benzodiazepines and/or opioids, have been shown to prolong MV and length of hospital stay, as well as have the potential to impair neurodevelopment later in infancy.[29] One study observed that daily interruption of sedatives in critically ill children was feasible and led to reduced sedation use, earlier extubation and shorter lengths of stay without increasing the UE rate.[30] In our study, receiving sedatives before UE was a risk factor for reintubation at 7 days but not at 24 and 72 hours.

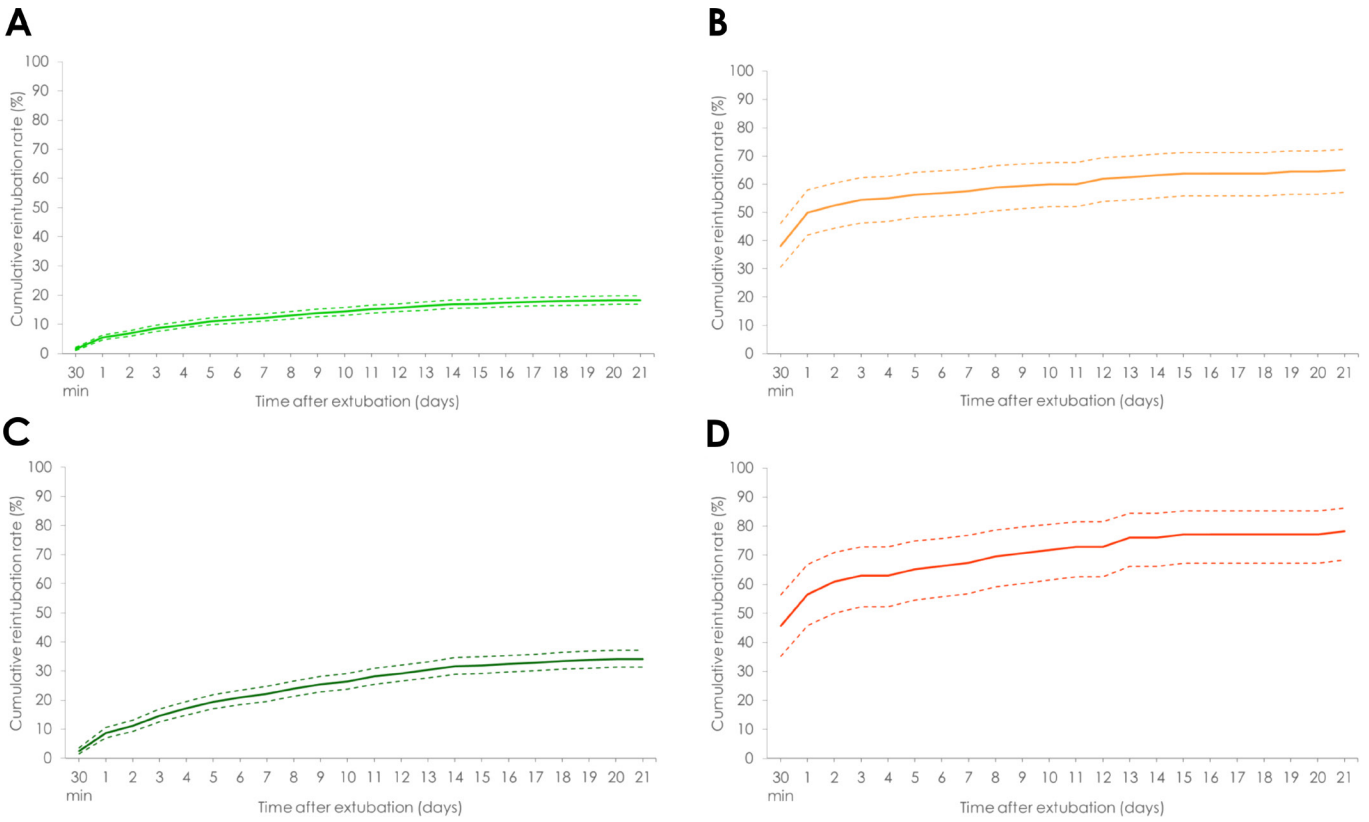

Figure 2 Cumulative reintubation rates over time after planned extubation and unplanned extubation. In the global population, reintubation rates by 30 min after extubation were statistically higher after unplanned than planned extubations (61 of 160 (38.1%) vs 44 of 2792 (1.6%), p<0.001), within 24 hours (8 of 160 (50.0%) vs 154 of 2792 (5.5%), p<0.001), 72 hours (87 of 160 (54.4%) vs 242 of 2792 (8.7%), p<0.001) and 7 days (9 of 160 (57.5%) vs 343 of 2792 (12.3%), p<0.001) after an extubation. From 24 hours to 7 days, reintubations after planned extubations increased from 154 to 343 of 2792 (rate +6.8%) and after unplanned extubations from 80 to 92 of 160 (rate +7.5%), at similar rates (p=0.721). For the extremely low gestational age neonates (ELGANs), unplanned extubation compared with planned extubation was associated with a higher risk of reintubation: within 30 min (26 of 1055 (2.5%) vs 42 of 92 (45.7%), p<0.001), 24 hours (92 of 1055 (8.7%) vs 52 of 92 (56.5%), p<0.001), 72 hours (154 of 1055 (14.6%) vs 58 of 92 (63.0%), p<0.001) and 7 days (233 of 1055 (22.1%) vs 62 of 92 (67.4%), p<0.001) after an extubation. Crude cumulative rates. The dotted lines correspond to an (exact binomial) CI calculated for each rate at each time point. (A) After planned extubation (entire population), (B) after unplanned extubation (entire population), (C) after planned extubation (ELGANs) and (D) after unplanned extubation (ELGANs).

This could be due to the respiratory effect of sedation as well as to the underlying disease that motivates its use.

In our study, no difference in mortality was found between patients with planned extubation only and with UE, and the latter group had a longer median NICU stay than the former—a finding suggesting that costs are higher in UE patients, consistent with other studies.[10 11 13 31] In the ELGANs, after adjustment for duration of MV, UE was not associated with an increased risk

Table 2 Risk factors associated with reintubation within 24 hours after the first unplanned extubation (UE)

Variable	No reintubation within 24 hours n=69	Reintubation within 24 hours n=69	Univariable model HR, 95% CI	P value
Gestational age, weeks				**0.017**
<26	12 (17.4)	30 (43.5)	2.76, 1.07 to 7.13	**0.036**
≥26–<28	22 (31.9)	14 (20.3)	1.21, 0.43 to 3.35	0.719
≥28–<32	17 (24.6)	11 (15.9)	1.12, 0.39 to 3.22	0.835
≥32–<37	10 (14.5)	5 (7.3)	1.00 (ref)	
≥37	8 (11.6)	9 (13.0)	1.47, 0.49 to 4.40	0.487
SGA	9 (13.0)	14 (20.3)	1.44, 0.80 to 2.60	0.221
Night shift at extubation (from 19:00 to 07:00)	35 (50.7)	29 (42.0)	0.75, 0.47 to 1.21	0.245
Sedatives in the 6 hours before UE (n=114)	32/55 (58.2)	47/59 (79.7)	2.516, 1.15 to 4.08	**0.017**
Ongoing weaning from ventilation at time of unplanned extubation (n=132)	26/55 (47.3)	7/59 (11.9)	0.23, 0.10 to 0.50	**<0.001**
Total duration of mechanical ventilation at the time of first UE (days)	3.5 (1.3–7.4)	5.8 (1.4–13.0)	1.03, 1.00 to 1.05	**0.038**

One episode of extubation related to palliative care decisions was excluded from this analysis.
SGA was defined by ZS Ohlsen <−1.28.
No multivariable model was found.
SGA, small for gestational age.

Table 3 Outcomes of patients at discharge from the NICU, by the presence/absence of UE at any time of NICU stay

Variable	No UE (n=2141) n (%) or median (IQR)	With UE (n=139) n (%) or median (IQR)	Crude analysis HR, 95% CI	P value	Adjusted analysis* aHR, 95% CI	P value	Adjusted analysis† aHR, 95% CI	P value
Mortality at discharge from hospital	224 (10.5)	11 (7.9)	0.75, 0.40 to 1.40	0.369	0.63, 0.33 to 1.21	0.162	0.54, 0.27 to 1.08	0.081
Length of stay, days	14 (7–38)	56 (7–38)		<0.001‡				
Length of stay, days (excluding patients who died)	n=1917 16 (7–40)	n=20 29.5 (10–56)		0.111‡				
	No UE <28 weeks (n=597) n (%) or median (IQR)	**UE <28 weeks (n=78) n (%) or median (IQR)**	**Crude analysis HR or OR, 95% CI**	**P value**	**Adjusted analysis* aHR or aOR, 95% CI**	**P value**	**Adjusted analysis† aHR or aOR, 95% CI**	**P value**
Mortality at discharge from hospital	123 (20.6)	6 (7.7)	HR 0.63, 0.27 to 1.47	0.339	aHR 0.61, 0.26 to 1.41	0.246	aHR 0.61, 0.25 to 1.46	0.265
Length of stay, days	43 (14–65)	72.5 (56–90)		**<0.001**‡				
Length of stay, days (excluding patients who died)	n=474 49 (34–69)	n=7 67 (55–97)		0.056‡				
Corrected age at the end of the last period of NIV, GA in weeks	33.3 (31.1–35.6)	35.7 (33.3–37.6)		<0.001‡				
BPD at 36 weeks' GA	250/466 (53.7)	55/77 (71.4)	OR 2.49, 1.42 to 4.39	**0.002**	aOR 2.51, 1.42 to 4.43	**0.002**	aOR 1.24, 0.66 to 2.33	0.502

Binary outcomes were studied using a logistic mixed model, with centre level a random effect as intercept. Mortality was studied using a frailty model, with centre level a random effect.
Length of stay and corrected age at the end of the last period of NIV were not modelled in crude and adjusted analyses using a mixed linear regression model due to the non-normality of residuals.
*Adjusted for gestational age in categories (<26/26–27.99/28–31.99/32–36.99/≥37), SGA and sex.
†Adjusted for gestational age in categories (<26/26–27.99/28–31.99/32–36.99/≥37), SGA, sex and total duration of mechanical ventilation.
‡Mann-Whitney test.
aHR, adjusted HR; aOR, adjusted OR; BPD, bronchopulmonary dysplasia; GA, gestational age; n, number; NICU, neonatal intensive care unit; NIV, non-invasive ventilation; SGA, small for gestational age; UE, unplanned extubation.

of BPD. The impact of UE on pulmonary morbidity was related to the duration of MV, which is a risk factor for UE. In this subgroup, patients who were not reintubated after UE had no different risk of BPD, with and without adjustment for duration of MV, compared with those without a history of UE. Studies have shown that in case of reintubation after a UE, patients required increased ventilatory support compared with previous settings.[10 14] Thus, reintubation after UE (and the underlying condition requiring reintubation) was more responsible for respiratory morbidity than the UE itself.

This study has several strengths. First, it is a large multicentre cohort of intubated patients, with many UEs and clinical outcome data. Second, prospective data were collected for each UE episode, including original data about weaning from MV and sedatives, as well as outcomes at discharge for all the patients.

This study has several limitations. The main limitation is the possible under-reporting of UE with the type of reporting we used, as the rate found for ELGANs was lower than in North American studies.[10 17] This might also be related to French care habits, where respiratory care is shared between nurses and senior physicians; in some units, babies are handled by two nurses for aspiration or repositioning. The external validity of the results might be limited by French habits regarding sedation, weaning from ventilation and reintubation criteria. Another limitation is the 'passive' definition of UE, without confirmation by end-tidal CO_2 detector or laryngoscopy. Other limitations were the absence of data regarding ventilation settings at the time of extubation, and the absence of definition of 'weaning' and of 'sedatives' (name/type of molecule); its observational methodology cannot determine the causality of the factors associated with UE. Finally, airway complications of UE such as subglottic stenosis were not collected.

Perspectives

This study confirms that UE is a frequent and potentially severe adverse event. Given the desirability of reducing the duration of MV of neonates,[32–34] it suggests a need to assess patients' readiness to be successfully extubated and confirms the need for RCTs comparing extubation criteria and weaning protocols. It also calls for rationalising the use of sedatives in ventilated neonates beyond specific painful situations (enterocolitis, postsurgical care), because it might affect the duration of ventilation.

CONCLUSION

This study nested in the SEPREVEN trial showed that reintubation occurred much more frequently after UE than after planned extubation. Reintubation was however not systematic after UE: 42% of neonates had not been reintubated at 7 days. Cardiopulmonary complications at UE were not rare; severe bradycardia occurred in 21.2% and CPR was performed in 4.4% of UE cases. These results should encourage NICUs to work on policies to prevent this potential severe adverse event.

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REFERENCES

1 da Silva PSL, Reis ME, Aguiar VE, *et al*. Unplanned extubation in the neonatal ICU: a systematic review, critical appraisal, and evidence-based recommendations. *Respir Care* 2013;58:1237–45.

2 Sharek PJ, Horbar JD, Mason W, *et al*. Adverse events in the neonatal intensive care unit: development, testing, and findings of an NICU-focused trigger tool to identify harm in North American Nicus. *Pediatrics* 2006;118:1332–40.
3 Watson N, Meister D, Yedlin N, *et al*. Risk factors for unnplanned extubation in adult ICU patients: a case-controlled retrospective study. *Crit Care Med* 2018;46:513.
4 Al-Abdwani R, Williams CB, Dunn C, *et al*. Incidence, outcomes and outcome prediction of unplanned Extubation in critically ill children: an 11-year experience. *J Crit Care* 2018;44:368–75.
5 Bertoni CB, Bartman T, Ryshen G, *et al*. A quality improvement approach to reduce unplanned extubation in the NICU while avoiding sedation and restraints. *Pediatr Qual Saf* 2020;5:e346.
6 Galiote JP, Ridoré M, Carman J, *et al*. Reduction in unintended extubations in a level IV neonatal intensive care unit. *Pediatrics* 2019;143:e20180897.
7 Merkel L, Beers K, Lewis MM, *et al*. Reducing unplanned extubations in the NICU. *Pediatrics* 2014;133:e1367–72.
8 Klugman D, Melton K, Maynord PO, *et al*. Assessment of an unplanned extubation bundle to reduce unplanned extubations in critically ill neonates, infants, and children. *JAMA Pediatr* 2020;174:e200268.
9 Aydon L, Zimmer M, Sharp M. Reporting the incidence of unplanned extubation in the neonatal intensive care unit. *J Paediatr Child Health* 2018;54:784–7.
10 Hatch LD 3rd, Scott TA, Slaughter JC, *et al*. Outcomes, resource use, and financial costs of unplanned extubations in preterm infants. *Pediatrics* 2020;145:e20192819.
11 Pavlek LR, Dillard J, Ryshen G, *et al*. Short-term complications and long-term morbidities associated with repeated unplanned extubations. *J Perinatol* 2021;41:562–70.
12 Sawyer T, Foglia EE, Ades A, *et al*. Incidence, impact and indicators of difficult Intubations in the neonatal intensive care unit: a report from the national emergency airway registry for neonates. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F461–6.
13 Veldman A, Trautschold T, Weiss K, *et al*. Characteristics and outcome of unplanned extubation in ventilated preterm and term newborns on a neonatal intensive care unit. *Paediatr Anaesth* 2006;16:968–73.
14 Kambestad KK, Huack A, Nair S, *et al*. The adverse impact of unplanned extubation in a cohort of critically ill neonates. *Respir Care* 2019;64:1500–7.
15 Nesbitt G, Guy KJ, König K. Unplanned extubation and subsequent trial of noninvasive ventilation in the neonatal intensive care unit. *Am J Perinatol* 2015;32:1059–63.
16 Cho JE, Yeo JH. Risk factors for unplanned extubation in ventilated neonates in South Korea. *J Pediatr Nurs* 2022;62:e54–9.
17 Le Blanc G, Jabbour E, Patel S, *et al*. Organizational risk factors and clinical impacts of unplanned extubation in the neonatal intensive care unit. *J Pediatr* 2022;249:14–21.
18 Caeymaex L, Astruc D, Biran V, *et al*. An educational programme in neonatal intensive care units (SEPREVEN): a stepped-wedge, cluster-randomised controlled trial. *Lancet* 2022;399:384–92.
19 Caeymaex L, Lebeaux C, Roze JC, *et al*. Study on preventing adverse events in neonates (SEPREVEN): a stepped-wedge randomised controlled trial to reduce adverse event rates in the NICU. *Medicine (Baltimore)* 2020;99:e20912.
20 NCC MERP. 2022. Available: https://www.nccmerp.org/ [Accessed 21 May 2022].
21 Shalish W, Kanbar L, Keszler M, *et al*. Patterns of reintubation in extremely preterm infants: a longitudinal cohort study. *Pediatr Res* 2018;83:969–75.
22 Shalish W, Keszler M, Davis PG, *et al*. Decision to extubate extremely preterm infants: art, science or gamble *Arch Dis Child Fetal Neonatal Ed* 2022;107:105–12.
23 Giaccone A, Jensen E, Davis P, *et al*. Definitions of extubation success in very premature infants: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F124–7.
24 Hatch LD, Grubb PH, Markham MH, *et al*. Effect of anatomical and developmental factors on the risk of unplanned extubation in critically ill newborns. *Am J Perinatol* 2017;34:1234–40.
25 Popernack ML, Thomas NJ, Lucking SE. Decreasing unplanned extubations: utilization of the Penn state children's hospital sedation algorithm. *Pediatr Crit Care Med* 2004;5:58–62.
26 Nelson MU, Pinheiro JMB, Afzal B, *et al*. Experiences of a regional quality improvement collaborative to reduce unplanned extubations in the neonatal intensive care unit. *Children (Basel)* 2022;9:1180.
27 da Silva PSL, Fonseca MCM. Factors associated with unplanned extubation in children: a case-control study. *J Intensive Care Med* 2020;35:74–81.
28 Bol B, van Zanten H, Wielenga J, *et al*. Protocolized versus nonprotocolized weaning to reduce the duration of invasive mechanical weaning in neonates: a systematic review of all types of studies. *J Perinat Neonatal Nurs* 2020;34:162–70.
29 Donato J, Rao K, Lewis T. Pharmacology of common analgesic and sedative drugs used in the neonatal intensive care unit. *Clin Perinatol* 2019;46:673–92.
30 Verlaat CWM, Heesen GP, Vet NJ, *et al*. Randomized controlled trial of daily interruption of Sedatives in critically ill children. *Paediatr Anaesth* 2014;24:151–6.
31 Lee HC, Bennett MV, Crockett M, *et al*. Comparison of collaborative versus single-site quality improvement to reduce NICU length of stay. *Pediatrics* 2018;142:e20171395.
32 Elward AM, Warren DK, Fraser VJ. Ventilator-associated pneumonia in pediatric intensive care unit patients: risk factors and outcomes. *Pediatrics* 2002;109:758–64.
33 Fischer HS, Bührer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2013;132:e1351–60.
34 Jensen EA, DeMauro SB, Kornhauser M, *et al*. Effects of multiple ventilation courses and duration of mechanical ventilation on respiratory outcomes in extremely low-birth-weight infants. *JAMA Pediatr* 2015;169:1011–7.