Implementation of an evidence-based extubation readiness bundle in 499 brain-injured patients - a before-after evaluation of a quality improvement project

Antoine Roquilly, M.D. (1), Raphaël Cinotti, M.D. (2), Samir Jaber, M.D.,Ph.D. (3), Mickael Vourc’h (2), Florence Pengam (1), Pierre Joachim Mahe, M.D. (1), Karim Lakhal, M.D. (2), Dominique Demeure Dit Latte, M.D. (1), Nelly Rondeau, M.D. (2), Olivier Loutrel, M.D. (1), Jérôme Paulus, M.D. (1), Bertrand Rozec, M.D., Ph.D. (2), Yvonnick Blanloeil, M.D., Ph.D. (2), Marie-Anne Vibet (4,5), Véronique Sebille, Ph.D. (5,6), Fanny Feuillet (5,6), Karim Asehnoune, M.D., Ph.D. (1)

Affiliations
1. Intensive Care Unit, Anesthesia and Critical Care Department, Hôtel Dieu - HME, University Hospital of Nantes, France
2. Intensive Care Unit, Anesthesia and Critical Care Department, Laennec, University Hospital of Nantes, France
3. Intensive Care Unit, Anesthesia and Critical Care Department Saint Eloi University Hospital of Montpellier, France
4. INSELM U 657, Paris, France
5. Plateforme de Biométrie, Cellule de promotion de la recherche clinique, University Hospital of Nantes, France
6. EA 4275 SPHERE "Biostatistics, Pharmacoepidemiology & Human Science Research", UFR des Sciences Pharmaceutiques, Nantes University, France

Corresponding Author
Karim Asehnoune, M.D.,Ph.D., CHU de Nantes, Service d’Anesthésie Réanimation, 1 place Alexis Ricordeau 44093 Nantes Cedex 1.
e-mail address karim.asehnoune@chu-nantes.fr
Tel (+33) 240 08 3005. Fax (+33) 240 08 4682

The work was performed at the Nantes University Hospital
1 place Alexis Ricordeau 44093 Nantes Cedex 1.

Authors’ Contributions:
AR, RC, SJ, KA contributed to the study design, data analyses, interpretation of results, writing and revision of the manuscript; MAV, FF, VS contributed to the statistical analysis and revised the manuscript; MV, FP, PJM, KL, DDDL, NR, OL, JP, BR, YB contributed to data collection, manuscript writing and revision. All authors have approved the final manuscript for publication.

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Scientific knowledge on the subject: Complications associated with prolonged mechanical ventilation frequently develop in brain-injured patients. Strategies to decrease ventilator time have been poorly documented to date in this specific population.

What this study adds to the field: Implementation of an evidence-based extubation readiness bundle associating protective ventilation, early enteral nutrition, local protocol for the probabilistic treatment of hospital-acquired pneumonia (HAP) and systematic approach to extubation, was associated with a reduction in the duration of mechanical ventilation and in the rates of HAP as well as of unplanned extubation.
Abstract

Rationale: Mechanical ventilation is associated with morbidity in brain-injured patients. This study aims to assess the effectiveness of an extubation readiness bundle to decrease ventilator time in brain-injured patients.

Methods: Before/after design in two intensive care units (ICUs) in one university hospital. Brain-injured patients ventilated > 24 hours were evaluated during two phases (a 3-year control phase followed by a 22-month intervention phase). Bundle components were: protective ventilation, early enteral nutrition, standardization of antibiotherapy for hospital-acquired pneumonia and systematic approach to extubation. The primary endpoint was the duration of mechanical ventilation.

Results: 299 and 200 patients respectively were analyzed in the control and the intervention phases of this before/after study. The intervention phase was associated with lower tidal volume ($P<0.01$), higher PEEP ($P<0.01$), and higher enteral intake in the first 7 days ($P=0.01$). The duration of mechanical ventilation was 14.9±11.7 days in the control phase and 12.6±10.3 days in the intervention phase ($P=0.02$). The hazard ratio (HR) for extubation was 1.28 (95% confidence interval (95%CI) 1.04-1.57; $P=0.02$) in the intervention phase. Adjusted HR was 1.40 (95%CI, 1.12-1.76, $P<0.01$) in multivariate analysis and 1.34 (95%CI, 1.03-1.74; $P=0.02$) in propensity score-adjusted analysis. ICU-free days at day-90 increased from 50±33 in the control phase versus 57±29 in the intervention phase ($P<0.01$). Mortality at day 90 was 28.4% in the control phase and 23.5% in the intervention phase ($P=0.22$).

Conclusion: The implementation of an evidence-based extubation readiness bundle was associated with a reduction in the duration of ventilation in brain-injured patients.

Key words: Mechanical Ventilation, Brain injury, Weaning, Ventilator-induced lung injury, extubation.
Introduction

Weaning from mechanical ventilation is a major issue in the intensive care unit (ICU) (1). Brain-injury is a major cause of respiratory failure and a frequent cause of prolonged mechanical ventilation (2). Although primary brain insults are the main determinants of outcomes in critically ill neurologic patients, mechanical ventilation morbidity has been associated with poor neurological recovery and death in this specific population (3-5). Reduction of mechanical ventilation duration could improve health-related quality of life and it reduces the medical costs associated with critically ill patients (6, 7).

The standardization of medical care has been shown to improve the outcomes of critically ill patients. We hypothesized that the systematic application of a limited number of specific interventions could reduce ventilator time in brain-injured patients. In this setting, four main targets appeared attractive in this population. First, protective ventilation, defined as low tidal volume and positive end-expiratory pressure (PEEP), is attractive since brain injury potentiates ventilator-induced lung injuries (8, 9) and since PEEP does not alter brain perfusion (10, 11). Second, early enteral feeding decreases the rate of infection as well as the duration of mechanical ventilation in surgical and trauma patients (12, 13). Third, optimal protocols of probabilistic antibiotherapy to treat hospital-acquired pneumonia (HAP) are mandated since inadequate antibiotherapy is associated with alteration of outcomes in ICU patients (14). Consideration of local epidemiology is necessary when implementing international guidelines for antibiotherapy of HAP (15-17). Fourth, extubation of patients without complete awareness could be safe (19, 20), reducing the risk of unplanned extubation (18, 19) and decreasing the duration of ICU stay (20).

We hypothesized that the implementation of an evidence-base care bundle including protective ventilation, early enteral nutrition, standardization of antibiotherapy and systemic approach to extubation can accelerate extubation readiness in brain-injured patients (21). We therefore conducted a before/after study to investigate the implementation of an evidence-based bundle to decrease ventilator
time in brain-injured patients. Some of the results of this study have been previously reported in the form of an unpublished abstract (22).
Materials and methods

Ethics statement

The protocol was approved by the local ethics committee of Nantes hospital (Groupe Nantais d’Ethique dans le Domaine de la Santé, Nantes, France). Consent was waived because the project was a prospective improvement process within a collaborative institutional quality improvement program applied to all brain-injured patients hospitalized in our ICUs.

Patients and setting

The present study was performed in two ICUs of a university hospital. Data from all adult brain-injured patients (traumatic brain-injured, subarachnoid hemorrhage, stroke or other) who required mechanical ventilation for more than 24 hours were collected and analyzed. Brain injury was considered when a Glasgow Coma Scale $\leq 12$ was associated with at least one anomaly related to an acute process on head tomographic tomodensitometry (extradural hematoma, subarachnoid hemorrhage, brain contusion, hematoma, brain edema, skull fracture, stroke, abscess). Exclusion criteria were early decision to withdraw care (taken in the first 24 hours in ICU), death in the first 24 hours or inclusion in a randomized controlled trial.

General Care for brain-injured patients

As previously described (23, 24), all patients were sedated with a continuous intravenous infusion of fentanyl (2-5 $\mu$g.kg$^{-1}$.hr$^{-1}$) and midazolam (initiated at 0.1 mg.kg$^{-1}$.hr$^{-1}$ and increased up to 0.2-0.5 mg.kg$^{-1}$.hr$^{-1}$ in case of intracranial hypertension). Intracranial pressure was monitored with an intraparenchymal probe placed in the most affected side (Codman, Johnson and Johnson Company, Raynham, Mass., USA.) in patients who were considered at increased risk of intracranial hypertension (25). When control of intracranial pressure was poor despite osmotherapy or ventricular drainage, sodium thiopental was used with a loading dose (2-3 mg.kg$^{-1}$) followed by continuous administration (2-3 mg.kg$^{-1}$.hr$^{-1}$) adapted to intracranial pressure evolution and to serum level monitoring (blood level of thiopental between 20 and 30 $\mu$g.ml$^{-1}$). No daily interruption of sedation was performed during the period of intracranial hypertension. Sedation was discontinued as soon as the risk of intracranial
hypertension was considered as low on head tomographic tomodensitometry (no cortical sulcal effacement, no midline shift and no compressed peri-mesencephalic cisterns).

**Study protocol**

**Study design**

A before/after study design was used. The before period (control phase) consisted of all consecutive patients with severe brain-injury who were admitted to the participating ICUs three years before the educational program began (January 2007-December 2009). The intervention was introduced over a 12 month period (January-December 2010), during which no patient data were collected. The intervention phase consisted of all consecutive severe brain-injured patients admitted to the participating ICUs during a 22 month period (January 2011-October 2012).

**Control phase**

During a 3 year control phase, ventilatory setting, enteral nutrition, probabilistic antibiotherapy for HAP and decision for extubation were performed at the discretion of the attending physician. We performed a retrospective analysis of prospectively recorded data regarding: demographic characteristics, ventilatory setting, nutritional support, pathogens involved in HAP, duration of mechanical ventilation, hospital stay and mortality. The ideal body weight was calculated from the patient’s height (ideal body weight of male patients was calculated as equal to 50+ 0.91(centimeters of height - 152.4); that of female patients was calculated as equal to 45.5+0.91(centimeters of height-152.4)).

**Interphase**

During a 12 month period, we developed a 4 point bundle to decrease ventilator time based on a review of the literature and on analysis of the pathogens involved in HAP in our ICUs. Four targets were defined: protective ventilation, early enteral nutrition, optimization of the probabilistic antibiotherapy for HAP and a systematic approach to extubation (Table 1). During this phase, all physicians, residents, physiotherapists and nurses received formal training for the processes and procedures related to the 4 point bundle. Based on the prospective follow-up of the pathogens involved
in HAP during the control phase in our ICUs, two criteria have been defined for prescription of probabilistic antibiotherapy against multiple-drug-resistant bacteria (previous 48-hour antibiotherapy and/or hospitalization lasting more than 9 days). We also considered that cephalosporinase is the main mechanism of resistance for *Enterobacteriaceae* in our ICUs, and we therefore recommend the use of cefepime, which is not affected by these enzymes. Moreover, methicillin-resistant *Staphylococcus aureus* (*S. aureus*) was infrequent in our ICUs and this bacterium was not considered in probabilistic antibiotherapy. This protocol is reassessed annually. During the control phase, sedation was already standardized according to international guidelines (26, 27) and the management of sedation was therefore not included in the bundle interventions.

**Intervention phase**

During a 22-month period, the recommended procedure was to conform to the extubation readiness bundle (Table 1) and patients were followed up until day 90.

**Outcomes**

The primary outcome was the duration of mechanical ventilation. Secondary outcomes were the compliance with bundle elements, the number of ventilator-free days at days 28 and 90, the rates of extubation failure, of unplanned extubation, of tracheotomy, of HAP; ICU length of stay, the number of ICU-free days at day 90 and the mortality at day 90.

Compliance with antibiotherapy for HAP was not applicable in the control phase. Compliance with the systematic approach to extubation (undelayed extubation) was considered in the two phases when tube removal was performed within 48 hours after all of the requirements for extubation were met (inspiratory support < 10 cm H2O, Glasgow Coma Scale ≥ 10 and cough) (20).

The number of ventilator-free days was defined as the number of days from day 1 to day 28 (or day 90 as stated) on which a patient breathed spontaneously and was alive.

Pneumonia was considered when two signs (among body temperature > 38°C; leukocytosis > 12 000/mL or leukopenia < 4000/mL and purulent pulmonary secretions) were associated with the appearance of a new infiltrate or changes in an existing infiltrate on chest x-ray (28). Diagnosis was
confirmed by a respiratory tract sample using a quantitative culture with a predefined positive threshold of $10^4$ colony-forming units per milliliter (CFU/mL) for a bronchoalveolar lavage or non-bronchoscopic sample, $10^6$ CFU/mL for an endotracheal aspirate. Hospital-acquired pneumonia was defined as pneumonia that occurred 48 hours after admission that had not been incubating at the time of admission.

**Statistical analysis**

In a previous study by Mascia et al. (8), brain-injured patients who developed VILI had a 25% decrease in the number of ventilator-free days. Our study was designed to detect a 25% relative reduction in the duration of mechanical ventilation, which was estimated at 13 ± 10 days in the control phase (29) with a power of 90% and a type I error of 5%. Considering this power analysis, 398 patients are needed. The control phase has been *a priori* set to a 3-year duration and 299 patients were included in this phase. Finally, the preintervention to postintervention ratio was set as 3:2, and a total of 500 patients were included in the two phases.

The primary analysis consisted in comparing the duration of mechanical ventilation between the two phases by means of a Student’s $t$-test. A stratified log-rank test was then applied. To consider death as a competing event, individuals presenting this event were censored at this time-point (mechanical ventilation equal to the duration of survival).

A sensitivity analysis with a Fine and Gray model was *a posteriori* applied in order to consider the potential bias associated with the treatment of death. Extubation was defined as the principal event and death before extubation was defined as a competing risk (30). Proportional risk assumption was not verified for the treatment phase, so a time-dependent variable was included in the model. A cut-off was observed in the graphics and an optimal cut-off was obtained by minimizing the AIC criterion.

In order to consider potential bias associated with the before/after study design, we decided *a posteriori* to perform two complementary sensitivity analyses with an adjustment for demographic characteristics: 1/ A multivariate analysis was performed using a Cox regression model including variables differing between the two phases in bivariate analyses (with a $p$ value <0.10). Variables used
for adjustment were: cardiac failure, simplified acute physiology score-II, Glasgow Coma Scale, initial pathology, extra-ventricular drainage for hydrocephalus and decompressive craniectomy; 2/ A propensity score method was applied to balance covariates in the two phases and to reduce bias. Propensity score is defined as the conditional probability of being in the intervention phase given the covariates. It was estimated using logistic regression, including variables recorded on ICU admission. A propensity score method was applied to balance covariates in the two phases and to reduce bias. Propensity score was defined as the conditional probability of being in the intervention phase given the covariates. It was estimated using logistic regression, including variables recorded on ICU admission. At each step of the algorithm an intervention subject \( i \) was randomly selected and the difference between his propensity score and the propensity score of all control subjects was calculated (\( \Delta ci, i=1,\ldots,m \) where \( m \) was the number of intervention subjects; \( c=1,\ldots,n \) where \( n \) was the number of control subjects). In order to select the lowest distance between propensity scores for all intervention subjects (\( Di1, Di2,\ldots, Din \) for subject \( i, i=1,\ldots,m \)), a distance caliper was used whose size is a quarter of a standard deviation of the logit of the propensity score. All control subjects with a distance \( \Delta ci \) lower than the caliper size were retained for each intervention subject (control subjects for which \( \Delta ci \) is higher than the caliper size are not retained). Finally, Mahalanobis distances were calculated between each previously retained control subject and the intervention subject. The closest control and intervention subject, regarding Mahalanobis distance, was then removed from the pool, and the process was repeated for all intervention subjects (31). This caliper matching method was used to match 153 (76.5%) patients in the intervention phase and 153 patients in the control phase. A stratified log-rank test and a Cox regression model were performed on this matched sample.

In order to assess treatment effect heterogeneity across initial pathology, a subgroup analysis was performed using a Cox regression model (traumatic brain injury, subarachnoid hemorrhage, stroke and other conditions). Interaction between phase and initial pathology subgroups was tested. To estimate time trends effect, a time series analysis on aggregated data was performed. Segmented linear regression was used. In order to determine the effect of adherence to best practices, the factors
associated with the duration of mechanical ventilation were investigated through a multivariate Cox regression model.

The normality of the variables was tested with a Kolmogorov-Smirnoff test. Continuous parametric data were expressed as the mean (SD), and non-parametric data were expressed as the median and interquartile range (IQR). Categorical data were expressed as numbers and percentage, as well as the absolute difference (95% confidence interval, 95%CI). For demographic characteristics and secondary endpoint χ2 test, Student’s t-test or Wilcoxon rank-sum test were used as appropriate. All statistical tests were two-sided. A two-sided p value less than 0.05 was considered statistically significant. An independent statistician performed the analyses with SAS statistical software (SAS 9.3 Institute, Cary, NC) and R statistical software (R 3.0).
Results

Population

Demographic characteristics at baseline are reported in Table 2. Of 7,590 patients admitted in the participating ICUs, 299 brain-injured patients (49.3% traumatic brain-injured, 30.9% subarachnoid hemorrhage, 18.8% stroke, 1% cancer or meningitis) were included in the control phase, and 200 in the intervention phase (39% traumatic brain-injured, 36.5% subarachnoid hemorrhage, 16% stroke, 8.5% cancer or meningitis) \( P < 0.01 \) (see flow chart, Figure 1). In the intervention phase, extra-ventricular drainage \( (P < 0.01) \) and decompressive craniectomy \( (P = 0.03) \) were performed more frequently than in the control phase.

Compliance with bundle elements

Intervention adherence is reported in Table 3. The rates of adherence to tidal volume and PEEP recommendations were 33.6% and 37.8% in the control phase respectively, and 42.6% and 62.6% in the intervention phase \( (P = 0.09 \) and \( P < 0.01 \)). When considering tidal volume and PEEP as continuous values, the mean tidal volume was significantly lower and the mean PEEP was significantly higher in the intervention phase than in the control phase \( (P = 0.02 \) and \( P < 0.01 \) respectively, Figures 2A-B). These differences lasted during the first 5 days of mechanical ventilation (data not recorded afterward). The rates of enteral nutrition on day-1 and of input target reached on day-3 were significantly higher in the intervention phase than in the control phase \( (P < 0.01 \) for both comparisons). Probabilistic antibiotherapy was conformed to the protocol in 79 (83.2%) episodes of HAP. The percentage of patients extubated within the first 48 hours after all requirements were met (ventilatory weaning, Glasgow Coma Scale \( \geq 10 \) and cough) increased from 57.5% patients in the control phase to 68.9% in the intervention phase \( (P = 0.03) \). The percentage of patients in whom care complied with the whole set of best practices increased from 6.0% in the control phase to 21.1% in the intervention phase \( (P < 0.01) \).

Primary outcome: Duration of mechanical ventilation

The mean duration of mechanical ventilation was 14.9 ± 11.7 days in the control phase and 12.6 ± 10.3 days in the intervention phase \( (P = 0.02) \). No secular time trends unrelated to the intervention
under study was highlighted (see supplemental analysis). When considering death as a competitive event (stratified log-rank test), the median duration of mechanical ventilation was 17 (9-25) days in the control phase and 12 (7-19) days in the protocol-guided phase ($P=0.02$), with an hazard ratio (HR) for weaning from the mechanical ventilation in the intervention phase of 1.28 (95% confidence interval (95%CI), 1.04-1.57; $P=0.02$; Figure 3.A). In sub-group analysis, the benefit was consistent under all conditions, and the test for interaction between phase and initial pathology subgroups was not significant ($P$ for interaction = 0.55; Figure 3.B). Using the Fine and Gray model with a time-dependent effect, a cut-off was defined at 10 days. Before 10 days of mechanical ventilation, the HR was 1.04 (95%CI, 0.89-1.21, $P=0.64$). After 10 days of mechanical ventilation, the HR was 1.28 (95%CI, 1.01-1.62, $P=0.04$). In order to account for potential confounding factors associated with a before/after design, three sensitivity analyses were performed to assess the robustness of this result. Using a cox multivariate proportional hazards model adjusted on variables unbalanced between the 2 phases ($P<0.10$, Table 1), the adjusted HR for being alive and free of mechanical ventilation was 1.40 (95%CI, 1.12-1.76, $P<0.01$) in the intervention phase. After propensity matching based on variables potentially associated with the intervention phase (see Table 2), the HR was 1.34 (95%CI, 1.03-1.74, $P=0.02$).

We then estimated the contribution of best practices to the probability of extubation (Table 4). Only tidal volume $\leq$ 8 ml.kg$^{-1}$ (HR 1.38, 95%CI 1.08-1.76; $P<0.01$) and PEEP $>3$ cmH$_2$O (HR 1.30, 95%CI 1.00-1.69; $P=0.05$) were associated with a reduction in the duration of mechanical ventilation.

**Secondary outcomes**

Secondary outcomes are provided in Table 5. The percentage of patients with HAP decreased after bundle implementation. At day-90, both ventilator-free days and ICU-free days increased in the intervention phase compared with the control phase. No significant difference in the mortality rate at day-90 was apparent between the two phases.

**Extubation-related complications**
In the control phase, 27 (9%) reintubations were required compared with 22 (13.8%) in the intervention phase ($P=0.11$, Table 5). The rate of unplanned extubation decreased from 9.4%, to 4.5% ($P<0.01$). The rate of tracheostomy was 10% in the control phase and 8.7% in the intervention phase ($P=0.62$).
Discussion

The present study shows for the first time that implementation of an evidence-based extubation readiness bundle in brain-injured patients can reduce the duration of ventilator support. This bundle can be mainly effective in patients with a duration of mechanical ventilation exceeding 10 days, corresponding to patients with a difficult or prolonged weaning (32). The rates of HAP and of unplanned extubation were also lower in the intervention phase as compared with the control phase. The reduction in mechanical ventilation support was well tolerated regarding mortality.

When caring for critically ill patients, standardized protocols have been shown to improve outcomes in several conditions such as sedation (33), sepsis management (34) or surgical procedures (35). In acute stroke units, the implementation of an evidence-based protocol to prevent extra-cerebral complications has been shown to improve patient outcomes after discharge (36). We reported the effectiveness of a bundle developed to reduce the duration of mechanical ventilation in brain-injured patients.

Protective ventilation relies on the association of a low tidal volume with a positive end-expiratory pressure. Lung protective ventilation was initially shown to reduce the duration of mechanical ventilation in patients with acute respiratory distress syndrome (37). Few data are available in brain-injured patients because they are most likely excluded from randomized clinical trials evaluating such strategies. Thus, no consensus has been reached regarding protective ventilation in neurologic critically ill patients (38). As a result, protective ventilation was poorly applied in neurological patients in a recent large observational study (2) and the application of high tidal volume is still recommended as a means to induce moderate hypocapnia (39). In the experimental setting, brain injuries were shown to potentiate ventilator-induced lung injury (9) and a tidal volume higher than 9 ml.kg\(^{-1}\) was associated with the subsequent development of acute lung injury and with brain hypoxemia in patients with subarachnoid hemorrhage (8, 40). In a recent meta-analysis pooling studies with relatively short durations of mechanical ventilation (mean duration: 6.9 hours) in patients without ARDS, protective ventilation was associated with a decreased of ARDS/ALI rate and of mortality risk.
(41). In this meta-analysis, protective ventilation was associated with a low increase in capnia (from 38 to 41 mmHg) which could be damaging in brain-injured patients. However, the lung compliance of these patients is frequently not altered and we assume that the prevention of hypercapnia could easily be achieved in brain-injured patients by increasing the respiratory rate instead of increasing the tidal volume. In the current study, low tidal volume and PEEP were the only interventions independently associated with the probability of successful extubation. Since tidal volumes (> 10 ml/kg) were associated with ARDS and death in stroke patients (42), interventions aiming to reduce the use of such tidal volumes could be particularly relevant in brain-injured patients. Interestingly, the favorable effects of protective ventilation on the duration of mechanical ventilation were consistent for all of the neurological conditions studied, but the effects could have been more pronounced in stroke patients.

Critically ill patients frequently experience episodes of enteral feeding interruption, and nutritional goals are frequently not reached, thereby requiring early nutritional support. Early enteral nutrition remains a controversial issue mainly because of potential problems regarding tolerance and risk of HAP. Nutrition guidelines recommend achieving only 65% of calorie goals in the first week (43). Early enteral nutrition provided within the first 48 hours after ICU admission has not been shown prospectively to alter mortality (44). However, we have previously reported that early enteral nutrition was a protective factor regarding the risk of HAP in traumatic brain-injured patients (29). For these reasons, we chose early initiation of enteral nutrition and to reach the targeted input in the first 5 days. Consistent with two meta-analyses on early enteral nutrition in ICU (13, 45), the current management bundle was associated with a decrease in HAP that may have contributed to the reduction in the duration of ventilatory support.

Trauma and central nervous system diseases are recognized as major independent risk factors for pneumonia in critically ill patients (46). In several randomized studies, HAP reached up to 40-50% of brain-injured patients (47-49). This high percentage of infection can partially be explained by the prolonged duration of mechanical ventilation in this population (1). Moreover, a central nervous system injury-induced immune deficiency alters host response to
pathogens and increases the rate of pneumonia in a neuro-ICU (50). Given the frequency and the morbidity of HAP, optimization of antibiotherapy is a major objective when caring for brain-injured patients. Indeed, delay in the administration of appropriate antibiotic therapy for HAP is associated with worse outcomes in the ICU (14). Optimization of empirical antibiotic therapy decreases the duration of mechanical ventilation in septic critically ill patients (51) and may therefore reduce ventilator time for brain-injured patients. However, implementation of international guidelines for antibiotherapy of HAP is controversial (16, 17), probably because it is essential to consider local epidemiology (15) and patient conditions when choosing probabilistic antibiotherapy (52). In the current study, adaptation of international guidelines to local epidemiology was associated with a non-significant trend toward a decrease in probabilistic antibiotherapy failure.

The decision to extubate is particularly challenging in comatose patients (53). On one hand, extubation failure increases hospitalization duration and mortality in general ICU patients (54) and on the other hand, delayed extubation is associated with unplanned extubation and with altered outcomes of brain-injured patients (20). Thus, the prediction of successful extubation is particularly important since up to 10% of neurological patients require re-intubation (55). Interestingly, Coplin et al. suggested that prolonged intubation should be avoided when the only concern is an impaired neurological status (20). Several studies have reported a low risk for extubation failure in patients with a Glasgow Coma Scale between 8 and 10 provided that patients are able to cough (19, 56). In a large interventional study, the rate of re-intubation decreased when extubation was mandated as soon as the Glasgow Coma Scale was above 8 and associated with cough (18). Using more liberal criteria, we currently report a decrease in the rate of unplanned extubation. Since unplanned extubations are associated with duration of hospitalization and death (57), this result may partially explain the beneficial effects of our bundle. However, the decrease in unplanned extubation was approximately equal to the increase in extubation failure, suggesting that the Glasgow Coma Scale could be a poor criterion for the
prediction of extubation success. Finally, the overall rate of extubation-related complications was not altered in the intervention phase compared with the control phase. This result argues for the development of scores for early detection of brain-injured patients at risk of extubation failure. Such a score should allow the early extubation of patients with a low risk of extubation failure, without exposing some high-risk patients to post-extubation respiratory failure.

Several limitations should be noted here. First, this two-phased intervention study did not make it possible to demonstrate causality. This design was chosen because it was not possible to randomly assign the bundle in the same ICU without significant cross-contamination. Moreover, before/after studies provide a good level of evidence (58), with an acceptable estimation of intervention effect compared with randomized control trials (59, 60). However, a before/after design may be confounded by secular trends and we cannot exclude that some care improvements other than the bundles elements (such as management of sedation) participated in the reduction in morbidity. We therefore performed a time series analysis that did not demonstrate a secular time trends and did not conclude to a difference in the mean duration of mechanical ventilation between the two periods. This result did not contradict our conclusion based on individual analysis. Indeed, interrupted time-series methods lose power because data are aggregated at the monthly level and moreover, the autoregressive error model cannot control all of the variability in the number of patients per month. Second, even if the rate of antibiotherapy failure was low in the intervention phase, the adaption of antibiotherapy to the local epidemiology observed in the preceding years limits the generalizability of this specific element. However, ATS/IDSA guidelines state that the initial empiric therapy for HAP is more likely to be appropriate if a protocol for antibiotic selection is adapted to local patterns of antibiotic resistance, with each ICU collecting this information and updating it on a regular basis (28). Third, no intervention targeted an improvement in the management of sedation, though it is a major determinant of the duration of mechanical ventilation. Moreover, the reported doses of sedative drugs exceeded those frequently reported in studies evaluating scale-based sedation (61,
62). However, in most trials evaluating sedation, hypnotics are titrated to achieve light sedation (RASS scores between -2 and +1), when a heavy sedation is recommended for the prevention of intracranial hypertension in brain-injured patients (27). Finally, similar doses of sedative drugs were described in a recent meta-analysis reporting the sedation of brain-injured patients (63).

Fourth, overall bundle compliance ranged from 42.6% to 83.2% according the process-of-care variables, which is similar to other before/after studies which reported ranges from 5% to 87% (64). Some low rates of compliance have demonstrated that barriers for implementing bundles remain important. However, these interventions were selected because they implied multidisciplinary teamwork (nurses, clinicians, physiotherapists) which has been shown to synergistically improve patient outcomes and health-care processes (65). Moreover, a group of evidence-based treatments, instituted rapidly and together over a specific timeframe, is frequently associated with better outcomes than when they are executed individually.

In conclusion, the implementation of a four-point extubation readiness bundle in brain-injured patients, including a strategy for protective ventilation, early enteral nutrition, adaptation of antibiotherapy to local epidemiology of HAP and a systematic approach to extubation was associated with a reduction in the duration of mechanical ventilation and in the rate of associated complications. The non-significant decrease in hospital mortality pleads for a large multi-center trial investigating the effects of such a strategy.
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Conflict of interest
Authors have no related conflict of interest to disclose.

Previous presentation
Some of the results of this study have been previously reported in the form of an unpublished abstract (Société Française d’Anesthésie Réanimation annual meeting, Paris, France, Septembre 19-22, 2012).
References


patients according to time to liberation from mechanical ventilation. *Am J Respir Crit Care Med* 2011;184:430–437.


Table 1 – Evidence based weaning bundle

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<th>Intervention</th>
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<td><strong>Lung protective ventilation</strong></td>
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<tr>
<td>1. Tidal volume</td>
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<td>2. PEEP</td>
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<td>3. Respiratory rate</td>
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<td><strong>Nutrition support</strong></td>
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<td>1. Day of initiation</td>
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<td>2. Input target</td>
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<td><strong>Probabilistic antibiotherapy for hospital acquired pneumonia</strong>*</td>
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<td>1. Low risk of MDR bacteria</td>
</tr>
<tr>
<td>2. High risk of MDR bacteria</td>
</tr>
<tr>
<td><strong>Systematic approach to extubation</strong></td>
</tr>
<tr>
<td>1. Ventilatory weaning</td>
</tr>
<tr>
<td>2. Tube removal</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* Adapted to local epidemiology of pathogen involved in hospital-acquired pneumonia: low risk of MDR was defined as pneumonia before day-10 and previous antibiotherapy shorter than 48 hours; High risk of MDR bacteria was considered until day-10 or after previous antibiotherapy longer than 48 hours.

MDR: Multiple Drug Resistant, PEEP= positive end expiratory pressure.

The management of the sedation was standardized and no formal modification was performed between the two periods of the study.
### Table 2 - Population characteristics

<table>
<thead>
<tr>
<th></th>
<th>Whole cohort</th>
<th>Propensity-matched population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control phase</td>
<td>Intervention phase</td>
</tr>
<tr>
<td>Number of patients</td>
<td>299</td>
<td>200</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>50 (19)</td>
<td>52 (17)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>188 (62.9)</td>
<td>124 (62.0)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>72.2 (15.2)</td>
<td>73.8 (17.4)</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>168 (9)</td>
<td>168 (10)</td>
</tr>
<tr>
<td>Medical history, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>100 (33.4)</td>
<td>30 (15.0)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>36 (12.0)</td>
<td>25 (12.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (7.7)</td>
<td>24 (12.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>74 (24.8)</td>
<td>47 (23.5)</td>
</tr>
<tr>
<td>Severity Scores, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS II</td>
<td>38 (13)</td>
<td>41 (13)</td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td>8 (4)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Initial pathology, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>147 (49.3)</td>
<td>78 (39.0)</td>
</tr>
<tr>
<td>Sub-arachnoid hemorrhage</td>
<td>92 (30.9)</td>
<td>73 (36.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>56 (18.8)</td>
<td>32 (16.0)</td>
</tr>
<tr>
<td>Other (cancer, meningitis)</td>
<td>3 (1.0)</td>
<td>17 (8.5)</td>
</tr>
<tr>
<td>Neurological status on ICU admission, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum injury</td>
<td>33 (11.0)</td>
<td>18 (9.0)</td>
</tr>
<tr>
<td>Extra-ventricular drainage for hydrocephalus</td>
<td>72 (24.2)</td>
<td>70 (35.0)</td>
</tr>
<tr>
<td>Decompressive craniectomy</td>
<td>14 (4.7)</td>
<td>19 (9.5)</td>
</tr>
</tbody>
</table>

ICU: intensive care unit, SAPS II: simplified acute physiology score.
Table 3 - Measures of compliance

<table>
<thead>
<tr>
<th>Control phase</th>
<th>Intervention phase</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>299</td>
<td>200</td>
</tr>
</tbody>
</table>

**Lung protective ventilation on day 1**

1. Tidal volume, N (%)
   - <6 ml.kg\(^{-1}\) of ideal body weight: 7 (2.5) vs. 7 (3.9) 0.02
   - 6-8 ml.kg\(^{-1}\) of ideal body weight: 87 (30.9) vs. 70 (38.7)
   - 8-10 ml.kg\(^{-1}\) of ideal body weight: 136 (48.2) vs. 88 (48.6)
   - > 10 ml.kg\(^{-1}\) of ideal body weight: 52 (18.4) vs. 16 (8.8)

2. PEEP, N (%)
   - 0 cmH\(_2\)O: 90 (30.6) vs. 11 (5.6) <0.01
   - 1-3 cmH\(_2\)O: 93 (31.6) vs. 56 (28.3)
   - > 3 cmH\(_2\)O: 111 (37.8) vs. 131 (66.2)

**Tidal volume, mean (SD)**

- 8.9 (1.9) vs. 8.1 (1.4) <0.01

**Nutrition support**

1. Initiation
   - Day 1, N (%): 80 (33.2) vs. 88 (56.1) <0.01
   - ≥ Day 2, N (%): 161 (66.8) vs. 65 (43.9)
   - Day of initiation, mean (SD): 2.6 (1.8) vs. 1.5 (1.2) <0.01

2. Time to achieve an input of 25 kCal.kg\(^{-1}.\)day\(^{-1}\)
   - ≤ Day 3: 49 (25.1) vs. 88 (65.7) <0.01
   - Days 4-5: 64 (32.8) vs. 17 (12.7)
   - ≥ Day 6: 82 (42.1) vs. 29 (21.6)

   Mean time (SD): 6.1 (3.9) vs. 3.7 (3.2) <0.01

3. Total enteral intake in the first 7 days (kCal), mean (SD)
   - 4300 (2650) vs. 8300 (12300) 0.01

**Glasgow coma scale on extubation day ↑**

- Mean (SD): 11 (2) vs. 11 (3) 0.39
- Glasgow ≤ 10, N (%): 38 (17.9) vs. 58 (39.2) <0.01
- Glasgow 11-12, N (%): 129 (60.9) vs. 48 (32.4)
- Glasgow 13-15, N (%): 45 (21.2) vs. 42 (28.4)

**Compliance with bundle elements, N (%)**

1. Ventilatory setting
   - Tidal volume ≤ 8 ml.kg\(^{-1}\) on day 1: 94 (33.6) vs. 77 (42.6) 0.09
   - PEEP > 3 cm H\(_2\)O in day 1: 111 (37.8) vs. 131 (66.2) <0.01

2. Nutrition support
   - Enteral nutrition initiated on Day-1: 80 (33.2) vs. 88 (56.1) <0.01
   - Target of enteral support reached ≤ Day-3: 49 (25.1) vs. 88 (65.7) <0.01

3. Antibiotic therapy for HAP
   - NA vs. 79 (83.2) ∞ NA

4. Systematic approach to extubation (undelayed extubation)
   - (&): 122 (57.5) vs. 102 (68.9) 0.03
   - (&&): Assessment not applicable

**Overall bundle compliance**

- 18 (6.0) vs. 42 (21.1) <0.01

\* Assessed in 95 HAP

† Assessed in 212 patients in the control phase and 148 patients in the intervention phase (not applicable for death prior to extubation or tracheotomy);

(&) The compliance with the systematic approach to extubation (undelayed extubation) was considered when tube removal was performed within 48 hours after all requirements are met (ventilatory weaning, Glasgow coma scale ≥ 10 and cough);

(&&) The compliance was considered when bundle interventions were not applicable: in patients without HAP (for the antibiotic therapy protocol); in dead or tracheotomized patients (for the systematic approach to extubation).

HAP: hospital acquired pneumonia, PEEP: positive end-expiratory pressure, NA: not applicable
Table 4 – Association of best practice with probability of weaning from mechanical ventilation

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Hazard Ratio</th>
<th>[95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume ≤ 8 ml.kg⁻¹</td>
<td>1.38</td>
<td>[1.08; 1.76]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PEEP &gt; 3 cm H₂O</td>
<td>1.30</td>
<td>[1.00; 1.69]</td>
<td>0.05</td>
</tr>
<tr>
<td>Early enteral nutrition</td>
<td>1.18</td>
<td>[0.92; 1.51]</td>
<td>0.19</td>
</tr>
<tr>
<td>Undelayed extubation (&amp;)</td>
<td>1.07</td>
<td>[0.82; 1.40]</td>
<td>0.63</td>
</tr>
<tr>
<td>Compliance with all bundle elements</td>
<td>1.49</td>
<td>[0.97 ; 2.27]</td>
<td>0.07</td>
</tr>
</tbody>
</table>

PEEP: positive end-expiratory pressure. The association of the bundle elements with the duration of mechanical was assessed with an univariate analysis. (&) Undelayed extubation was considered when tube removal was performed within 48 hours after all requirements were met (inspiratory support < 10 cm H₂O, Glasgow Coma Scale ≥ 10 and cough)
<table>
<thead>
<tr>
<th></th>
<th>Control phase</th>
<th>Intervention phase</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>299</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation, days, mean (SD)*</td>
<td>14.9 (11.7)</td>
<td>12.6 (10.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, median (IQR)**</td>
<td>17 (9-25)</td>
<td>12 (8-19)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ventilator-free days at day 28, mean (SD)</td>
<td>3.7 (5.3)</td>
<td>5.5 (6.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ventilator-free days at day 90, mean (SD)</td>
<td>54 (33)</td>
<td>64 (29)</td>
<td>0.01</td>
</tr>
<tr>
<td>Extubation management, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall extubation-related complication (&amp;)</td>
<td>55 (18.4)</td>
<td>36 (18)</td>
<td>0.91</td>
</tr>
<tr>
<td>Extubation failure</td>
<td>27 (9.0)</td>
<td>27 (13.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Unplanned extubation</td>
<td>28 (9.4)</td>
<td>9 (4.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tracheotomy</td>
<td>29 (10.0)</td>
<td>17 (8.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hospital acquired pneumonia, N (%)</td>
<td>172 (57.5)</td>
<td>95 (47.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Probabilistic antibiotherapy failure, N (%)</td>
<td>14 (27.5)</td>
<td>8 (8.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome, N (%)</td>
<td>19 (6)</td>
<td>7 (3.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>ICU length of stay, median (IQR)*</td>
<td>20 (11-32)</td>
<td>18 (12-29)</td>
<td>0.48</td>
</tr>
<tr>
<td>ICU-free days at day 90, mean (SD)</td>
<td>50 (33)</td>
<td>57 (29)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in ICU</td>
<td>75 (25.1)</td>
<td>45 (22.5)</td>
<td>0.51</td>
</tr>
<tr>
<td>at day 90</td>
<td>85 (28.4)</td>
<td>47 (23.5)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

ICU: intensive care unit
* gross analysis (Student’s t-test), ** calculated from stratified log-rank test with consideration of death, (&) defined as extubation failure and/or unplanned extubation.
**Figure 1 - Flow chart**
MV: mechanical ventilation, RCT: randomized clinical trial

**Figure 2 - Evolution of tidal volume and of positive end-expiratory pressure during the first 5 days of mechanical ventilation**

Tidal volume and positive end-expiratory pressure (PEEP) were recorded at 8:00 am from days 1 to 5. IBW: ideal body weight. Data represent mean ± SD. ** * p<0.01 versus control phase

**Figure 3 - Kaplan-Meier curves for mechanical ventilation**

(A) The hazard ratio for weaning from the mechanical ventilation was 1.28 (95%CI, 1.04-1.57; p=0.02) using a stratified log-rank analysis, 1.40 (95%CI, 1.12-1.76; p<0.01) using a multivariate cox model and 1.34 (95%CI, 1.03-1.74, p=0.02) after matching with a propensity analysis. Multivariate cox model was adjusted on cardiac failure, simplified acute physiology score II, Glasgow Coma Scale, initial pathology, extra-ventricular drainage for hydrocephalus and decompressive craniectomy.

(B) Hazard ratio for weaning from mechanical ventilation in traumatic brain injured patients, subarachnoid hemorrhage patients, stroke patients and other conditions.
Fig 1 - MV: mechanical ventilation, RCT: randomized clinical trial
361x270mm (72 x 72 DPI)
Fig 2 - Tidal volume and positive end-expiratory pressure (PEEP) were recorded at 8:00 am from days 1 to 5. IBW: ideal body weight. Data represent mean ± SD. ** p<0.01 versus control phase
174x50mm (72 x 72 DPI)
Fig 3A - (A) The hazard ratio for weaning from the mechanical ventilation was 1.28 (95%CI, 1.04-1.57; p=0.02) using a stratified log-rank analysis, 1.40 (95%CI, 1.12-1.76; p<0.01) using a multivariate cox model and 1.34 (95%CI, 1.03-1.74, p=0.02) after matching with a propensity analysis. Multivariate cox model was adjusted on cardiac failure, simplified acute physiology score II, Glasgow Coma Scale, initial pathology, extra-ventricular drainage for hydrocephalus and decompressive craniectomy.
Fig 3B - (B) Hazard ratio for weaning from mechanical ventilation in traumatic brain injured patients, subarachnoid hemorrhage patients, stroke patients and other conditions.

255x79mm (300 x 300 DPI)
Online supplemental data

Implementation of an evidence-based fast-track weaning bundle in 499 brain-injured patients: a before-after multicenter study

Supplemental analysis 1 – Time series analysis of the duration of mechanical ventilation

Supplemental analysis 2 - Adjustment on the propensity for the intervention phase

Supplemental analysis 3 - Fine and Gray model
Supplemental analysis 1 – Time series analysis of the duration of mechanical ventilation

To estimate time trends effect, a time series analysis on aggregated data was performed (mean duration of mechanical ventilation by month). Segmented linear regression was used.

Initially, linear regression with auto-correlated errors was applied; it didn’t show an overall trend (p=0.93). Then, we used segmented linear regression with autocorrelated errors, which divides the time series into pre- and post-intervention segments. This type of analysis is performed on aggregated data.

In pre-intervention phase, an upward trend is detected (p<0.01). In post-intervention phase, there is no significant trend (p=0.98). Means comparison test shows no significant difference between duration of mechanical ventilation at the beginning of the pre-intervention phase and duration of mechanical ventilation at the beginning of the post-intervention phase (p=0.31).

This time series analysis highlights no secular time trends unrelated to the intervention under study was highlighted.

Figure S1. Time-evolution of the duration of mechanical ventilation

Table S1. Segmented linear regression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>t Statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>11.30</td>
<td>1.63</td>
<td>6.92</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pre-intervention trend</td>
<td>0.21</td>
<td>0.08</td>
<td>2.70</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Post-intervention trend</td>
<td>0.15</td>
<td>7.63</td>
<td>0.02</td>
<td>0.98</td>
</tr>
<tr>
<td>Means comparison</td>
<td>-0.18</td>
<td>0.18</td>
<td>-1.02</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Supplemental analysis 2 - Adjustment on the propensity for the intervention phase

Caliper matching method

Variables used for matching:
- Medical history of cardiac failure
- Extra-ventricular drainage for hydrocephalus
- Decompressive craniectomy
- Initial condition (Traumatic brain injury, sub-arachnoid hemorrhage, stroke, other)
- Coma Glasgow Scale
- Simplified Acute Physiology Score-II

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of matched patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control phase</td>
<td>153</td>
<td>50.00</td>
</tr>
<tr>
<td>Intervention phase</td>
<td>153</td>
<td>50.00</td>
</tr>
</tbody>
</table>

→ 94 patients lost
Figure S2. Kaplan-Meier curve for mechanical ventilation in the 306 matched patients (153 by group)

Cox model: Hazard ratio for successful extubation 1.34 (95% confidence interval 1.03-1.74, \(P=0.02\))
Supplemental analysis 3 - Fine and Gray model

The Figure S3 displays the estimated CIF of the two competing events in each treatment phase.

![Figure S3: Cumulative incidence function curves](image)

Before 10 days of mechanical ventilation: $HR = 1.04 [0.89 ; 1.21] - p = 0.640$

After 10 days of mechanical ventilation: $HR = 1.28 [1.01 ; 1.62] - p = 0.039$