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pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

EN ANESTHÉSIE RÉANIMATION

par

Laure FIEUZAL

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Présentée et soutenue publiquement le 09 septembre 2021

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Faiblesse acquise en réanimation :

Établissement d'un protocole de mobilisation précoce

et évaluation de son impact

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Président : Monsieur le Professeur Antoine ROQUILLY

Directeur de thèse : Monsieur le Docteur Julien LORBER

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Intensive Care Unit Acquired Weakness:

Establishment of an early mobilization protocol

and evaluation of its impact

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Président : Monsieur le Professeur Antoine ROQUILLY

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Et enfin, **à François**, dont la pensée me pousse à me dépasser tous les jours.

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INTRODUCTION

A. Incidence

Weakness is a frequent consequence of prolonged hospitalization in intensive care unit (ICU). Intensive care unit acquired weakness (ICUAW) is a syndrome including a polyneuropathy, a myopathy, or a combination of both without any other etiology than the hospitalization in the ICU (1,2).

This syndrome is diagnosed in 40% of patients ventilated for more than 7 days, its incidence in the ICU varying from 30 to 50% depending on the diagnostic method used (3).

B. Diagnostic

The ICUAW affects the limbs proximally and symmetrically, and the respiratory muscles, sparing the head and neck. Osteotendinous reflexes are most often diminished or abolished. The diagnosis is clinical, based on the use of the Medical Research Council (MRC) scale, used in most studies (4). This score evaluates the capacity of mobilization of the four limbs, rated from 1 to 5. The diagnosis weakness is made from a score of 48 points or less out of a total of 60, corresponding to a threshold of 80% of physiological mobilization (Appendix I).

Electrophysiology studying nerve conduction (electroneuromyogram) was used to diagnose ICUAW (5). This examination has a good correlation with clinical examination, but various presentations were found (polyneuropathy, myopathy, or both) without a therapeutic impact of this categorization. To avoid fastidious examination, clinical diagnostic of ICUAW based on MRC is the reference in absence of alternative hypothesis (1,6) (Appendix II).

C. Associated factors

Factors statistically associated with the occurrence of ICUAW are the initial severity (Simplified Acute Severity Score second version, SAPS II), multiple organ failure, use of

norepinephrine, hyperlactatemia), the existence of inflammation (systemic inflammatory response syndrome, sepsis), hydroelectrolytic disorders (hyperglycemia, plasmatic hyperosmolarity), the use of some treatments (curare, parenteral nutrition) or their prolonged administration (duration of sedation and mechanical ventilation). Female gender is also a factor associated with the occurrence of ICUAW (7).

D. Prognostic

This syndrome is associated with an immediate negative impact in the ICU. It is associated with more frequent extubation failures, occurring in half of the affected patients. The probability of ventilatory weaning is decreased by 30%, due to impaired diaphragmatic function, found in 80% patients with ICUAW (8).

The cost of hospitalization in intensive care is increased by 30%. In patients with ICUAW, the probability of being discharged alive from the ICU is reduced by 40%, and from the hospital by 30% (9).

Long-term survival is also lower. Mortality at 1 year is increased by 13%, this association persisting at 5 years. Patients who survive have sequelae: muscle strength is measured to be 25% lower at 5 years, the results of functional tests (six-minute walk test) are worse, and quality of life scores (SF-36 test or Short Form Health Survey) are lower (9-11)

E. Prevention, Early Mobilization

While there is no curative method for ICUAW, preventive methods can reduce its occurrence. Beyond the prevention of associated factors, the application of early mobilization, from the first days in ICU seems to be effective in limiting the ICUAW incidence and short-term consequences (12). Early mobilization increases ventilator free days, decreases the length of stay in ICU and improves functional scores at discharge (13,14). These results are confirmed in series of patients admitted to surgical ICU or after acquired brain injury (15-17). Long-term consequences have not been demonstrated, due to a lack power and heterogeneity of the existing studies (18).

F. Safety

Complications occurring during early mobilization sessions in ICU have a low incidence. Previous trials evaluating an early mobilization protocol did found very few adverse events (13-15, 19). The main adverse events after a session are tachycardia, hypotension, and desaturation. They occur respectively less than 4 times per 1000 mobilization sessions and only in exceedingly rare cases motivating a corrective medical intervention (20). The prevention of serious adverse events during sessions is made possible by the establishment of criteria that guarantee the clinical stability of patients (21, 22).

G. Recommendations

Because of the expected benefit on the outcome of ICU patients and the low immediate risk, a formalized expert recommendation regarding early mobilization was written by the *Société de Réanimation de Langue Française (SRLF)* in 2013. It recommends the initiation of mobilization within the first 48 hours, for all ICU patients, except in uncontrolled acute situations. It requires the joint decision of the medical, paramedical and physiotherapy teams and, at best, the drafting of a protocol to facilitate its application. The techniques used must be adapted to the patient's state of consciousness and participation, which are assessed daily, as well as the tolerance at each stage (23).

Early mobilization is a part of the current recommendations of the American College of Critical Care Medicine to reduce incidence and duration of delirium along with early stop sedation and pain management (24).

H. Local Practices

No evaluation of the incidence of ICUAW was previously performed in the Surgical Intensive Care Unit at the University Hospital of Nantes.

Some known risk factors are nevertheless systematically prevented by standards of care already applied in this service, with the aim of preventing other complications.

These include:

- Prevention of hyperglycemia for patients admitted for severe traumatic brain injury by continuous insulin administration adapted to capillary glucose levels
- Early enteral feeding within 48 hours after admission, in absence of digestive contraindications
- Limited prescription of curare and sedation at the minimal dose and duration for an early return to consciousness and spontaneous ventilation for all patients, guided by the Richmond Agitation Sedation Scale (RASS) (Appendix III).

However, no standardization concerning mobilization has been written in this service before 2019. The prescription and performance of mobilization was left to the discretion of physicians and paramedical staff.

I. Aim of the study

In accordance with the formalized expert recommendation of the *Société de Réanimation de Langue Française* (23), we wrote in 2019 a local care protocol standardizing the indications and the method for early mobilization of patients hospitalized in the Surgical Intensive Care Unit at the University Hospital of Nantes.

The drafting of this protocol was associated with its promotion and the training of the physicians and all the staff.

We hypothesized that the implementation of this protocol associated with this continuous training would increase the application of the recommendations and decrease the complications of ICUAW.

We conducted a before-after study of the implementation of this standard of care to assess its application and impact on patient outcomes.

MATERIALS and METHODS

A. Type of study

We performed a retrospective, monocentric, non-interventional, before-after study analyzing the mobilization of patients ventilated for more than 48 hours between January 1, 2016, and May 1, 2021.

No additional clinical or paraclinical examinations was imposed by the study protocol. The patients were followed during their hospital stay and for some of them, during the post-ICU consultations at 6 months, planned within the *AtlanRéa* cohort (a follow up cohort for the severe injured patients in which the surgical ICU of the Nantes University Hospital participates).

B. Population

All patients admitted to the Surgical Intensive Care Unit of the University Hospital of Nantes between January 1, 2016, and December 31, 2017 for the before phase, and from September 1, 2020, to May 1, 2021 for the after phase, who were invasively ventilated for more than 48 hours were included.

Patients under the age of 18 and those in situation of withdrawal of life sustained therapy during hospitalization were excluded. We also excluded burned and tetraplegic patients, for whom specific mobilization protocols were already implemented in the department (25). Patients admitted for severe infection with SARS-CoV-2 in the after phase were also excluded, to ensure a comparable patient population between the two phases.

C. Intervention

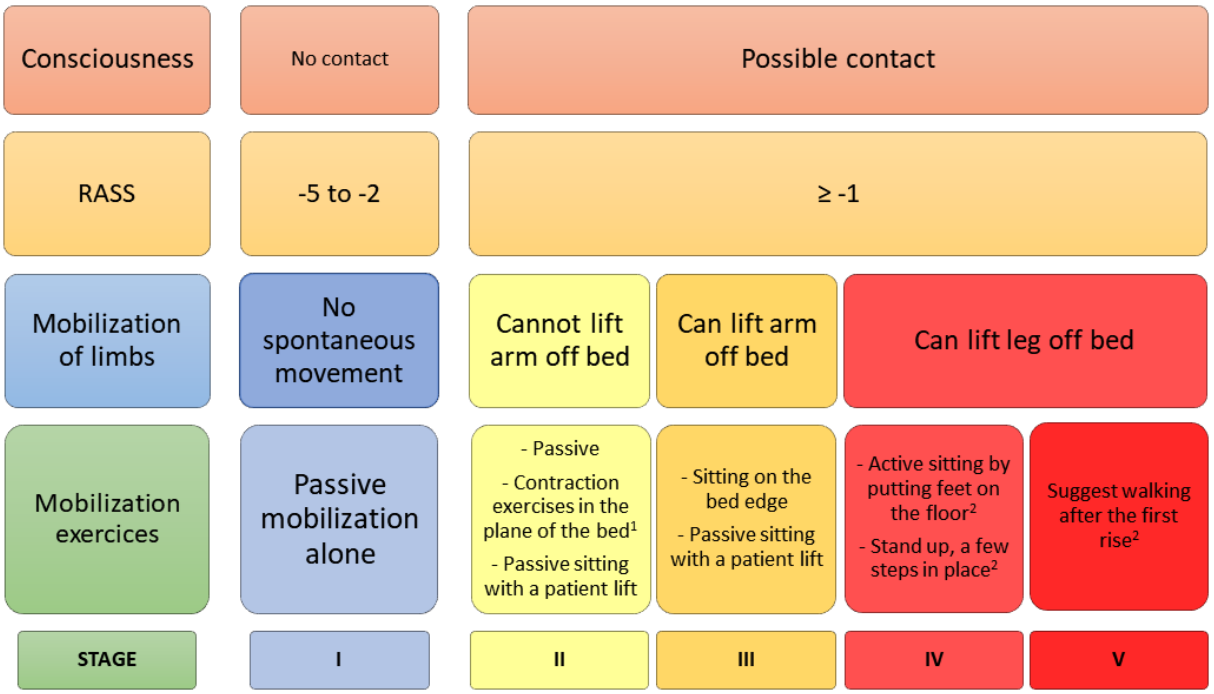
1. "Before" phase

Before 2019, no protocol guiding mobilization was established in the Surgical Intensive Care Unit of Nantes University Hospital and no strategy for screening patients who could benefit from it was standardized. The mobilizations sessions were performed by a physiotherapist (PT) in charge of 21 patients, assisted by nurses (2 in charge of 5 patients) and nursing assistants (NA) (1 in charge of 4 patients) in accordance with the decree 2003-413 of August 27, 2003, relating to the health establishments practicing the ICU. Physical therapy was performed on a daily handwritten medical prescription (Appendix IV), and the type of activity was at the initiative of the physiotherapist in absence of a complementary mention.

The lift to chair without the patient participation was carried out by the nurses and the nursing assistants, using a fixed patient lift, available in each room. The paramedical staff was trained in the use of this equipment during their initial training. These mobilizations were performed on handwritten medical prescription or on the initiative of the staff in charge of the patient.

2. "Drafting protocol" phase

In accordance with the formalized expert recommendations of the *Société de Réanimation de Langue Française* (23) a working group in charge of the development of mobilization, the mobilization team, composed of physicians and some voluntary paramedical staff members was created in September 2018. Based on previous effective protocols (13-15, 24) and guided by the recommendations, an early mobilization protocol, adapted to the resources of the service was drafted (Figure 1).



Legend: 1: with the use of the Physiotherapy Kit; 2: with the use of the manual standing aid; RASS: Richmond Agitation and Sedation Scale.

Figure 1: Stages and exercises according to the patient's level of consciousness and weakness

The patients included in the study were classified into 5 stages according to two criteria: consciousness and weakness. The level of consciousness was defined by the Richmond Agitation Sedation Scale (RASS) (Appendix III) used routinely in the ICU department. The level of the ICUAW was defined by movement exercises against gravity of the upper and lower limbs that can be performed in the patient's bed.

In addition to the inclusion and exclusion criteria for early mobilization, temporary contraindications were added, which were to be reassessed daily. They were selected based on previous publications regarding the safety of early mobilization in ICU (22). They concerned unstable patients, or patients with a surgical contraindication to mobilization (Table 1).

Table 1 : Temporary contraindications to mobilization

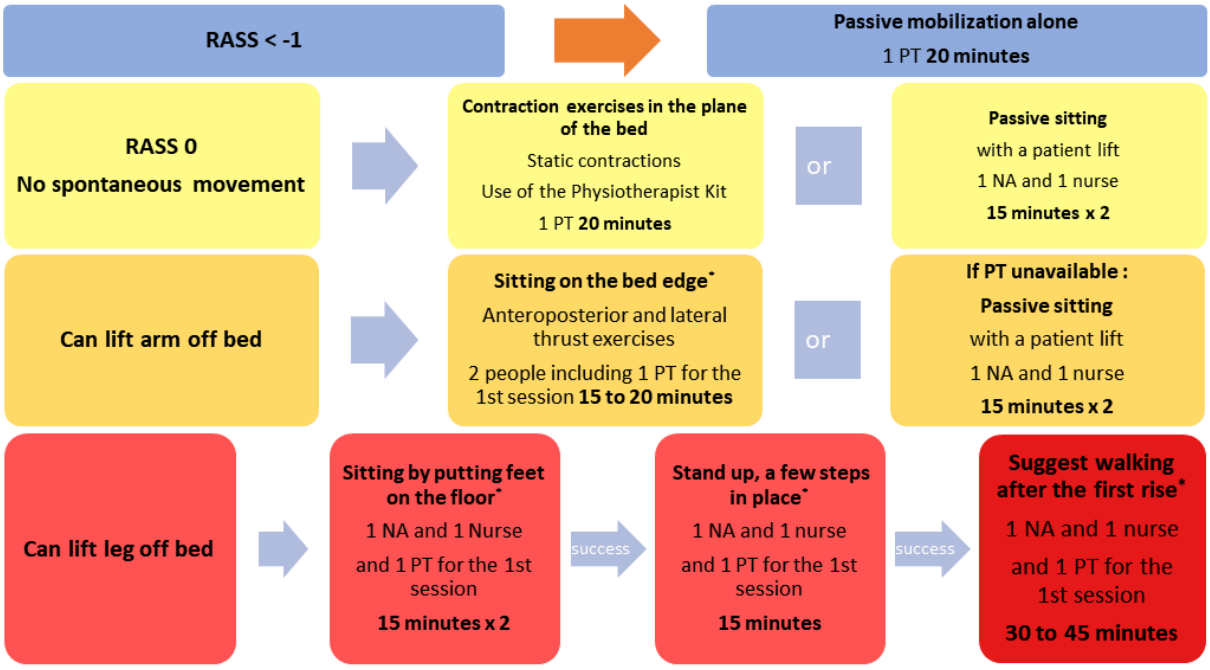
Respiratory	ARDS, use of curare FiO^2 > 0,6 or x2 in 12 hours
Hemodynamic	Norepinephrine > 0.5 µg/kg/min or x2 in 4 hours Uncontrolled hemorrhagic shock
Cardiogenic	Ongoing treatment with dobutamine Myocardial infarction < 5 days
Neurologic	Severe traumatic brain injury < 48 hours Intracranial hypertension (on ICP sensor or transcranial doppler)
Surgical	Surgical prescription of a mobilization restriction

ARDS: Acute Respiratory Distress Syndrome; FiO^2: fraction of inspired oxygen; ICP: intracranial pressure.

The creation of a "Physiotherapy Kit" was imagined jointly by the department physiotherapists. It was composed of material allowing muscular contraction exercises in bed and thus particularly adapted to stage II patients, unable to move against gravity. It contained balls, elastics, and dumbbells to improve prehension and muscle strength.

The protocol was written in a progressive way. A failed exercise should lead to a new attempt of the same exercise during the next session. A success should lead to repetition of the exercise until the criteria for moving on to the next stage are met. Moving to a higher stage did not exclude repeating the exercises of the previous stages.

A workload estimation was made. The duration and the personnel required for each exercise were estimated jointly by the NAs, the nurses and the PT participating in the work group (Figure 2).



*Legend: RASS: Richmond Agitation and Sedation scale; PT: Physiotherapist; NA: Nursing Assistant; *: Requires the presence of the physiotherapist for the first session*

Figure 2: Durations and personnel required to perform the exercises at each stage

Each stage had several exercises presented gradually from the most to the least beneficial on the recovery of muscle strength, passive activities shown less impact (27).

After evaluation of the availability of the caregivers in relation to the number of patients under their supervision, the exercises were scheduled at least every 48 hours for each patient. The care organization was helped by labels whose colors correspond to each stage, available in the rooms. After stage evaluation in the morning, the label was posted on the door of the room by the nurse in charge. It allows the physiotherapy team to be daily informed of the progress.

The early mobilization protocol was validated in a department meeting on June 06, 2019.

3. Staff training and communication phase

None of the exercises in the protocol was unknown to the nursing staff prior to 2019. Those mobilizations were all already performed in the department out of protocol, except for those using the "Physiotherapy Kit". The physiotherapist was trained to this type of exercise in his initial training. The kit also contained a manual for the rest of the staff. The change consisted therefore in the standardization of early mobilization in the department through the application of the protocol.

The paramedical team (NAs and nurses) was trained from June 2019 on the daily assessment of the stage of the patients when they took up their post in the morning. This training was carried out during informal meetings in the department, organized by the members of the mobilization team. Information was also delivered through social networks during a "mobilization week" from June 10 to 15, 2019. Cards summarizing the protocol (Appendix V) were integrated into the care standardization booklet for the caregivers in the rooms.

At the same time, the physicians received a course on June 06, 2019, concerning the acquired weakness in the intensive care unit and the protocol was presented to them. They were given the mission to promote mobilization by adapting their prescriptions in three ways:

- Limiting the length and dose of sedatives prescribed at the minimum necessary
- Adding analgesics when needed for the mobilization sessions
- Treat delirium when necessary to get the cooperation of patients.

Prescribers were also reminded that confusion was not a contraindication to mobilization and may be a treatment for it (14,24). They were also encouraged to coordinate the staff members during their visits and check the effective realization of mobilization for their patients during the day.

4. Implementation

A testing phase took place from June 10 to September 27, 2019, during which the entire protocol was applied. The mobilization team trained the rest of the staff at the patient's bedside. This phase highlighted a difficulty in planning mobilization, and a need for coordination between the nurses, the NAs, and the PT. Daily care planning sheets were created and filled in by the different caregivers. These sheets were collected regularly to check that the programming was carried out correctly and to analyze the exercises performed (Appendix VI).

The first Physiotherapy Kit was available for daily use from September 2020, then a second one obtained the following year.

5. Promotion

Posters summarizing the protocol were placed on November 15, 2019, (120x176cm size) in treatment rooms and in the meeting room. It was containing the different stages schematized, the necessary personnel and contraindications to mobilization (Figure 3).

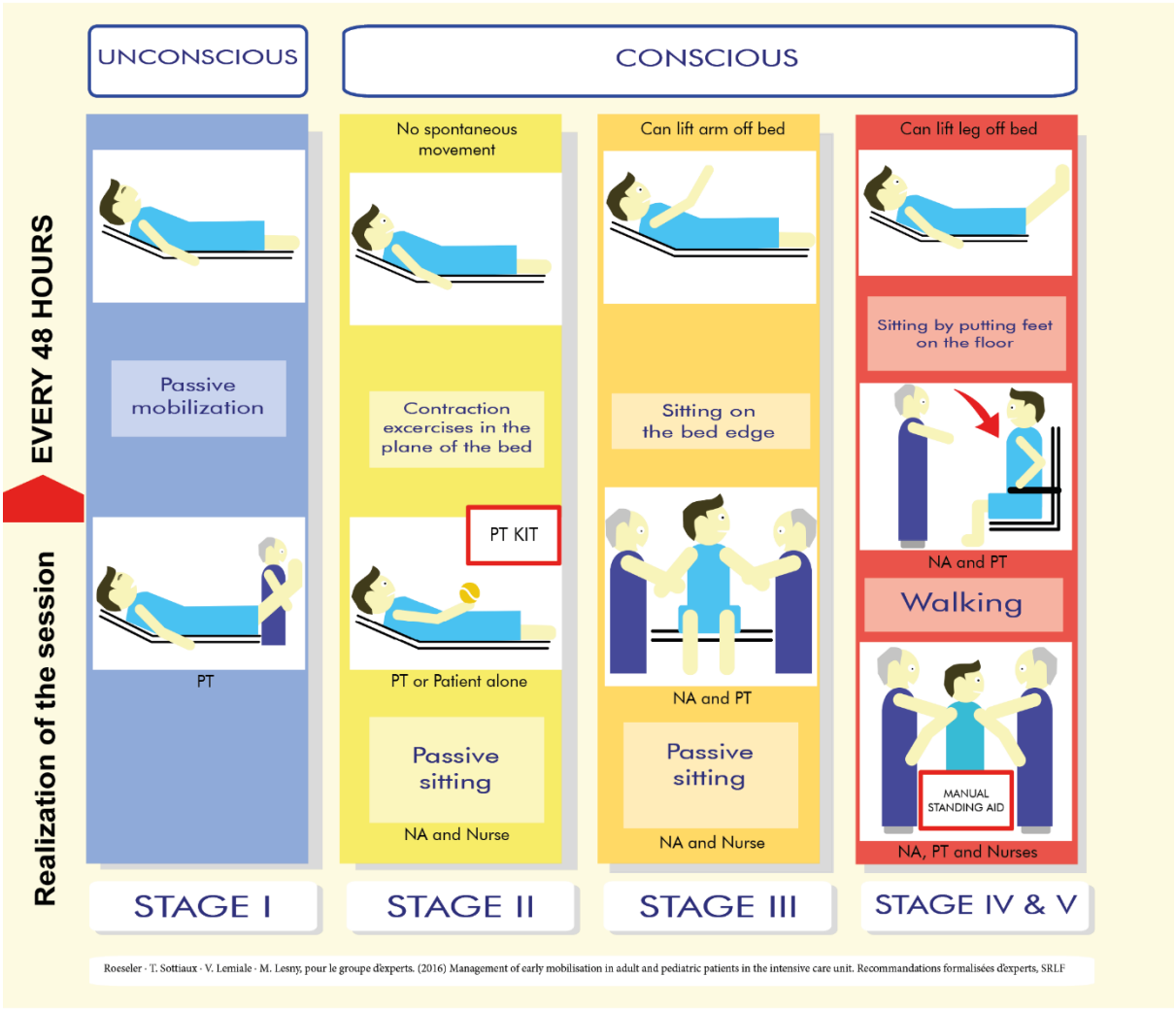


Figure 3: Schematic of the stages and personnel involved in each exercise (extract from the communication poster, full poster on Appendix VII)

The protocol was integrated into department's practice booklet, the SONAR (*Standardisation et Optimisation des soiNs en Anesthésie Réanimation*) in August 2020. This booklet was given to each new prescriber at arriving. It is planned to be available in a computerized version on the SONAR application in the next update. The daily prescription sheets were modified, including onwards a checkbox indicating the stage (Appendix IV).

The mobilization protocol was again presented to the entire department on October 8, 2020, at a department protocol seminar.

6. Continuing Education

Training was continued through regular courses to new prescribers each semester in May and November, during which they were encouraged to clearly write "mobilization" and the stage of their patients on their prescriptions. They were also encouraged to treat any pain or confusion that might interfere with effective mobilization, and to coordinate the mobilization sessions. The need to prescribe sedation at minimal doses and duration when necessary was reiterated.

Demonstrations at the patient's bedside, from stage scoring to the execution of exercises, were daily continued by the members of mobilization team to the rest of the paramedical staff. The objective was to continuously disseminate the application of the protocol.

Table 2: Summary of training and promotion methods for the early mobilization protocol

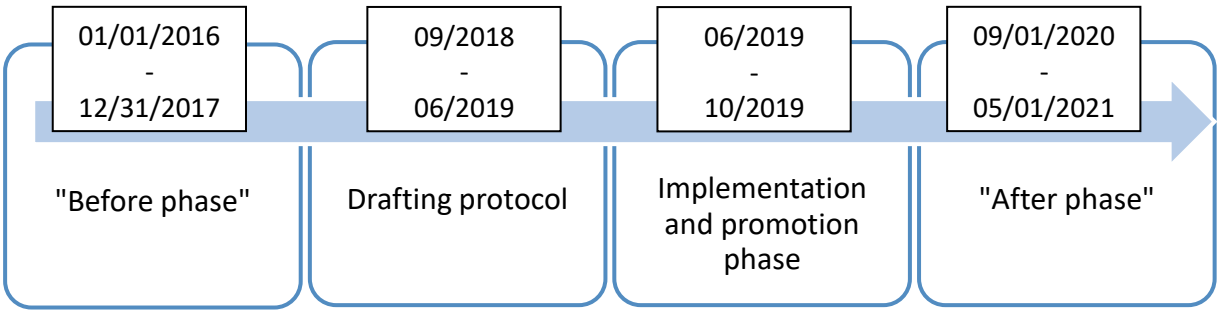
Training	Promotion	
06/04/2019		Course to prescribers
	06/06/2019	Service meeting, presentation, and validation of the protocol
	06/10/2019	Cards summarizing the protocol integrated into the care standardization booklet and labels for each stage available in each room
06/10 to 06/15/2019		**Mobilization week** Meetings in the department, organized by the members of the mobilization team and training of the paramedical team Publication of information on social networks
06/10 to 27/09/2019		**Testing phase** Application of the entire protocol Training department staff at the patient's bedside by the mobilization team
	10/01/2019	Creation of daily care planning sheets
	11/15/2019	Poster display
12/2/2019		Course to prescribers
06/04/2020		Course to prescribers
	09/11/2020	Integration into department’s practice booklet, the SONAR
	10/08/2020	Presentation of the protocol at department protocol seminar
11/12/2020		Course to prescribers
	10/26/2020	Posting of a reminder sheet in the treatment rooms encouraging the paramedical team to rate the stages
	03/2021	Modification of the daily prescription sheets: checkbox stages
Continuous		Training department staff at the patient's bedside by the mobilization team

Legend: SONAR: Standardisation et Optimisation des soiNs en Anesthésie Réanimation.

D. Data Collection

Data were collected for the before phase from January 1, 2016, to December 31, 2017, and for the after phase from September 1, 2020, to May 1, 2021, for all patients over 18 years old, hospitalized in surgical ICU, ventilated more than 48 hours, not in situation of withdrawal of life sustained therapy subject, and whose reason for admission was not spinal cord injury or severe burns.

Figure 4: Timeline for establishment and evaluation of the early mobilization protocol



These data were collected independently of care, on paper and computerized patient records via the *Millenium* software, after discharge from the department. Some data were collected at 6 months, from post-ICU consultation reports for the patients in the *AtlanRéa* cohort. These were patients whose reason for admission was severe traumatic brain injury or septic shock and who agreed to attend these consultations. Due to a suspension of these consultations since March 2020, data for the after phase were only collected from patient records when available.

Demographic data, comorbidities, previous autonomy, reason for admission, and severity factors (including SAPS II, an ICU clinical and biological score at admission correlated with mortality in ICU) were collected at admission. Information collected during hospitalization concerned sedation, length of stay in the intensive care unit and in hospital, duration of mechanical ventilation and its possible weaning failures, and mortality at discharge and at 6 months. Quality of life scores (IADL and sf-36) were available at 6 months for the patient in the *AtlanRéa* cohort from post-ICU consultations.

Concerning mobilization, the data collected were the number of prescribed mobilizations, the number of sessions performed, the delay of performance, the type of exercise performed, and the immediate complications observed. The failure for performing a session was also collected as well as its reason.

E. Judging criteria

The aim of this before-after study was to evaluate the application of early mobilization as a standard of care in the Surgical Intensive Care Unit of the University Hospital of Nantes, through the drafting of a protocol.

For this purpose, we used the “time before verticalization” as the primary endpoint. It was defined as the delay in days, between admission into the ICU and the occurrence of the first verticalizing event. Verticalizing event could be "sitting on the bed edge", "sitting on the armchair", "getting up" or "walking".

The secondary endpoints were to specify the application of the mobilization protocol by the number and type of exercises performed and to evaluate its impact during the stay in ICU, at discharge and at 6 months.

F. Statistics

The number of patients needed was estimated on the BiostaTGV website (28). A preliminary analysis of the first 30 patients in 2016 found a median time before verticalization of 10 days and a standard deviation of 7.24. Using this estimate, a total of 212 patients, was expected to unmask a difference of 3 days for the primary endpoint using a 2-tailed test with 90% power and alpha risk at 0.05. The average number of patients ventilated for more than 48 hours in the Surgical Intensive Care Unit of the University Hospital of Nantes was on average 220 for the last 3 years. Excluding the patients in situation of withdrawal of life sustained therapy, the burned and the tetraplegic patients the expected number of patients in the "before" group was 200 for the two years 2016 and 2017. We planned with a ratio of 2:1 an "after" group of 100 patients.

We performed a stratified analysis by admission type because of a clear decrease in the number of trauma patients in the after period. The strata were “trauma patients” (including brain injured patients and polytraumatized patients) and “non-trauma patients” (including patients admitted for planned or unplanned surgery and other reasons, represented by medical causes and postoperative complications). For the univariate analysis, patients were described according to those 2 groups.

Continuous variables were described by their median, the first and third interquartile [Q1; Q3]. Categorial variables were described by number and percentage (n, %). The comparative analysis of the quantitative variables used a Mann Whitney’s non-parametric U test. Chi² test was used to compare qualitative variables.

A survival analysis was performed for the primary outcome. Multivariate analysis was performed using a Fine and Gray model. Because death and discharge from ICU were competing event to mobilization, we used this method developed for survival analysis in the presence of competing risks. The sub-distribution Hazard Ratios (sd-HR) and its 95% confidence interval was estimated. Sd-HR can be defined as the hazard of the event of interest in the presence of competing risks. Results were presented using a cumulative incidence function. The SAPS II, the number of days free from sedation, the number of invasive ventilation days and the occurrence of delirium were entered a priori in the multivariate analysis because of their potential impact on mobilization (17). Because of a low occurrence, side effects analysis was only descriptive.

Statistics were performed independently of cares and data collection.

G. Ethics

This study was validated by the Ethical Committee for Research in Anesthesia and Intensive Care (ref: IRB 00010254 - 2020 – 252). It was not raising any ethical problem and was not falling within field of application of the regulations governing research involving the human being, as defined in Article L.1121-1 and R.1121-2, and therefore no consent was required.

Because of its methodology, this study involved only the application of routine care and was considered as an evaluation of professional practices according to the criteria of the *Agence Nationale de Sécurité du Médicament*.

After advice from the non-interventional research unit of the Nantes University Hospital (CNI), and in accordance with the recommendations of the *Commission Nationale de l'Informatique et des Libertés*, all collected data were coded in a file with an anonymous number for each patient. The code was recorded in a correspondence table independent of the data table. The data collection was carried out independently of the care.

Since January 2017, all patients of the Nantes University Hospital received information on the potential use of their medical data for clinical research purposes and had the possibility to object to it.

Physicians and paramedics of the department were informed of the evaluation of professional practices.

RESULTS

During the two phases, between January 1, 2016, and December 31, 2017, and from September 1, 2020, to May 1, 2021, all the ventilated patients for more than 48 hours were included. After application of the exclusion criteria, a total of 318 patients were enrolled in the study. 5 patients were excluded from analysis because of missing information on primary outcome. Au total of 313 patients was included in analysis (205 in the before group, and 108 in the after group). The stratification was made by admission type, trauma (n=161) or non-trauma patients (n= 152).

Table 3 shows the repartition of admission type during each phase. There were more trauma patients in the before phase (59.5 vs 36.1%), and more non-trauma patients in the after phase (63.9 vs 40.5%).

Table 3: Admission type

	Before (n=205)	After (n=108)
Isolated Traumatic Brain injury (%)	61 (29.8)	14 (13.0)
Polytraumatized patient (%)	61 (29.8)	25 (23.1)
Total trauma patients (%)	**122 (59.5)**	**39 (36.1)**
Planned surgery (%)	23 (11.2)	17 (15.7)
Unplanned surgery (%)	55 (26.8)	47 (43.5)
Others (%) (Including surgical complications, cardiac arrests, and septic shocks)	5 (2.4)	5 (4.6)
Total non-trauma Patients (%)	**83 (40.5)**	**69 (63.9)**

After stratification, the baseline characteristics were similar in the subgroups (Table 4), except for prior autonomy in each subgroup and severity (SAPS II) lower in the after phase in the non-trauma population.

Table 4: Baseline characteristics of subgroups

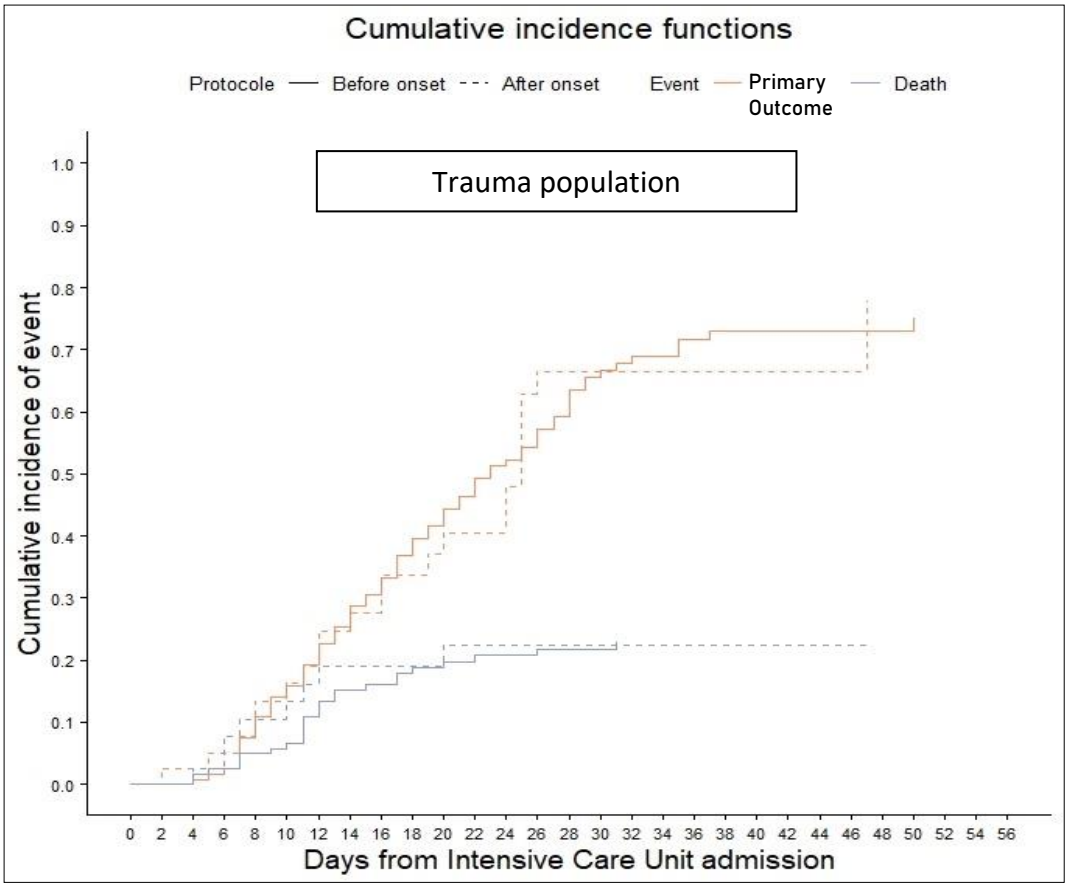
	Trauma patients (n=161)		Non trauma patients (n=152)	
	Before (n=122)	After (n=39)	Before (n=83)	After (n=69)
Age, years (mean (SD))	47 (19)	52 (18)	62 (14)	64 (14)
Gender male (%)	91 (74.6)	33 (84.6)	57 (68.7)	48 (69.6)
Body Mass Index, kg/m² (mean (SD))	25.3 (4.8)	25.1 (5.0	26.9 (6.6)	28.0 (9.3)
Comorbidities (mean (SD))				
Respiratory	6 (4.9)	1 (2.6)	22 (26.5)	13 (18.8)
Neurological	7 (5.7)	3 (7.7)	7 (8.6)	7 (10.1)
Cardiac	8 (6.6)	4 (10.3)	18 (22.0)	15 (21.7)
Diabetes	8 (6.6)	2 (5.1)	13 (15.9)	19 (27.5)
Renal	9 (7.4)	0 (0.0)	16 (19.5)	14 (20.3)
Albuminemia (g/L) (median [IQR])	30 [25-33]	28 [25-33]	20 [17-27]	21 [18-26]
Prior autonomy: walking without technical assistance (%)	115 (95.8)	32 (84.2) *	71 (87.7)	49 (73.1) *
Severity at admission				
SAPS II (*median [IQR]*)	47 [40-52]	45 [37-50]	51 [45-54]	44 [37-50] *
Use of amines (%)	138 (85.7)	104 (85.2)	60 (72.3)	54 (78.3)
Glasgow Coma Scale (*median [IQR]*)	8 [5-13]	8 [5-13]	15 [13-15]	15 [15-15]
Acute Kidney Injury (%)	82 (51.9)	58 (48.7)	56 (68.3)	42 (60.9)
Severe ARDS (%)	46 (28.6)	32 (26.2)	27 (32.5)	16 (23.2)

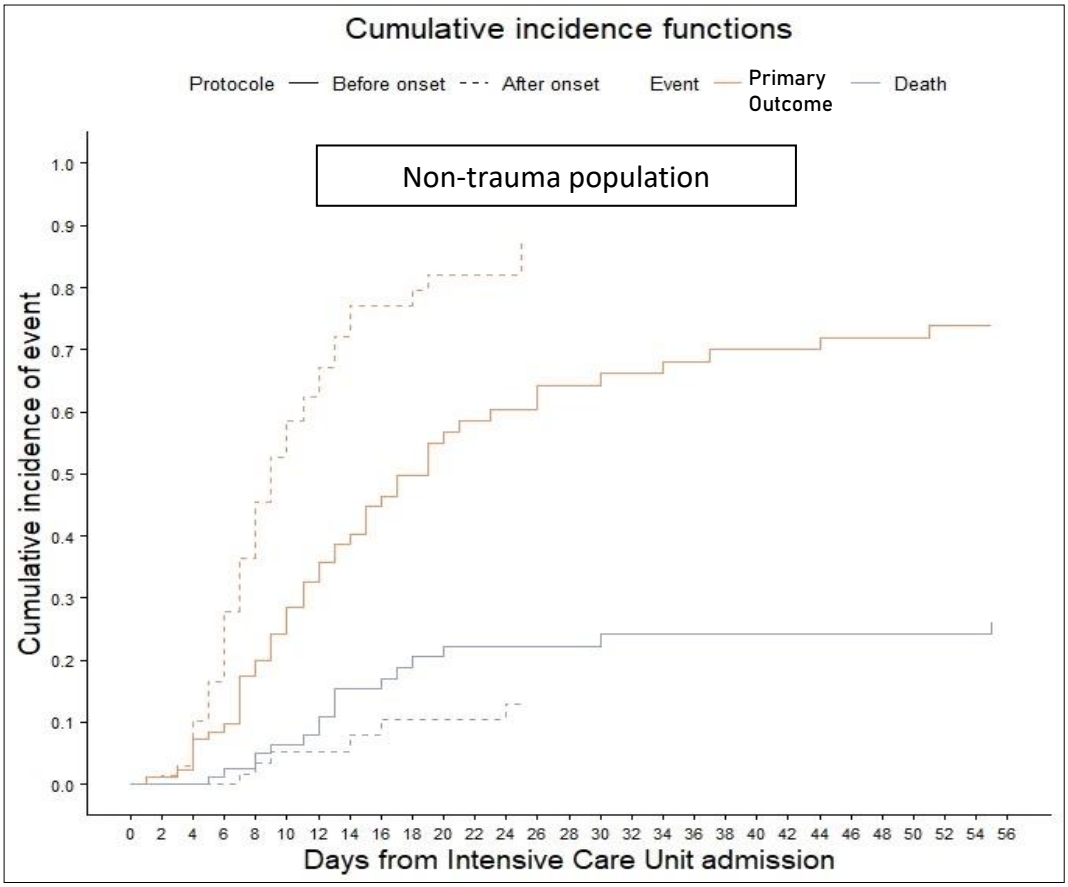
*Legend: * p<0.05.*

Respiratory: chronic obstructive pulmonary disease or respiratory chronic failure, Neurological: peripheral neuropathy, Cardiac: cardiac chronic failure, Renal: chronic renal failure defined by creatinine clearance < 30mL/min.
SAPS II: Simplified Acute Physiology Score, using first 24h worst clinical and biological parameters at ICU admission, predicting mortality, ranging from 0 to 163, worse when high.
ARDS: Acute respiratory distress syndrome.

A. Trauma population

In the trauma patient, the proportion of mobilized patients reflecting the application of protocol was not different between the two phases (56.4% vs 65.6% mobilized patients, p 0.399). The time before verticalization for these patients did not differ between the 2 phases, with a median of 16.00 [10.25-24.75] vs 17.00 [11.00-25.00] days and no difference found in the cumulative incidence of verticalization (Figure 5). The median number of sessions per patient per day in ICU did not differ (8,4 vs 11,1 sessions per patient for 100 days in ICU). The proportion of patients mobilized when intubated was 20,5 vs 12,2% of all the trauma patients, without a significative difference (p=0.064).





Legend: Primary Outcome: occurrence of the first verticalization.

Figure 5: Time before verticalization for each population described by cumulative incidence function

No difference was found in other outcome in ICU or at discharge (Table 5). A trend to decrease time before verticalization, length of sedation, invasive mechanical ventilation and stay in ICU seemed to be observed, by one day on median, but none of those result was significatively different.

Table 5: Outcome of trauma patients

	Before	After	p value
Time before verticalization from ICU admission	17.0 [11.0, 25.0]	16.0 [10.5, 25.0]	0.622
Length of sedation administration	6.0 [4.0, 11.0]	5.0 [3.0, 9.0]	0.359
Length of unconsciousness	9.0 [5.0, 13.0]	8.0 [4.0, 12.5]	0.400
Length of stay in ICU free from sedation	12.0 [7.0, 20.0]	12.0 [4.5, 18.0]	0.498
Length of invasive mechanical ventilation	13.0 [8.5, 20.0]	12.0 [6.5, 19.0]	0.383
Extubation failure	25 (20.5)	7 (17.9)	0.908
Length of stay in ICU	19.5 [12.0, 30.5]	17.0 [11.0, 25.5]	0.275
Delirium occurrence (%)	37 (30.3)	11 (28.2)	0.959
Death in ICU	28 (23.0)	9 (23.1)	1.000
Death in hospital	29 (23.8)	9 (23.1)	1.000
Death at 6 months	35 (31.0)	9 (40.9)	0.509

Legend: All values expressed in days, median [IQR] except for delirium occurrence, extubation failure and death expressed in number (%) of available data.

Variables that may interfere with mobilization (defined *a priori)* were included in the multivariate analysis (Table 6). Prior autonomy was not associated with time before verticalization. Severity at admission defined by SAPS II and length of invasive mechanical ventilation were found to be associated with slightly later verticalization (Sd-HR respectively 0.98 and 0.96). Delirium occurrence seemed to be associated with earlier mobilization (sd-HR 1.80 p 0.004).

Table 6: Outcome of trauma patients: Multivariate analysis

Covariates	sd-HR [95%CI]	p value
After protocol	0.94 [0.58 - 1.52]	0.800
Prior autonomy	1.19 [0.54 - 2.61]	0.670
SAPS II	0.98 [0.96 - 0.99]	0.008
Length of stay in ICU free from sedation	1.02 [1.00 - 1.04]	0.060
Length of invasive mechanical ventilation	0.96 [0.93 - 0.99]	0.013
Delirium occurrence	1.80 [1.20 - 2.69]	0.004

B. Non-trauma population

In the non-trauma population, the proportion of mobilized patients was 57.0% before and 68.1% after implementation of protocol. The time before verticalization from ICU admission was shorter by 3 days on median (8.00 [6.00-10.50] vs 11.00 [7.00-19.00], p=0.002) and shorter on cumulative incidence (Figure 4). The number of median sessions increased from 6,25 to 12,9 sessions per patient for 100 days in ICU.

Other outcomes are presented in table 7. The length of sedation administration and its effects was shorter in the after phase. Duration of invasive mechanical ventilation and of hospitalization in ICU were also shorter. We did not find any significant difference in other outcomes at ICU discharge or at 6 months.

Table 7: Outcome of non-trauma patients

	Before	After	p value
Time before verticalization from ICU admission	11.0 [7.0-19.0]	8.0 [6.0-10.5]	0.002
Length of sedation administration	5.0 [3.0-10.5]	3.0 [3.0-5.0]	0.002
Length of unconsciousness	5.0 [3.0-9.0]	3.0 [2.0-5.0]	0.001
Length of stay in ICU free from sedation	9.0 [4.0-16.0]	6.0 [3.0-10.0]	0.051
Length of invasive mechanical ventilation	9.0 [6.0-15.5]	6.0 [4.0-10.0]	<0.001
Extubation failure	15 (18.1)	9 (13.0)	0.533
Length of stay in ICU	14.0 [9.5-23.5]	10.0 [7.0-15.0]	0.002
Delirium occurrence (%)	24 (28.9)	25 (36.2)	0.432
Death in ICU	20 (24.1)	14 (20.3)	0.715
Death in hospital	25 (30.1)	17 (24.6)	0.568
Death at 6 months	30 (40.0)	19 (51.4)	0.349
Back to prior activity at 6 months	27 (42.9)	13 (33.3)	0.454

Legend: All values expressed in days, median [IQR] except for delirium occurrence, extubation failure and death expressed in number (%) of available data.

Table 8: Outcome of non-trauma patients: Multivariate analysis

Covariates	sd-HR [95%CI]	p value
After protocol	2.04 [1,34 - 3,11]	0.001
Prior autonomy	0.85 [0,47 - 1,54]	0.580
SAPS II	1.01 [0,99 - 1,03]	0.260
Length of stay in ICU free from sedation	1.03 [1,01 - 1,05]	0.004
Length of invasive mechanical ventilation	0.96 [0,94 - 0,98]	0.001
Delirium occurrence	1.34 [0,89 - 2,02]	0.160

Effect of the protocol establishment on verticalization was persistent after adjustment on duration of consciousness (length of stay in ICU free from sedation), and length of mechanical invasive ventilation (Table 8) with an sd-HR of 2.04. Severity defined by SAPS II and prior autonomy were not associated with the time before verticalization. The length of stay free from sedation was associated with a slightly earlier verticalization. Length of invasive mechanical ventilation was associated with a later verticalization. In this population, delirium occurrence was associated with an earlier verticalization (sd-HR 1.34) but without a significant result.

The type of exercise was different in this population after the protocol implementation. The best type of exercise performed during ICU stay was more often active in the after phase (47,8 vs 31,3%). (Figure 5).

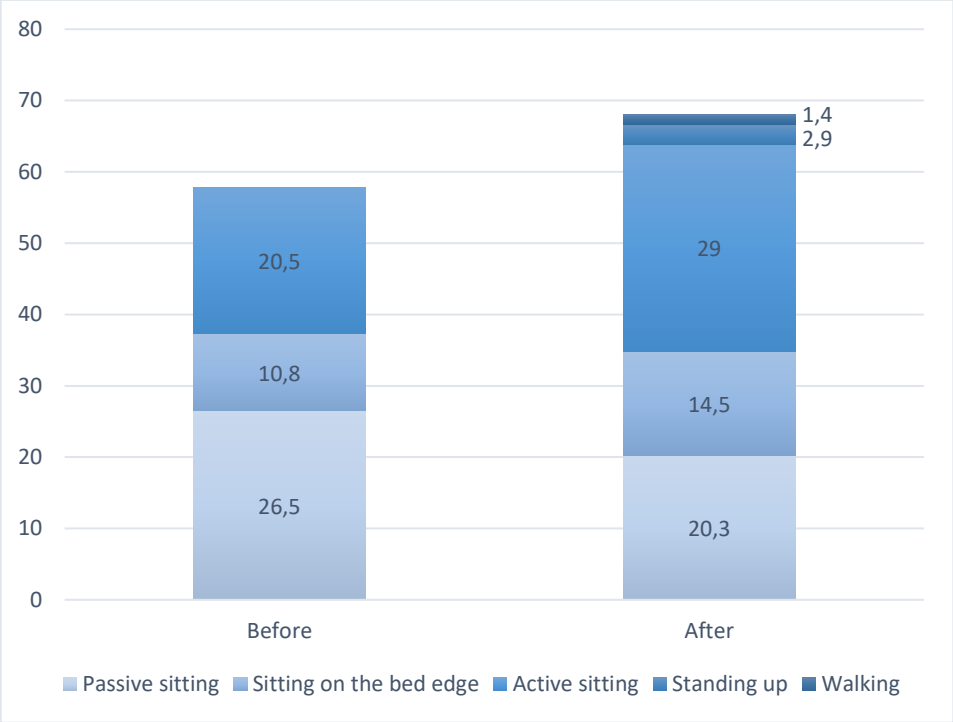


Figure 6: Best exercise performed in % for each phase (non-traumatic population)

C. Safety

Safety was evaluated during mobilizations. 1168 sessions were performed during the study. 29 (2.4%) were stopped prematurely (19 sessions in the before phase and 10 in the after phase). The 36 side effects reported are described in table 9. Respiratory effects were peripheral pulse oximetry (Spo^2) decrease or polypnea. The minimal Spo^2 value reported was 88%. Hemodynamic effects were tachycardia, dizziness, and hypotension.

5 of these events were considered as severe event. All those side effects were corrected spontaneously by ending the session or by a medical intervention (intravenous fluid therapy or increase oxygen supply).

Table 9: Side effects reported during mobilizations

	Frequency, n (per 1000 sessions)
Pain	11 (9,4)
Tiredness	8 (6,8)
Respiratory effect	10 (8,5)
Desaturation	8
Polypnea	2
Hemodynamic effect	7 (5,9)
Tachycardia	4
Dizziness	2
Hypotension	1
Total	**36 (30,8)**

No accidental ablation of an invasive dispositive was reported. 25,6% patients had a mobilization out of bed during invasive mechanical ventilation. No fall was reported during any session.

D. Failure to mobilization planning

Reasons for not performing session were collected (Table 10). The main cause was the absence of cooperation found in 15.3% of all patients and more often in 19.9% of trauma patients. Lack of material, member of staff or patient unavailability were reported in very few cases (<1% patients).

Table 10: Reasons for not performing sessions

	All patients n=313	**Trauma patients n=161**	**Non trauma patients n=152**
Absence of cooperation	48 (15.3)	32 (19.9)	16 (10.5)
Surgical contraindication	22 (7.0)	17 (10.6)	5 (3.3)
Failure of performing	12 (3.8)	9 (5.6)	3 (2.0)
Patient refusal	12 (3.8)	3 (1.9)	9 (5.9)

*Legend: All values in parenthesis are %, *: significatively different p<0,05*

DISCUSSION

Our monocentric study shows the acceptability and feasibility of early mobilization in a surgical intensive care unit while the recommendations were not previously applied. Perform a before-after study was efficient to quickly evaluate the application of a local early mobilization protocol as a standard of care.

The drafting of this protocol, its implantation and continuous formation was indeed associated for non-trauma population with an increase from 57 to 68.1% in the proportion of patients mobilized, an increase of the number of sessions performed by patients per day in ICU, a reduction of time before verticalization by 3 days and an augmentation of active exercises in this population. Administration of sedation and length of unconsciousness was also shorter.

Our primary outcome is particularly relevant because not only highlighting a protocol prescription but also an early protocol application, shortening the time to verticalization. Verticalization including sitting on armchair, sitting on the bed edge, or standing up is supposed in previous studies to be the best way to improve axial tonus. The proportion of active exercises increasing with protocol implementation is also supposed to be more beneficial for the patient recovery (15,17,29,30).

Those results on verticalization were not found in the trauma population composed of traumatic brain injured patients and polytrauma patients. No decrease of length of sedation was also found. It can show barriers to the application of the entire protocol in this population compared to non-trauma patients. Indeed, in multivariate analysis, severity defined by SAPS II was associated with an increase of time before verticalization (sd-HR 0.98 [0.96 - 0.99], p=0.008) while this association was not found in non-trauma population. No evidence was found in literature that initial severity should restrain mobilization. But observational studies show this is a frequent barrier to mobilization implementation, including for brain damaged patients (16, 31). Education work needs to be done in our department to ensure that trauma patients get mobilized despite their initial severity. Some barriers were however not modifiable. In this population, proportion of absence of cooperation and surgical contraindication was significantly higher than in non-trauma

population. Despite the absence of difference in the application of the mobilization protocol in trauma population, we reported a trend to decrease of at least one day in median on the time before verticalization, the length of sedation and unconsciousness, length of invasive mechanical ventilation and length of stay in ICU. Those results were not significant, but the number of patients was low in trauma population in the after phase (39 patients). A lack of power due to stratification may explain the absence of statistical difference on the ICU outcomes in the trauma group. Continuing data collection in this group may confirm the trend we observed for this population.

One of the limits of our study is the difference of population between the two phases, due to the variation in the distribution of admission type as presented in table 3. This limit is due to the before-after study type because of the admitted population may change in the department during time. Performing a randomized controlled trial to evaluate comparable populations would have been a loss of chance for the control group, knowing early mobilization was recommended since 2013. We also wanted to implement early mobilization as a standard of care in the department. We explain decrease of trauma admissions in the after phase by the data collection period. Without collecting data between May and August in the after phase, the period of summer known to be associated with more trauma patient admission was not included (32). Moreover, the after period included in France 72 days of prohibition of movement for sanitary reasons because of SARS-CoV-2 pandemic. Restrictive public health interventions due to this pandemic were evaluated to be associated with a trauma number decrease of 25% in other countries (33). Differences between the two populations were partially corrected by the stratification by admission type, but this stratification was responsible for a loss of power. A propension score could be applied on the global population to have more robust results for the purpose of publication.

Our protocol included recommendations during courses, in booklet and on posters about sedation prescription. Prescribers were encouraged to prescribe it at minimal doses and duration when necessary to facilitate weaning from ventilation, participation to care and effective mobilization. As a result, the benefice we observed in our study may be explained by reduction of sedation length, early performance of the sessions or both of those actions. We have decided not to evaluate the impact of these actions separately but together. Indeed, our protocol was created as a bundle, as rehabilitation in ICU needs to be

multifactorial to be effective on the outcome of patients (34). For the future, mobilization could be further improved by applying more precises and stringent rules for decreasing sedation. A daily stop sedation could be used, a protocol that has shown its benefit decreasing length of sedation and ICU stay and increase ventilator free days (35). This action may help increasing mobilization in all the populations, not only in non-trauma patients.

Another limit common to the before-after studies is the possible interference during time of practice changes. Mobilization may have been increased after 2013 guidelines and after randomized controlled trials in favor of its effectiveness in ICU notably published in 2016 (15). Another change between 2016 and 2020 is the prescription of lower doses of sedation, associated with an improvement of patient outcome especially a shorter duration of mechanical ventilation and a shorter ICU length of stay (24). A time series analysis of the evolution of the primary endpoint could correct this bias. Thus, a progressive improvement in patient mobilization and verticalization after the protocol implantation would reinforce its validity.

Application of the protocol was safe. Severe adverse events were only on 4,2 per 1000 sessions, and all side effects were rapidly corrected. No accidental removal of an invasive material was reported in this study. Unlike previous trials (13-15), we did not excluded patients with impaired autonomy in our observational study, as the recommendation insists on mobilization application for all patients. Previous autonomy was not associated with verticalization in our study in none of the populations. Those results show impaired autonomy is not a barrier to mobilization in our department and safety is also guaranteed in this population. The safety results during the two periods show that the department staff was used to mobilize patients in or outside of bed with precaution, even before 2016. The contraindications for mobilization in the protocol were also restrictive enough to exclude unstable patients. It also can show that people with invasive material were less mobilized for fear of a severe side effect. Indeed, our study found a low rate of mobilization when intubated (25,6% of the mobilized patients), and invasive mechanical ventilation was associated to an increase time before verticalization in both populations in multivariate analysis. Despite the recommendations precising that "*ventilated patients should not be deprived of active mobilization or ambulation only because of the presence of an endotracheal tube and/or mechanical ventilation*" (23), this seems to be a barrier to

mobilization in our department. The low rate of mobilization when intubated was increased in the after phase from 23% to 30% of mobilized patients and from 13% to 18% for active mobilization, showing a better application of recommendation in invasive ventilated patients in the after phase. Considering the safety results, the rate of mobilization, especially when intubated, could be improved in surgical intensive care units by more frequent bedside demonstrations explaining the role of each staff member during the sessions. We believe this could enhance the sense of safety for all members of the department. Less restrictive criteria for mobilization in the department could also be chosen in regards of the safety results. Some side effects were also avoidable, notably pain, the most frequent side effect observed. This last cause highlighted a need for the physicians to anticipate it before mobilization sessions and add premedication on their prescriptions.

A notable fact of our results is the low rate of application of the protocol. In non-trauma population, number of sessions was only 12,9 per patient per 100 days in ICU after protocol implementation. Proportion of mobilized patients was increased by 11,1% and 21,9% patients were never mobilized during ICU stay. This low implementation rate was expected, as it has been found in many other studies implementing a new care protocol (36,37). It can be explained firstly by the almost total absence of formalization of mobilization before our protocol in the department. Thus, the change in practices is such that application is slow. Secondly, the compliance of a team to a new medical practice is a long process (38). Our training period may have been too short to increase greatly early mobilization protocol adherence.

Some barriers are, moreover, inherent to the mobilization practice for which strategies exist (31,39). Establishing a protocol is one of these strategies. We also have considered the existing material and human resources to propose length and type of exercises in relation with the surgical ICU in University Hospital of Nantes capacity. The protocol was written interdisciplinary, with collaboration of nurses, nursing assistants, physicians, and physiotherapists because implementing our early mobilization program required continued commitment from all disciplines. Despite this commitment, institutions who successfully implemented mobilization as routine activities have dedicated teams for mobilization, including dedicated PTs (17,40). Dedicated PT is also associated with progression to out-of-bed mobility (29). Only one PT works in our department (except for

burned patients), in charge of respiratory and motor physiotherapy for 21 patients. No dedicated nurse or NA was available to evaluate patient accessibility to mobilization every day and this workload was added to their daily tasks. This can explain some missing sessions. Our department was however equipped with tools helping verticalization, not available in every institution: 2 manual standing aid and fixed patient lifts in each room. No additional costs were required except for the PT kits acquisition. Costs for material and human resources need to be considered when implementing an early mobilization protocol. This study was not designed to evaluate costs. But decreasing length of ICU stay, immediate and long-term morbidity and improve functional recovery can offset the cost of mobility (41). This financial consideration leads us to propose the addition of a dedicated paramedical team to mobilization including a dedicated PT to increase the mobilization of patients in surgical ICU at Nantes University Hospital.

CONCLUSION

This study demonstrates the acceptability, feasibility, and safety of an early mobilization protocol as a standard of care in the surgical intensive care unit of the University Hospital of Nantes. This protocol establishment, including mobilization instructions, sedation optimization and pain management, is associated with an improvement of mobilization compared to national recommendation alone.

Implementation of this protocol in the department helped by a continuous training was associated with a decrease of time before mobilization, of length of sedation and of length of stay in the intensive care unit for non-trauma patients. These results were not found in the trauma patient population. A propension analysis could be used to verify these results on the whole population. Efforts needs to be done to correct barriers in our department. Continuing education and formalize sedation gestion is needed to increase application of early mobilization during time.

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APPENDICES

I. Medical Research Council scale for muscle strength

Muscle (for each side)	MRC scale for muscle strength
Shoulder abductors	Grade 5: Normal
Elbow flexors	Grade 4: Movement against gravity and resistance
Wrist extensors	Grade 3: Movement against gravity over (almost) full range
Hip flexors	Grade 2: Movement of the limbs but not against gravity
Knee extensors	Grade 1: Visible contraction without movement of the limb (not existent for hip flexion)
Foot dorsiflexors	Grade 0: No visible contraction
Total (out of 60)	**MRC grade for each muscle given in full numbers**

II. Diagnostic criteria for ICUAW

1	Generalized weakness developing after onset of critical illness
2	Weakness is diffuse (involving both proximal and distal muscles) symmetric, flacid and generally spares cranial nerves
3	MRC sum score < 48 or mean MRC score < 4 in all testable muscle groups noted on ≥ 2 occasions separated by > 24 hours
4	Dependance on mechanical ventilation
5	Cause of weakness not related to the underlying critical illness have been excluded
Minimum criteria for diagnosing ICUAW: 1,2,3 or 4,5	

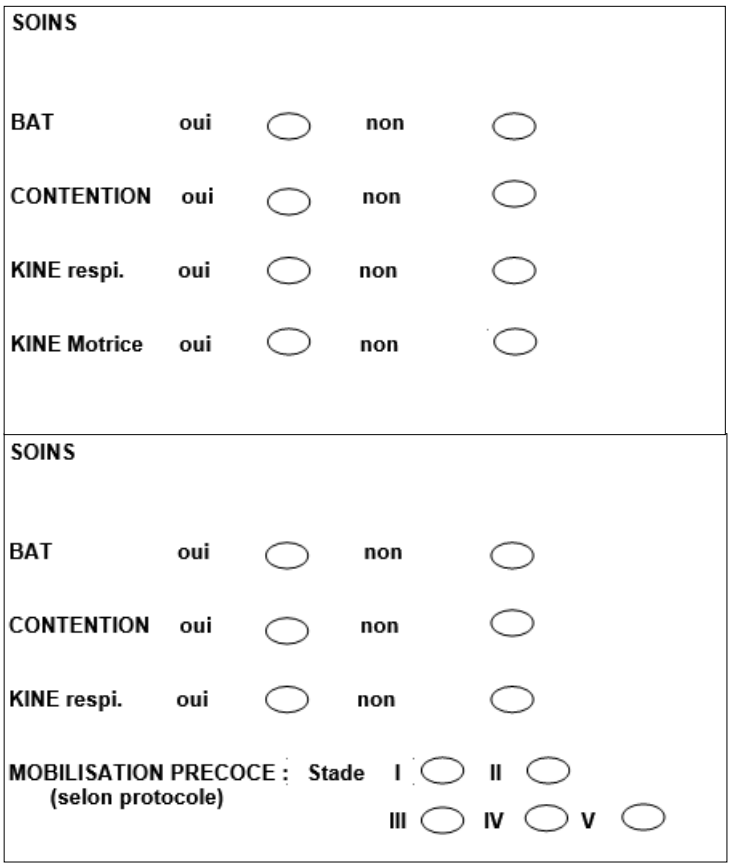
Stevens RD et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med. 2009.

III. Richmond Agitation and Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movement not aggressive vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to *voice* **(>10 seconds)**
-2	Light sedation	Briefly awakens with eye contact to *voice* **(<10 seconds)**
-3	Moderate sedation	Movement or eye opening to *voice* **(but no eye contact)**
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to *voice or physical* stimulation

Sessler CN, Gosnell M, Grap MJ, Brophy GT, O'Neal PV, Keane KA et al. The Richmond AgitationSedation Scale: validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 2002; 166:1338-1344.

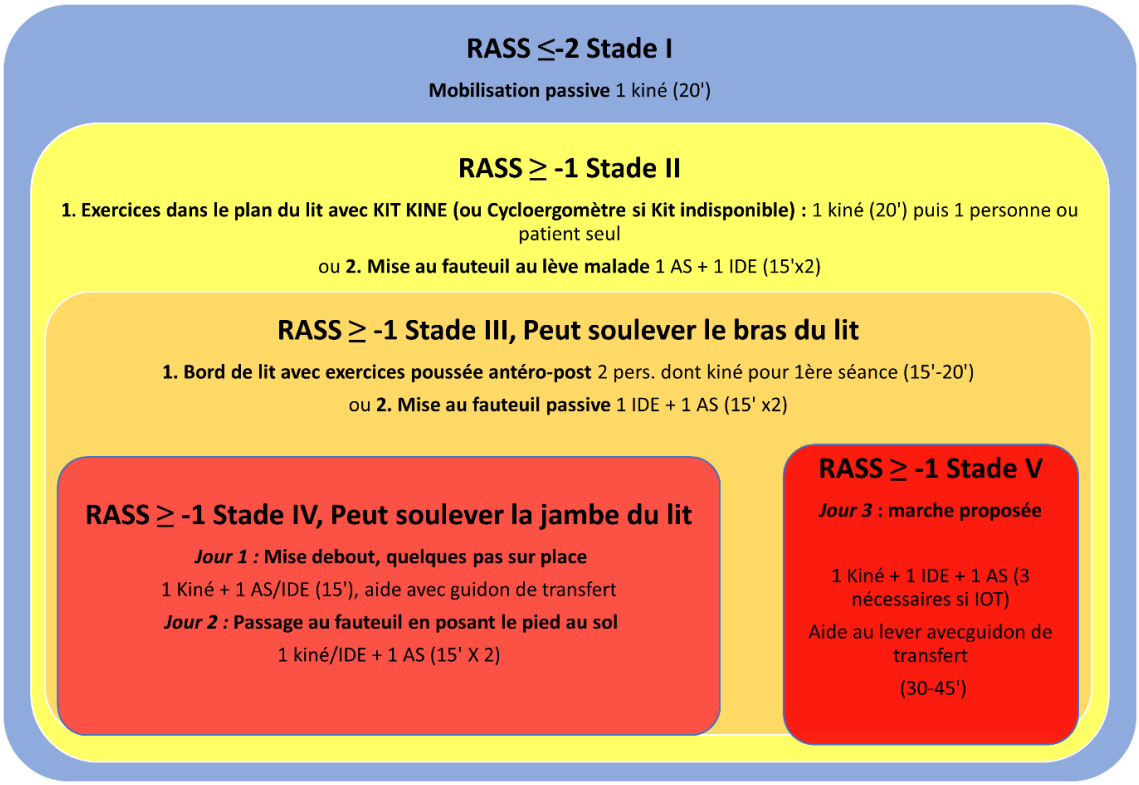
IV. Handwritten medical prescriptions for mobilization (before and after protocol)



V. Cards summarizing the protocol into care standardization booklet for caregivers

FICHE EXERCICE : Dépend du stade du patient, défini par l'équipe le matin

- Le passage à un stade supérieur n'exclue pas la poursuite des exercices précédents
- En cas d'échec de l'exercice, retenter à la séance suivante (noter les causes de l'échec sur la feuille de surveillance)

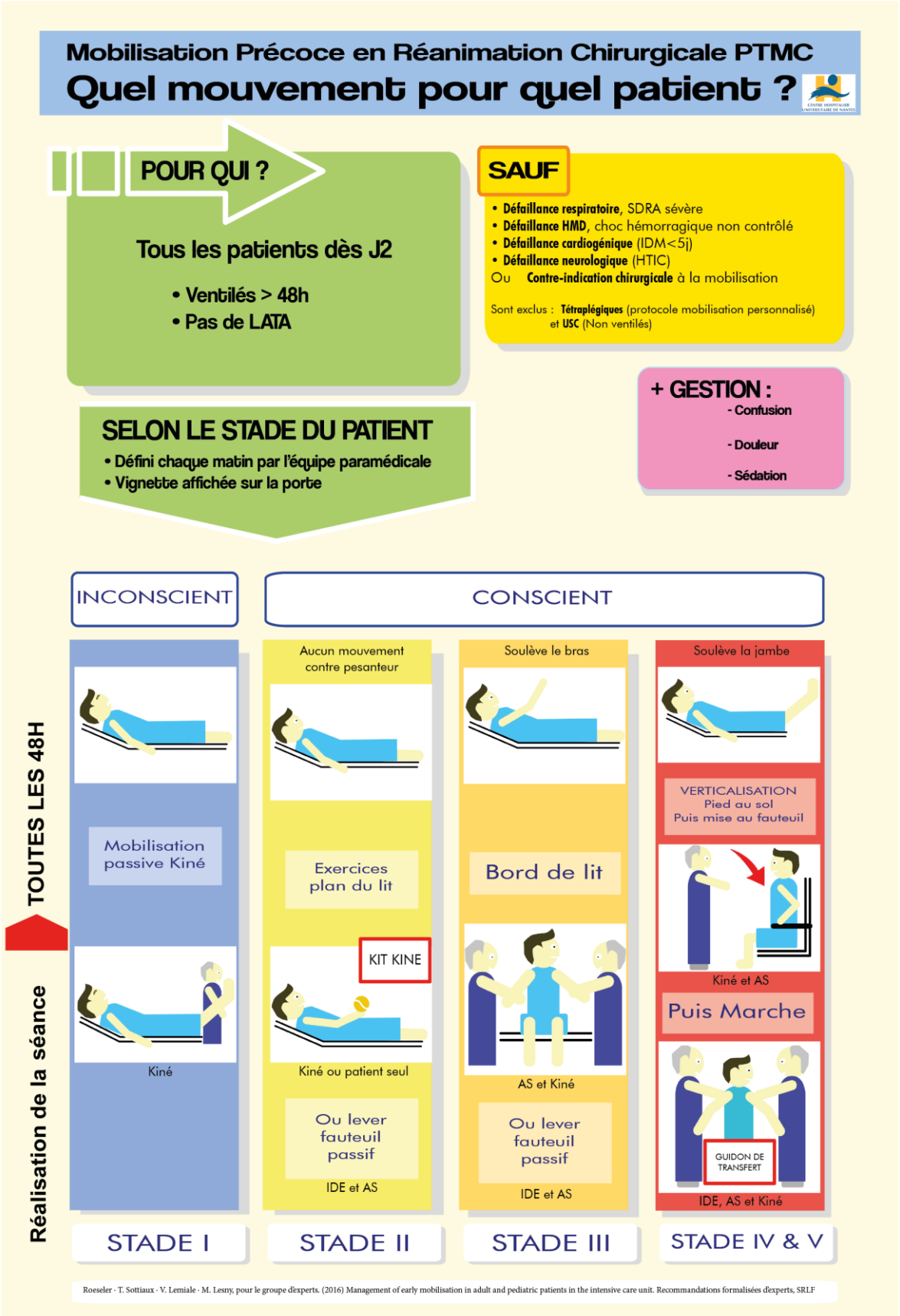


VI. Daily care planning sheets, extract

Date ……../……../……. SECTEUR

Chambre Noter le nom du patient	**Exercice prévu (A remplir ++ le matin pour coordination IDE/AS/Kiné)**	**Exercice réalisé** (à remplir par ceux qui ont effectué la séance)
7	Exercice prévu : …… Heure de réalisation prévue : …… Nécessité de la présence Kiné : □ Oui □ Non	□ Oui Durée : …… □ Non Raison : …… **Reprogrammé le :**……
8	Exercice prévu : …… Heure de réalisation prévue : …… Nécessité de la présence Kiné : □ Oui □ Non	□ Oui Durée : …… □ Non Raison : …… **Reprogrammé le :**……
9	Exercice prévu : …… Heure de réalisation prévue : …… Nécessité de la présence Kiné : □ Oui □ Non	□ Oui Durée : …… □ Non Raison : …… **Reprogrammé le :** ……

VII. Posters of the protocol placed in the department



VIII. List of figures and tables

IX. List of acronyms and abbreviations

ARDS	Acute Respiratory Distress Syndrome
CNI	Centre de recherche Non Interventionnelle
FiO^2	Fraction of inspired oxygen
IADL	Instrumental activities of daily living
ICP	Intracranial pressure
ICU	Intensive Care Unit
ICUAW	Intensive Care Unit Acquired weakness
SAPS II	Simplified Acute Physiology Score, second version
MRC	Medical Research Council
NA	Nursing assistant
PT	Physiotherapist
RASS	Richmond Agitation and Sedation Scale
Sd-HR	Sub distribution Hazard Ratio
SONAR	*Standardisation et Optimisation des SoiNs en Anesthésie Réanimation*
SRLF	*Société de Réanimation de langue française*
SF-36	Short Form Health Survey test

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NAME: FIEUZAL FIRST NAME: Laure

Title: Intensive Care Unit Acquired Weakness: Establishment of an early mobilization protocol and evaluation of its impact

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ABSTRACT

- **Introduction**: Intensive care unit Acquired weakness is frequent and has an immediate negative impact on the outcome of patients. Early mobilization is a recommended and safe method to prevent its occurrence.
- **Method:** An early mobilization protocol was implemented in 2019 in surgical intensive unit at the Nantes University Hospital, associated with a continuous training plan. The objective of this before-after study was to evaluate the application of this standard of care and its impact after implementation of this protocol.
- **Results:** 313 patients ventilated for more than 48 hours were compared between 2016-2017 (205 patients) and 2020-2021 (108 patients) stratified by admission type. Implementation of the early mobilization protocol was associated with a decrease in time before verticalization by 3 days, an increase in the proportion of mobilized patients and a decrease in sedation time in non-trauma population. No difference was found in the trauma population.
- **Conclusion**: Early mobilization had good acceptability and was applicable as a standard of care in the surgical intensive care unit of the Nantes University Hospital. The implementation of a protocol was associated with an improvement in the application of recommendations.

MESH terms

Intensive Care Unit Acquired weakness; Early mobilization; Early ambulation; Physical therapies modality; Rehabilitation; Patient care planning; Critical care standards.

NOM : FIEUZAL PRENOM : Laure

Titre de Thèse : Faiblesse acquise en réanimation : Etablissement d'un protocole de mobilisation précoce et évaluation de son impact

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RESUME

- **Introduction :** La faiblesse acquise en réanimation est fréquente et a un impact négatif immédiat et sur le devenir des patients. La mobilisation précoce est une méthode recommandée et sécurisée pour prévenir sa survenue.
- **Méthode :** Un protocole de mobilisation précoce a été mis en place en 2019 en réanimation chirurgicale au CHU de Nantes, associé à un plan de formation continue. L'objectif de cette étude avant après était d'évaluer l'application de ce standard de soin et de son impact après mise en place de ce protocole.
- **Résultats** : 313 patients ventilés plus de 48 heures ont été comparés entre 2016-2017 (205 patients) et 2020-2021 (108 patients) stratifiés par motif d'admission. L'application du protocole de mobilisation précoce était associée à une diminution du délai de verticalisation de 3 jours, une augmentation de la proportion de patients mobilisés ainsi qu'une diminution de la durée de sédation dans la population de patients non traumatisés. Il n'y a pas eu de différence observée dans la population des patients traumatisés.
- **Conclusion** : La mobilisation précoce est bien acceptée et applicable comme standard de soin dans le service de réanimation chirurgicale du CHU de Nantes. L'établissement d'un protocole est associé à une amélioration de l'application des recommandations.

MOTS-CLES

Faiblesse acquise en réanimation ; Mobilisation précoce ; Réhabilitation en réanimation ; Planification des soins ; Evaluation des pratiques professionnelles ; Standard de soin ;