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## Initial efficacy and tolerability of early enteral nutrition with immediate or gradual introduction in intubated patients

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**Abstract** *Objective:* To compare the initial (D7) calorie intake and

tolerability of two early enteral nutrition protocols in which the optimal flow rate was introduced either immediately or gradually. *Design:* Open, prospective, randomized study. *Setting:* Two medical-surgical intensive care units. *Patients:* One hundred consecutive intubated and mechanically ventilated patients. *Interventions:* Early enteral nutrition was started within 24 h following intubation, and the optimal flow rate (25 Kcal/kg day<sup>-1</sup>) was either introduced immediately or reached in increments. Flow rate of the nutritional solution was adapted to the residual gastric volume, measured every 8 h, and the use of prokinetic agents was encouraged. Vomiting, regurgitation, colectasia, and suspected aspiration were defined as serious adverse events requiring withdrawal of enteral nutrition. *Measurements and results:* When introduced immediately at optimal flow rate, early

enteral nutrition led to a significant improvement in actual calorie supply ( $p < 0.0001$ ). Although high residual gastric volume ( $> 300$  ml) was more frequent when optimal flow rate was introduced immediately ( $p = 0.04$ ), frequency of serious adverse events necessitating withdrawal of enteral nutrition was similar in the two groups ( $p = 0.64$ ). *Conclusions:* When residual gastric volume is measured regularly and prokinetic agents are used, enteral nutrition can be started early and be introduced at optimal dose regimen, thereby providing better calorie intake. Serious adverse events required early enteral nutrition withdrawal in only 15 patients, with no difference in frequency between the groups.

**Keywords** Early enteral nutrition · Calorie requirements · Residual gastric volume · Mechanical ventilation · Intensive care unit

### Introduction

Enteral route is preferred for critically ill patients requiring artificial nutrition [1–4], and especially those with respiratory failure. In this setting, enteral nutrition must be delivered with a strictly defined protocol, with regular monitoring of residual gastric volume (RGV) [1]. As far as possible, enteral nutrition should be started early, sometimes less than 24 h after admission [1–4]. Early enteral nutrition (EEN) can be poorly tolerated, however, with gastric repletion, regurgitation, vomiting, and a risk of aspiration pneumonia, especially during the first few days of treat-

ment [2, 5, 6]. Diarrhea is another potential complication of EEN [6]. To improve tolerability of EEN, the optimal flow rate is usually reached progressively, despite the lack of published data demonstrating the benefits of this approach [1, 6, 7]; however, gradual introduction of EEN can mean that patients do not receive their theoretical calorie requirements [2, 4, 8, 9].

The aims of this study were to compare, in intubated and mechanically ventilated patients, the initial (D7) efficacy in terms of calorie intake and tolerability of EEN with immediate vs. gradual introduction of optimal flow rate.

## Patients and methods

This prospective open randomized study was conducted in two medical-surgical intensive care units totaling 34 beds. It was approved by the ethics committee of Dupuytren University Hospital in Limoges, France, and written consent was provided by all patients or their families. All consecutive patients aged more than 18 years were eligible if they were intubated and ventilated for at least 72 h. Pregnant women, patients already included in the study, and (because of the risk of refeeding syndrome) malnourished patients (body mass index  $< 20 \text{ kg/m}^2$ ) were not eligible. Patients with the following contraindications to EEN were excluded: formally contraindicating enteral nutrition (e. g., occlusion, ileus, or gastrointestinal ischemia), contraindications to gastric probing (e. g., esophageal stenosis, surgery, or recent gastroesophageal trauma, hematemesis), and shock.

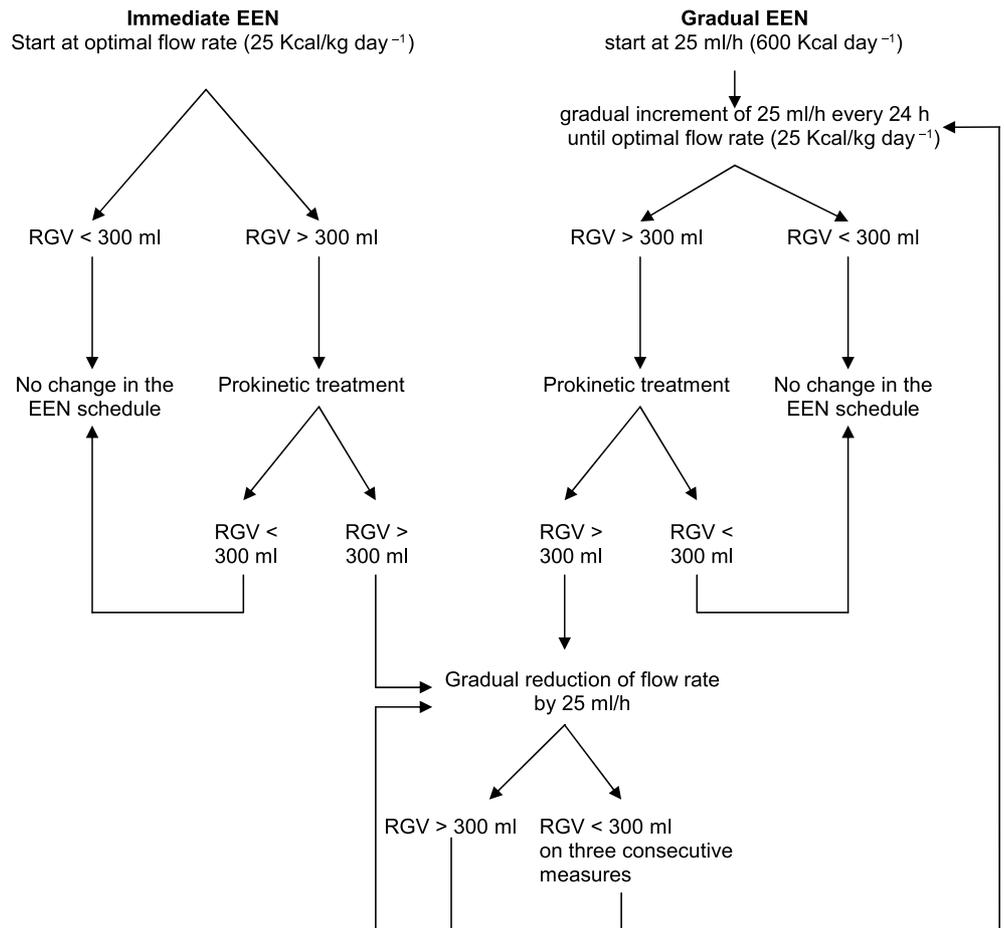
Age, gender, body mass index (BMI = weight/height in meters squared) and the reason for admission (medical, surgical, or traumatic) were recorded on admission. Severity at enrollment was assessed with the Simplified

Acute Physiology Score II (SAPS II) [10]. The in-ICU and in-hospital length of stay and mortality rate were also recorded.

### Early enteral nutrition protocol

Early enteral nutrition (EEN) was started within 24 h following intubation and was administered to all patients following the same protocol in the two centers. With the patient in semi-recumbent position (head of the bed elevated to  $30^\circ$ ), after aspiration of stomach contents, the nutritional solution containing 1 Kcal/ml (Nutrison Standard, Nutricia, Zoetermeer, The Netherlands) was administered via a multiperforated gastric tube equipped with an air intake (Salem probe CH 16 or 18, Vygon, Ecouen, France) at a constant flow rate, by a volumetric pump. The semi-recumbent position was maintained even in lateral decubitus. The patients were never placed in prone position. The optimal calorie supply was assumed to be  $25 \text{ Kcal/kg day}^{-1}$  [2, 6]. For obese patients (BMI  $> 30 \text{ kg/m}^2$ ), optimal calorie intake

**Fig. 1** Flow rate adjustment according to measurement of residual gastric volume (RGV) every 8 h; EEN, early enteral nutrition. Prokinetic treatment: erythromycin 200 mg bid or metoclopramide 10 mg tid



was calculated for a theoretical weight corresponding to a BMI of 30 kg/m<sup>2</sup>. Randomization to the two arms was stratified by center and balanced by using variable-sized blocks. In the immediate optimal flow group, solution was administered, from the outset, at the optimal flow rate of 25 Kcal/kg day<sup>-1</sup>. In the incremental group, the solution was initially delivered at a flow rate of 25 ml/h. The flow rate was then increased every 24 h by increments of 25 ml/h (600 Kcal on D1, 1200 Kcal on D2, etc.) until the optimal flow rate of 25 Kcal/kg day<sup>-1</sup> was reached. Residual gastric volume (RGV) was measured every 8 h by gentle aspiration of stomach contents with a 60-ml syringe, which were then reinstalled into the patient.

The EEN flow rate was adjusted to the RGV (Fig. 1). An RGV of < 300 ml required no change in the EEN schedule. In contrast, RGV > 300 ml indicated prokinetic treatment consisting of erythromycin 200 mg bid or metoclopramide 10 mg tid. If the RGV remained above 300 ml despite prokinetic treatment, the EEN flow rate was reduced gradually in steps of 25 ml/h every 8 h, and EEN could be interrupted if necessary. After EEN reduction or withdrawal, RGV values below 300 ml on three consecutive occasions 8 h apart warranted a gradual increase in the EEN flow rate in steps of 25 ml/h every 24 h (including in the immediate optimal flow rate group) until the optimal flow rate was reached.

The EEN could be discontinued for examinations (gastric endoscopy, transesophageal cardiac echography) or surgery. The length of interruption was recorded and EEN was resumed after the end of the intervention, at the same flow rate as when it was discontinued. Fentanyl was recommended for patients requiring opiate analgesia, and the total dose was recorded.

#### End points for EEN efficacy in terms of calorie intake

The calorie supply actually delivered to the patient was compared with the prescribed supply (which differed between the two arms) and with the theoretical optimal calorie intake (25 Kcal/kg day<sup>-1</sup> during the study period in the two groups).

#### Serious adverse events requiring EEN withdrawal

The EEN intolerance was defined as the onset of colectasia, suspected aspiration (tracheal aspirates looking digestive fluid), regurgitation (digestive fluid in the oropharynx), or vomiting. The EEN was stopped immediately in cases of colectasia or aspiration. Prokinetic treatment was prescribed in case of regurgitation or vomiting and EEN was stopped permanently in cases of relapse despite prokinetic treatment.

#### Tolerability of EEN

The number of patients who had at least one episode of RGV > 300 ml and the number of episodes of RGV above this value were compared between the groups. Diarrhea defined as an estimated > 300 ml of liquid stools a day and laxative agent (macrogol or lactulose) administration was also recorded.

#### Statistical analysis

The calorie intake and tolerability of EEN, including serious adverse events, were compared between the groups at the end of the study: D7 or on EEN withdrawal (in cases of serious adverse events, extubation, or death before D7).

In previous reports, actual calorie supply represents only about 75% of the prescribed dose [9]. With a target calorie supply corresponding to 95% of the optimal supply in the immediate optimal flow group, and with a first-order risk of 0.05 and a second-order risk of 0.80, 44 patients were required per group. We therefore decided to enroll 100 consecutive patients. Continuous variables are reported as the mean, standard deviation, and range, and categorical variables as the number of patients in each category and their relative frequencies. Mean values were compared between the groups by using Student's *t*-test. When values were not normally distributed around the mean, or when large numbers of patients had the same value, the Mann-Whitney *U*-test was used. Relative frequencies in the two groups were compared using the chi-square test, whereas Fisher's exact test was used for small groups. The *p*-values < 0.05 were considered to denote significant differences. Data management and calculations of indices and statistical tests used Statview version 5 and SAS version 6.12 (SAS Institute, Cary, NC, USA).

## Results

#### Characteristics of the population

Sixty-nine men and 31 women were enrolled in the study. There were 50 patients in each group. The mean age was 61 ± 16 years (range 18–90 years) and their mean BMI 26 ± 4 kg/m<sup>2</sup> (range 20–45 kg/m<sup>2</sup>). The reasons for ICU admission were medical in 68 cases, surgical in 11 cases, and trauma in 21 cases. The mean SAPS II score was 41 ± 14 (range 9–83). The mean ICU stay was 15 ± 11 days (range 2–65 days) and mean hospital stay 53 ± 68 days (range 4–405 days). Twenty-five patients died in the hospital, including 14 in the ICU. The mean duration of the study period was 119.8 ± 48.1 h (range 19–168 h) and mean duration of EEN was 117.7 ± 47.8 h

**Table 1** Characteristics and outcomes of patients in two groups of early enteral nutrition (EEN); SAPS II, Simplified Acute Physiology Score 2

	Gradual EEN (n = 50)	Immediate EEN (n = 50)	Significance (p)
Age (years)	64 ± 13	58 ± 19	0.07
Gender (M/F)	31/62	38/76	0.13
Body mass index (kg/m <sup>2</sup> )	27 ± 5	25 ± 3	0.12
SAPS II (points)	40 ± 11	42 ± 17	0.58
Reasons for admission (n)			
Medical	35 (70)	33 (66)	
Surgical	9 (18)	2 (4)	0.01
Traumatic	6 (12)	15 (30)	
Length of ICU stay (days)	15 ± 11	15 ± 11	0.95
Length of hospital stay (days)	51 ± 75	56 ± 59	0.72
ICU mortality (n)	8 (16)	6 (12)	0.56
In-hospital mortality (n)	11 (22)	14 (28)	0.49

Continuous variables are reported as the mean ± SD and categorical variables as the number of patients and relative frequencies in parentheses

(range 18–168 h). Forty-five patients were studied for a maximum of 7 days (168 h).

Age, gender, BMI, SAPS II, lengths of ICU and hospital stay, and mortality rates were similar in the two groups (Table 1). A randomization bias led to significantly more patients being admitted after surgery in the gradual group and more patients being admitted for trauma in the immediate optimal flow group. The EEN had to be discontinued for examinations or surgery in 22 patients, 12 (24%) in the immediate optimal flow group, and 10 (20%) in the gradual group ( $p = 0.63$ ). The mean duration of the interruptions was similar in the two groups ( $2.5 \pm 9$  h in the gradual group and  $0.8 \pm 2$  h in the immediate optimal flow group;  $p = 0.19$ ).

#### Calorie intake during the initial phase of EEN

The duration of the study and duration of EEN were similar in the two groups (Table 2). During the study period, calorie delivery corresponded on average to 76% of optimal calorie intake in the gradual group and 95% in the immediate optimal flow group ( $p < 0.0001$ ). Although optimal calorie requirements per day of the study ( $25 \text{ Kcal/kg day}^{-1}$ ) were identical in the two groups, the planned and actual calorie supplies were significantly

higher in the immediate optimal flow group than in the gradual group (Table 2). Similarly, daily calorie deficiency, defined as the difference between optimal calorie intake and actual calorie supply, was significantly lower in the immediate optimal flow group than in the gradual group, as was the cumulative calorie deficiency at the end of the study (Table 2).

#### EEN withdrawal and serious adverse events

The study was stopped before day 7 in 55 patients because of extubation ( $n = 32$ ), serious adverse events ( $n = 15$ ), or death ( $n = 8$ ), with no significant difference between the groups (Table 3). During study period, serious adverse events necessitating permanent EEN withdrawal were similarly frequent in the two groups (8 patients (16%) in the gradual group and 7 patients (14%) in the immediate optimal flow group;  $p = 0.65$ ). There were no episodes of clinical suspected aspiration pneumonia.

#### Tolerability

At least one episode of  $\text{RGV} > 300 \text{ ml}$  was observed in 18 patients and the number of patients was significantly

**Table 2** Calorie supply in the two groups during the study period; EEN, early enteral nutrition

	Gradual EEN (n = 50)	Immediate EEN (n = 50)	Significance (p)
Length of the study (h)	127 ± 46	113 ± 50	0.14
Length of EEN (h)	125 ± 45	112 ± 50	0.18
Optimal calorie supply (Kcal/day)	1800 ± 314	1836 ± 340	0.58
Expected calorie supply (Kcal/day)	1376 ± 282	1821 ± 353	<0.0001
Calories delivered (Kcal/day)	1297 ± 331	1715 ± 331	<0.0001
Calorie deficiency per day of study (Kcal/day)	503 ± 311	122 ± 283	<0.0001
Cumulative calorie deficiency at study end (Kcal)	2310 ± 1340	406 ± 729	<0.0001

Values are expressed as mean ± SD

**Table 3** Tolerability of early enteral nutrition (EEN) according to the protocol

	Gradual EEN (n = 50)	Immediate EEN (n = 50)	Significance (p)
Reasons for stopping EEN (n)			
End of the study	25 (50)	20 (40)	
Extubation	14 (28)	18 (36)	0.64
Death	3 (6)	5 (10)	
Serious adverse event	8 (15)	7 (14)	
Serious adverse events (n)			
Regurgitation	2 (4)	6 (12)	0.14
Vomiting	6 (12)	6 (12)	–
Colectasia	5 (10)	2 (4)	0.24
Residual gastric volume > 300 ml (n)	5 (10)	13 (26)	0.04
Prokinetic treatment (n)	9 (18)	12 (24)	0.46

Values in parentheses are relative frequencies

higher in the immediate optimal flow group (Table 3). Forty episodes of RGV > 300 ml were observed, 11 in the gradual group and 29 in the immediate optimal flow group ( $p = 0.037$ ). Two or more episodes of RGV > 300 ml requiring gradual reduction of flow rate were observed in 9 patients, two in the gradual group and seven in the immediate optimal flow group ( $p = 0.16$ ). Prokinetics tended to be administered more frequently to patients in the immediate optimal flow group (Table 3). The total fentanyl dose administered during the study period was similar in the two groups ( $3606 \pm 4830$  and  $4544 \pm 5118$   $\mu\text{g}$ ,  $p = 0.35$ ).

The number of patients who had at least one episode of diarrhea and the number of episodes of diarrhea were similar in the two groups. Thirty-five patients had at least one episode of diarrhea, of whom 28 (80%) had received a laxative agent. Sixty-five patients did not have diarrhea, of whom only 24 (37%) received a laxative agent ( $p < 0.0001$ ). Likewise, among the 48 patients who did not receive a laxative agent, only 7 (15%) had an episode of diarrhea. The number of episodes of diarrhea was strongly associated with prior use of laxative agent.

## Discussion

In this population of shock-free intubated patients receiving mechanical ventilation, early enteral nutrition administered with a strictly defined protocol (patient in semi-recumbent position with the head of the bed elevated to 30°, volumetric pump, reinstallation of the RGV sample, use of prokinetic agents) and started at the optimal dose regimen delivered 95% of theoretical calorie requirements during the initial phase of treatment (first 7 days). In contrast, incremental introduction of the optimal dose supplied only 75% of theoretical calorie requirements.

In previous reports, the calorie supply prescribed and actually delivered is often below patients' theoretical needs, because of late initiation, unjustified or excessively long interruptions, and failure to reinsert RGV samples [4, 5, 9].

A recent meta-analysis confirmed the value of EEN in critical-care patients, with fewer infectious complications and a shorter hospital stay [3]; however, tolerability of EEN is sometimes poor [2], especially in case of treatment with catecholamines, shock, or sedation [5], with vomiting in up to 26% of patients and upper digestive intolerance in 46%, as reflected by a high RGV [5]. Tolerability can be improved by using prokinetic agents [11] and a strictly defined EEN protocol [12]. The EEN is often introduced gradually, although there is no formal proof that this practice is beneficial [1, 7]. In our study, immediate introduction of the optimal dose of EEN was associated with significantly more episodes of RGV > 300 ml and with a trend towards more frequent use of prokinetic agents. Episodes of gastric repletion did not appear to precipitate serious adverse events requiring EEN withdrawal. Impact of RGV on the risk of serious adverse events is controversial [5, 13] and, although RGV monitoring is recommended, the optimal residual volume is also controversial (about 250 ml) [13]. Adjusting the flow rate of enteral nutrition to obtain a small RGV limits the risk of intolerance but can lead to unnecessary discontinuations and therefore to calorie deficiency. In contrast, too high an RGV target carries a higher risk of serious complications.

Finally, as reported elsewhere [14], diarrhea was associated with the prescription of laxative agents and was similarly frequent in the groups with immediate and gradual introduction of the optimal flow rate.

Our study had some limitations. Particularly, EEN was stopped in case of relapse vomiting or regurgitation similarly in the two groups (8 in the gradual group and 12 in the immediate group), but the volume of vomiting or regurgitation cannot be measured and can lead to misevaluation of calorie intake during the study. The goal of 25 Kcal/kg day<sup>-1</sup> could be discussed as another target could lead to other results. Aspiration was only clinically suspected and occurrence of aspiration pneumonia was not studied. Finally, this preliminary, small study (100 patients) needs to be confirmed by a larger trial.

## Conclusion

Enteral nutrition can be started early in shock-free patients intubated for mechanical ventilation. Provided that residual gastric volume is regularly measured and prokinetic agents are used, EEN can be introduced at the optimal dose regimen, thereby improving the calorie supply. Serious adverse events requiring EEN withdrawal (repeated

vomiting, regurgitation, and colectasia) were similarly frequent in the two groups. No cases of aspiration were clinically suspected, possibly because the patients were always placed in semi-recumbent position.

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