ORIGINAL ARTICLE

The prevalence and possible causes of enteral tube feeding intolerance in critically ill patients: A cross-sectional study

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Background: Enteral tube feeding intolerance (ETFI) is one of the most common complications of enteral nutrition (EN), which may lead to increased mortality and length of intensive care unit (ICU) stay. This study aimed to determine the prevalence of ETFI and effects on feeding intolerance on nutrition and clinical outcomes in Iran. **Materials and Methods:** This cross-sectional study was conducted in 2019 at the three general ICUs of Imam Reza Hospital in Mashhad, Iran, during 7 days on 245 patients. The collected data included demographic characteristics, primary diagnosis, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, duration of mechanical ventilation, and length of ICU stay. Feeding intolerance was assessed using daily questionnaires for 7 days. ETFI was determined as the interruption of EN based on gastrointestinal causes, including large gastric residuals, abdominal distension, vomiting, diarrhea, and subjective discomfort. **Results:** Overall, 245 critically ill patients (122 males and 123 females) were included in this study, with a mean age of 58.43 ± 19.2 years in three general ICUs. The highest prevalence rate of ETFI was 91.8%, which occurred on the 2nd day although the rate decreased in the following days. The minimum ETFI was observed on the last day (38.8%). Feeding intolerance was associated with the increased APACHE II scores ($P = 0.04$), SOFA scores ($P < 0.001$), and duration of mechanical ventilation ($P < 0.001$) compared with the tolerant patients. The most common causes of ETFI in the patients admitted to the ICU were gastric residual volume (GRV), large GRV, vomiting, and distension. **Conclusion:** ETFI was prevalent in almost two-third (66%) of the critically ill patients receiving EN based on the GRV. ETFI was associated with deteriorated nutritional status and clinical outcomes.

Key words: Critical care, enteral nutrition, intensive care unit, mortality

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INTRODUCTION

Enteral nutrition (EN) has numerous physiological advantages, including positive effects on gut integrity through the preservation of motility and the immune function by GALT, intestinal mucosal atrophy, prevention of bacterial translocation,[1] reduction of hyperglycemia,[2] and reduction of the length of hospital stay.[3] The complications associated with EN may be gastrointestinal (GI) or tube related, while the metabolic interruption of EN is frequently associated with GI complications.[4-8]

The most common complication of EN is enteral tube feeding intolerance (ETFI), which can diminish the enteral nutrient being delivered.[4-6] In a systematic review conducted in 2014, the prevalence of ETFI in intensive care units (ICUs) was reported to be 2%–75%, with the pooled estimate of 38%.[9]

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Some diagnostic criteria are generally recognized for ETFI. In gastric residual volume (GRV) assessment, the volume of <500 ml/12 h should not result in an effect on the delivery route of EN. In the presence of other clinical changes (e.g., abdominal pain, distension, nausea/vomiting), the measurement of GRV is recommended.[10,11] However, there is a lack of consensus regarding the definition of feed intolerance in terms of GRVs.[12] Accordingly, ETFI is an important obstacle against achieving adequate nutrition in ICU patents, resulting in increasing mortality and morbidity and length of ICU stay.[9] Furthermore, to the best of the authors' knowledge, the exact etiology of ETFI has not been adequately investigated and no study until now has yet examined the prevalence of ETFI and related factors. Thus, the aim of the present study was to determine the prevalence and probable causes of feeding intolerance in critically ill patients in Iran.

MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted at the ICUs. Data collection was performed during March 2018–September 2019. All the adult patients who were admitted to the three general ICUs of Imam Reza Hospital in Mashhad, Iran, using simple sampling from available ICU patients according to our inclusion criteria were enrolled. Included patients (n = 245) received enteral tube feeding (ETF) and were admitted for at least 72 h in the ICU. Adult patients with the age between 18 and 65 years and patients who had hemodynamic resuscitation and stabilization within the first 24–48 h were included in the study. All patients with absolute and relative contraindications to receive EN including the following criteria were excluded: all diseases that will be associated with ileus, including peritonitis and multiple trauma, result in retroperitoneal hematoma and peritonitis. Patients with intestinal obstruction, active GI bleeding, abdominal abscesses, severe malnutrition, intestinal fistula, and patients with disturbed hemodynamic condition needed to receive a vasopressor and inotropes. Patients who were in ICU for <7 days were also excluded. Intestinal nutritional support with energy ranging from 80% to 100% begins with the actual estimate of the patient's energy consumption, which is equivalent to 25 kcal of energy per kilogram of patient weight. The amount of formula required for each patient is determined individually by a nutrition expert and is initiated within the first 24–48 h of admission and administered in a bolus form at 3-h intervals (7 times in 24 h). Patients will be checked daily for GI dysfunction by their physician, and they will receive all of their usual drugs and therapy.

The study protocol was approved by the Ethics Committee of Iran-Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1398.057), and written informed consent was obtained from all patient companions prior to participation.

Data collection

General data were collected regarding the demographic characteristics, primary diagnosis, length of hospital and ICU stay, and duration of mechanical ventilation. The scores of the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) were also calculated. In each patient, the daily assessment of feeding intolerance was performed for 7 days, focusing on the method of ETF delivery, amount of provided enteral formula, achieved nutritional goals, time needed to reach the nutrition goals, ETF complications, occurrence of feeding intolerance, and probable causes of feeding intolerance. Some of the possible causes in this regard were postoperative ileus, acute mesenteric ischemia, bowel obstruction, hypokalemia, and GI bleeding.

The investigated strategies for the management of ETFI included the prescription of prokinetic drugs to enhance motility, decrease the rate of ETFI, terminate and restart ETF within 1 day, terminate ETF without restarting, and change the delivery route of feeding (nasogastric to nasojejunal).

Definition of enteral tube feeding intolerance

The diagnostic criteria for ETFI were defined as the presence of two or more combinations of symptoms such as GRV with abdominal distension and pain, nausea and vomiting, diarrhea, and subjective discomfort.[10,11]

The incidence of nausea, vomiting, and abdominal pain was also investigated, and diarrhea was defined as passing three or more liquid stools per day. In addition, abdominal distension was suspected clinically or radiologically by a clinician. GRV was examined every 6 h, and in case of being higher than 250 ml, feeding intolerance was confirmed. The mentioned definitions were based on the study by Blaser *et al.*, who investigated various definitions of ETFI based on the ESPEN guideline.[13]

Statistical analysis

Data analysis was performed in Statistical Package for the Social Sciences (SPSS) (Chicago, USA) (version 16) using descriptive statistics to define the baseline characteristics. The obtained results were expressed as mean and standard deviations in the case of quantitative data, and the qualitative data were expressed as frequency and percentage. Independent-samples t-test and Mann–Whitney U-test were used to compare the quantitative variables between two groups. Chi-square was applied to compare the qualitative variables between the study groups. In all the

statistical analyses, $P < 0.05$ was considered as statistically significant.

RESULTS

Overall, 245 critically ill patients (122 males and 123 females) were included in this study, with a mean age of 58.43±19.2 years. The baseline characteristics of the patients are presented in Table 1. The patients who developed ETFI were similar to those who were tolerant of enteral feeding during ICU admission in terms of age ($P = 0.09$), gender ($P = 0.34$), length of hospital stay ($P = 0.57$), and length of ICU stay ($P = 0.48$) [Table 1].

Totally, the most frequent diagnosis was poisoning, which was observed in 26.5% in all of the patients. In the patients with ETFI, the most common diagnosis was sepsis (27.8%), followed by poisoning (24.7%), respiratory disorders (16.7%), and GI disorders (13%) [Table 1].

Figure 1 depicts the prevalence of ETFI during 7 days of investigation. On the 1st day, 162 cases (66.1%) developed feeding intolerance. The highest prevalence of ETFI was observed on the 2nd day (91.8%), which decreased in the following days, and the lowest prevalence of ETFI was observed on day 7 (38.8%) [Figure 1]. Only 25 patients (10.2%) did not present with ETFI during the whole study period.

The mean scores of APACHE II ($P=0.042$) and SOFA ($P<0.001$) and duration of mechanical ventilation ($P < 0.001$) were significantly higher in the patients with ETFI compared to those who were tolerant of enteral feeding [Table 1].

Table 2 shows the frequency of the signs and symptoms of ETFI and their combination based on the determined diagnostic criteria. Accordingly, the majority of the patients who were feeding intolerant presented with GRV (250–500), large GRV (>500), nausea/vomiting, abdominal distension/pain, and severe diarrhea during the study period [Table 2]. According to signs and symptoms, large GRV plus GRV (100–500) had the highest frequency, followed by large GRV plus vomiting. However, the prevalence of large GRV plus distension and vomiting plus distension was variable on different days [Figure 2].

Among various causes of feeding intolerance that were investigated in the study, GI bleeding (51.4%) was considered to be the most frequent cause of ETFI, followed by hypokalemia (24.3%), postoperative ileus (8.1%), bowel obstruction (8.1%), major surgeries (5.4%), and acute mesenteric ischemia (2.7%).

Almost 61.7% of the patients with ETFI use prescribed medications in the current research. Among these cases, 49% received antiemetic or prokinetic drugs, while laxatives were rarely prescribed (15.4%) [Table 3]. Furthermore, the use of nonpharmacological strategies reduced the rate of ETF in 67 patients (41.4%).

In 59 patients (36.4%), ETF was resolved within a few hours and restarted within 1 day, while ETF resolved without restarting in 26 patients (16%) [Table 3]. Among these approaches, the frequency of receiving antiemetic or prokinetic drugs and changing ETF was more significant

Table 1: Baseline characteristics of the study populations between enteral tolerant and intolerant feeding groups

Characteristics	Total (*n*=245), *n* (%)	Intolerant group (*n*=162), *n* (%)	Tolerant group (*n*=83), *n* (%)	*P**
Age (years), mean±SD	58.43±19.2	56.9±18.41	61.3±20.49	0.090
Gender				
Male	122 (49.8)	77 (47.5)	45 (54.2)	0.34
Female	123 (50.2)	85 (52.5)	38 (45.8)	
Admission diagnosis				
Cardiovascular disease	10 (4)	4 (2.9)	6 (7.2)	NA
Respiratory disease	41 (16.7)	27 (16.7)	14 (16.9)	
Gastrointestinal disease	24 (9.8)	21 (13)	3 (3.6)	
Neurologic disease	3 (1.2)	1 (0.6)	2 (2.4)	
poisoning	65 (26.5)	40 (24.7)	25 (30.1)	
Sepsis disease	55 (22.4)	45 (27.8)	10 (12)	
Metabolic disease	3 (1.2)	3 (1.9)	0	
Hematologic disease	5 (2)	5 (3.1)	0	
Other diseases	39 (15.9)	16 (9.9)	23 (27.7)	
APACHE II, mean±SD	15.76±4.58	16.19±4.56	14.93±4.51	**0.042**
SOFA score, mean±SD	8.12±3.0	8.73±2.76	6.93±3.11	**<0.001**
Hospital stay (days), mean±SD	19.67±22.6	20.2±21.7	18.53±24.2	0.578
ICU stay (day duration of), mean±SD	16.77±18.78	17.38±17.5	15.57±21.1	0.48
Mechanical ventilation (days), mean±SD	10.50±14.73	13.48±16.9	4.58±5.16	**<0.001**

*Comparisons made between the tolerant and intolerant populations, Bolding used when $P<0.05$. APACHE II=Acute Physiology and Chronic Health Evaluation II; SOFA=Sequential Organ Failure Assessment; SD=Standard deviation; NA=Not applicable; ICU=Intensive care unit

Table 2: Basis for diagnosis of enteral tube feeding intolerance

GI symptoms and/or sign with ETFI	Day 1, *n* (%)	Day 2, *n* (%)	Day 3, *n* (%)	Day 4, *n* (%)	Day 5, *n* (%)	Day 6, *n* (%)	Day 7, *n* (%)
GRV (250-500)	88 (65.7)	133 (68.6)	92 (54.8)	89 (56)	60 (53.1)	57 (55.9)	45 (58.4)
Large GRV (>500)	20 (14.9)	28 (14.4)	30 (17.9)	21 (13.2)	18 (15.9)	17 (16.7)	15 (19.5)
Nausea/vomiting	17 (12.7)	22 (11.3)	36 (21.4)	31 (19.5)	24 (21.2)	23 (22.5)	11 (14.3)
Severe diarrhea	5 (3.7)	1 (5)	4 (2.4)	4 (2.5)	1 (9)	2 (2)	2 (2.6)
Abdominal distension/pain	4 (3)	10 (9.6)	6 (3.6)	14 (8.8)	10 (17)	3 (2.9)	4 (5.2)
Combination of symptoms and/or signs							
Large GRV and GRV (250-500)	108 (80.6)	161 (83)	122 (72.7)	110 (69.2)	78 (69)	74 (72)	60 (77.9)
Large GRV and nausea/vomiting	37 (27.6)	50 (25.7)	66 (39.3)	52 (32.7)	42 (37.1)	40 (39.2)	26 (33.8)
Large GRV and abdominal pain/distension	24 (17.9)	38 (24)	36 (21.5)	35 (22)	28 (32.9)	20 (19.6)	19 (24.7)
Nausea/vomiting and abdominal distension	21 (15.7)	32 (20.9)	42 (25)	45 (28.3)	34 (38.2)	26 (25.4)	15 (19.5)

ETFI=Enteral tube feeding intolerance; GI=Gastrointestinal; GRV=Gastric residual volume

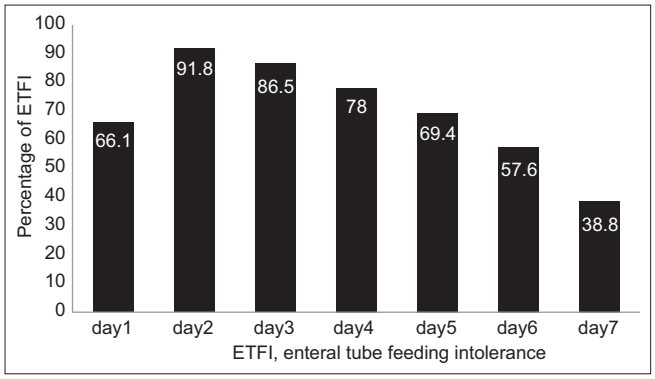

Figure 1: Prevalence of enteral tube feeding intolerance during 7 days

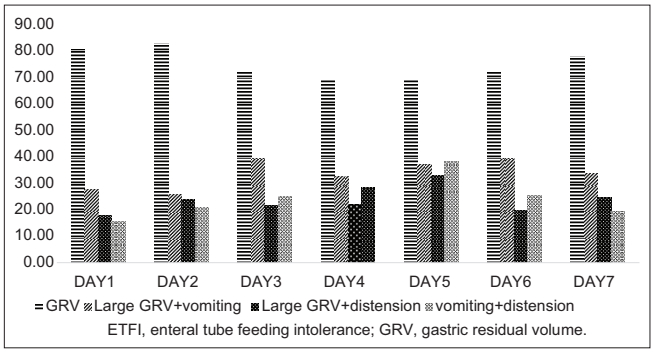

Figure 2: Combination of symptoms and/or signs of enteral tube feeding intolerance. GRV = Gastric residual volume

in the patients with feeding intolerance compared to those who were tolerant of enteral feeding ($P < 0.001$).

DISCUSSION

This was the first study to investigate and compare the prevalence of ETFI in critically ill patients since the admission of the patients to the ICU within a 7-day period. According to the findings, ETFI occurred in approximately two-thirds (66%) of the critically ill patients receiving ETF on the 1st day of ICU admission. In addition, the present study indicated that the prevalence of ETFI varied on different days, with an increase observed on the 2nd day, followed by a reduction in the following days. Therefore, it could be inferred that feeding intolerance convalesces during ICU admission, and the remission may be due to the medical and pharmacological strategies that are implemented for ETFI management in the ICU.[14]

In a study conducted in New Zealand on 754 patients receiving EN at the ICU and those with no ICU admission, Wang *et al*. (2014) reported that the incidence rate of feeding intolerance was 32% in all the hospitalized patients. Moreover, the prevalence of feeding intolerance was significantly higher in the patients admitted to the ICU (35.6%) compared to the other subjects (27.4%).[4]

Consistent with the current research, a retrospective analysis of the 2009 International Nutrition Survey (INS; an international observational period prevalence survey of nutritional practices and outcomes of 167 ICUs in 21 countries), the prevalence of feeding intolerance in the patients admitted to ICU was estimated at 30.5%.[15] The high incidence of feeding intolerance in our study could be attributed to several factors, such as the poor monitoring of EN, bolus/intermittent EN infusion with higher feeding speed, administration of nasogastric EN, starting the EN with a large volume, and the use of medications causing feeding intolerance. Furthermore, several studies have denoted considerable variation in the prevalence of ETFI, which is quite expected, as there are various FI definitions. This could also be attributed to heterogeneous patient populations in different studies.[4,13]

ETFI has several risk factors, while the main etiologies remain unclear. In the present study, the possible risk factors/causes of feeding intolerance were investigated. On the same note, MacIntosh *et al*. reported that old age may contribute to delayed gastric emptying in healthy participants and is considered to be a risk factor for feeding intolerance in critically ill patients.[16] However, the results of various studies are controversial regarding the effect of age on ETFI,[4,15] and our findings did not indicate increased age to be a risk factor for ETFI.

Table 3: Approaches for management of enteral tube feeding intolerance

Method of managing ETFI	ETFI, *n* (%)	NO ETFI, *n* (%)	*P*
Medication	100 (61.7)		
Antiemetic or prokinetic	79 (48.8)	12 (14.5)	**<0.001**
Laxative	25 (15.4)	3 (3.6)	0.05
Decrease rate of ETF	67 (41.4)	4 (4.8)	**<0.001**
Stop and restart ETF within day	59 (36.4)	8 (9.6)	**<0.001**
Stop ETF without restart	26 (16)	2 (2.4)	**<0.001**

Bold characters indicate when *P*<0.05. ETFI=Enteral tube feeding intolerance

Based on the data regarding gastric emptying, several high-risk populations could be identified for the diagnosis for ETFI, including patients with burn injuries,[17,18] head trauma,[19] sepsis, and multiple trauma.[20] In the current research, the most frequent diagnostic group among the patients with ETFI had sepsis (27.8%) and poisoning (24.7%). However, cardiovascular, metabolic, and neurological disorders were not prevalent in these patients. Similarly, Nguyen *et al*. reported that less than one-third of the patients with coronary artery injuries had delayed gastric emptying, as well as feeding intolerance.[20]

In the present study, the APACHE II and SOFA scores were significantly higher in the patients with feeding intolerance. Therefore, it could be inferred that ETFI may be a marker of disease severity rather than mortality rate.[11] Similarly, the findings of Nguyen *et al*. demonstrated that higher APACHE II scores during admission are associated with delayed gastric emptying, followed by ETFI.[20]

Among the probable causes of ETFI investigated in our study, GI bleeding was observed to be most frequent. In another study, Lee *et al*. assessed the probable causes of feeding intolerance, reporting that respiratory procedures accounted for the most frequent episodes and longer duration of feeding intolerance.[21]

Using various definitions of feeding intolerance leads to the inaccurate diagnosis of ETFI, thereby disrupting the management and treatment of ETFI and leading to negative clinical outcomes.[13] In a study performed by Reignier *et al*., two definitions of ETFI were used, and the prevalence of feeding intolerance was reported to be higher when defined as large GRV and/or vomiting/regurgitation as opposed to vomiting/regurgitation.[22]

Our findings can help researchers and clinicians to decrease the complication of EN during the 1st day of hospitalization in the ICU. The volume of gavage which received by patients, identification of the cause of enteral feeding intolerance and gavage residual volume should be carefully and accurately evaluated in ICU patients. Furthermore, adequate EN and appropriate pharmacotherapy during the 1st day to reduce the prevalence of intolerance and mortality in critically ill patients are necessary. Some limitations should be addressed. The most important limitation was the varied criteria used for the diagnosis of feeding intolerance. In addition, the patients had multiple signs simultaneously, which made it difficult to determine the actual GRV values. Finally, due to our sampling, selection bias should be considered which can affect the results of this study.

CONCLUSION

According to the results, ETFI was prevalent during enteral feeding and occurred in almost two-third (66%) of the critically ill patients receiving EN. ETFI was commonly defined based on the GRV. In addition, several risk factors were identified for ETFI, including cardiovascular and neurological disorders, GI bleeding, mechanical ventilation, and high APACHE II and SOFA scores. In conclusion, feeding intolerance convalesces during ICU admission and the remission may be due to the medical and pharmacological strategies that were adopted for ETFI management.

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Conflicts of interest
There are no conflicts of interest.

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