Chapter 15
Enteral Nutrition and Bowel Management

Irene Comisso and Stefano Bambi

15.1 Introduction

Artificial nutrition is commonly used in ICU patients, since several factors, such as altered state of consciousness or inability to self/nourishment, impede normal nutrients assumption. In ICU patients, nutritional support can help keep the immunitary system more efficient and balance anabolism and catabolism [1]. Although the association between malnutrition and ICU mortality is not clearly demonstrated, a recently published systematic review [2] confirmed the association between malnutrition (diagnosed through validated tools) and ICU-LOS.

Artificial nutrition can be administered both parenterally and enterally. The first requires adequate venous accesses (particularly, total parenteral nutrition can only be administered via a CVC), while enteral nutrition is administered using a feeding (gastric or intestinal) tube.

Enteral nutrition (EN) is normally preferred, since it is more physiological and apparently less prone to infectious complications [3] and protective toward liver and gut function, even in patients treated with vasopressor medications [1]. Despite these

I. Comisso et al., *Nursing in Critical Care Setting*,
https://doi.org/10.1007/978-3-319-50559-6_15

considerations, it is important to underline that EN is associated to complications in 80% of patients receiving it.

15.2 Nutritional Assessment

Several observations have been traditionally used to determine nutritional status. Patient's assessment includes recording of daily nutrient intake, actual weight, recent weight changes, and body measurements. These include body mass index (BMI), triceps skin fold (TSF) thickness, mid-upper arm circumference (MUAC), and mid-arm muscle circumference (MAMC). Table 15.1 summarizes parameters' characteristics.

A retrospective study involving 1373 patients found a significant correlation between MUAC and BMI (Pearson correlation coefficient 0.78; 95% CI: 0.76–0.80), stating that MUAC can be easily used as a surrogate indicator for malnutrition (cutoff value ≤22.5 cm) and as a predictor of BMI [7]. In another prospective study [10] on 1363 ICU patients' BMI used as continuous variable, MUAC, MAMC, and the SGA "muscle wasting" and "subcutaneous fat loss" categories showed predictive ability and clinical utility toward hospital mortality. Conversely, BMI and TSF did not perform adequately [10], thus suggesting that their absolute value might not always indicate a malnutrition condition, often depending on individual's physical constitution.

Recently published guidelines [11] suggest to perform nutritional assessment in ICU patients whose voluntary intake might be insufficient. In these guidelines, proposed nutrition assessment tools include the Nutritional Risk Screening (NRS) 2002 or the *Nut*rition *Ri*sk in *C*ritically Ill (NUTRIC) score.

NRS 2002 [12] score was created analyzing retrospectively the indications used for nutritional support and related outcomes in 128 studies. The score grades two variables (severe undernutrition and severe disease) from 0 to 3 points, with a correction factor

Table 15.1 Main body measurement characteristics

	BMI [4]	TSF thickness [5]	MUAC	MAMC
Formula/ measurement	Weight (kg)/height $(m)^2$	Measurement (using a caliper) of a skin fold at the midpoint between olecranon process of the ulna and acromion process of the scapula	Measurement (using a nonelastic tape) of nondominant arm, at midpoint between acromion and olecranon, in sitting or standing position [7]	MAMC = MUAC-(π*TSF) [8]
Normal values	18.5–24.99 kg/m^2; values lower than 16 kg/m^2 describe a severe anorexia condition; values higher than 30 kg/m^2 describe obese conditions	Male: 11–12.5 mm Female: 15–16.5 mm [5]	Male: 26–29 cm Female: 26–28.5 cm [5]	Male: 23–25 cm Female: 20–23 cm [5]
Limitations for use	Does not consider differences related to sex, age, and body proportions	Considerably influenced by vertical or horizontal displacement of the site of measurement and from the limb position (medial or lateral) chosen for the measurement [6]	Cutoff used for malnutrition may significantly vary between adult and elder patients No definitive consensus exists about the cutoff value for malnutrition [7]	No international values are available [9]

(1 point) for patients aged ≥70. A total score ≥3 suggests to begin nutritional support. It is important to underline that some information used to determine patient's actual nutritional status (such as recent weight loss or habitual food intake) might be difficult to obtain in ICU patients. Moreover, BMI calculation could be imprecise when real weight and height are not available.

NUTRIC score was firstly validated in 2011 [13] on 597 ICU patients. The score aims to define patients that might benefit from nutrition therapy. NUTRIC score considers six variables: age, baseline APACHE II score, baseline SOFA score, number of comorbidities, days from hospital to ICU admission, and interleukin 6 (IL-6). Other variables (procalcitonin, C-reactive protein, % of oral intake in the previous week, weight loss, and BMI) were studied but not included in the final model because they do not significantly increase the discriminative ability of the score. Mortality and days on mechanical ventilation were significantly associated with increased NUTRIC score. A further modified score, omitting IL-6, was validated [14], confirming score's attitude in identifying ICU patients that might benefit from nutritional support optimization.

NUTRIC score has been used within a quality improvement project [15], together with the institution routine screening method and the subjective global assessment (SGA) to determine nutrition risk in ICU patients. Findings from this study confirm that patients with highest NUTRIC scores had the longest hospital and ICU-LOS, probably related to a more severe clinical condition.

A comprehensive nutritional assessment should also include patient's energy requirement. Indirect calorimetry (IC) is considered the gold standard for energy requirements measurement. Nonetheless, IC equipment is costly and not available in all hospitals. IC measures the respiratory quotient (i.e., the ratio between carbon dioxide excretion and oxygen consumption, both in mL/min). Normally, the respiratory quotient ranges between 0.7 and 1.

Oxygen consumption and carbon dioxide excretion are also used to determine the [16],

$$\text{Resting energy expenditure}\left(\text{REE}\right)\left(\text{kcal}/\text{d}\right) = 1.44\left(3.9\text{VO}_2 + 1.1\text{VCO}_2\right)$$

Several equations have been used to predict energy requirements in hospitalized patients [17], with different, but not adequate, accuracy levels. Current guidelines [11] suggest to target energy requirements on 25–30 kcal/kg/d.

Bowel sounds are daily assessed to determine GI dysfunction. Nonetheless, bowel sounds accuracy might significantly differ between doctors and nurses and mislead the correct interpretation of GI function [18]. A recent observational study found low accuracy for bowel sounds assessment in patients with bowel obstruction. Also, judgment's agreement between involved doctors was found to be low [19]. Absent or reduced bowel sounds alone should not impede EN start. Nonetheless, absent or reduced bowel sounds might indicate an underlying dysfunction, and therefore a more complex GI evaluation (including abdominal distention, vomiting, pain) should be performed.

15.3 EN Administration

Recently released guidelines recommend EN initiation within 24–48 h from ICU admission [11]. ICU patients usually receive continuous EN at slow rates during the 24 h, and flows are gradually increased during the days after EN starts until the desired hourly volume is reached. This approach is susceptible for many interruptions, related, for example, to medical or nursing procedures or drug administration through the feeding tube. Recent approaches [20] suggest to target EN delivery on desired daily

volume, with hourly rates managed by nurses according to duration of planned and unplanned interruptions. Furthermore, literature findings show that EN can be started at target rates without complications. When high gastric volumes are not tolerated, a trophic feed, aiming to keep the GI tract functioning, can be adopted. In a recent meta-analysis, initial enteral full feeding compared to initial enteral intentional underfeeding does not seem to improve major outcomes such as mortality, hospital LOS and ICU-LOS, duration of mechanical ventilation, and incidence of infectious complications [21].

EN formulas contain both macro- (carbohydrates, proteins, lipids) and micronutrients and have different compositions according to calories, proteins, and micronutrients provided [22].

Main feeding tube characteristics refer to diameter, insertion site, and tip position and are listed in Table 15.2 [23–25].

Choice of feeding tubes should be oriented on patient's conditions and device's tolerance. Currently, no clear benefit can be addressed to post-pyloric feeding tubes. A recent systematic review and meta-analysis revealed lower incidence of pneumonia (moderate quality of evidence) and higher percentage of administered nutrients (low quality of evidence) when post-pyloric feeding was compared to gastric one; nevertheless, major outcomes such as ICU mortality or LOS do not seem to be affected by feeding site, so as complications affecting the GI tract and those related to tube insertion and management [26]. Confirmation of tube's position is a crucial point. Currently, chest radiograph is considered the gold standard to determine tip-tube position, especially in patients with altered consciousness and impaired reflexes [27]. Incorrect insertion of a NG feeding tube through the airways can lead to severe complications such as pneumothorax [28]. Other methods are suitable for this purpose, with stomach auscultation and determination of aspirated pH being most widely used [29]. Also, patient observation during and after

Table 15.2 Characteristics of feeding tubes

Bore	Insertion	Tip position
Large (≥14 Fr): preferred when gastric emptying is required; esophageal ulceration may occur Small (5–12 Fr): more comfortable for the patient; more at risk for incrustation and obstruction; preferred in patients ad greater risk for aspiration	Nasal: common route for insertion; allows better oral care (intubated) and patient's conversation (non-intubated) Saliva reduction, mouth dryness, and thirst may occur Oral: commonly used in premature neonates or small infants Transcutaneous: preferred when long-term artificial feeding is required	Stomach: common route for feeding in ICU; allows administration of hypertonic solutions Jejunal/duodenal: preferred when higher risk for aspiration is present

tube's positioning may provide information about incorrect positioning in the airways.

A cross-sectional study revealed poor correlation between chest radiograph NG tip-tube position confirmation and auscultatory method performed by a nurse (Prevalence and Bias Adjusted Kappa (PABAK) 0.188, $p = 0.111$) [30]. In this study, duodenal positioning was frequent (27.4%), and potentially harmful positioning (distal esophageal portion and lung) was not entirely negligible (1.3 and 1.3%, respectively). Furthermore, a low agreement between position assessment performed by doctors and nurses (Kappa = 0.215; $p = 0.118$), doctor and nursing researcher (Kappa = 0.142; $p = 0.114$), and nurses and nursing researcher (Kappa = 0.052; $p = 0.107$) confirmed poor interrater reliability of this method [30].

Measurement of gastric pH in 44 ICU patients revealed a mean value (± SD) of 4.2, with 59.1% of patients with values between 0 and 4 [31], although a statistically significant difference ($p < 0.05$) in gastric pH was observed whether patients were treated with antacid drugs (4.6 ± 1.7) or not (3.5 ± 1.8) [32]; pH ≤5.5 had a positive predictive value for correct gastric positioning of 98.9%, although two false-positive tests with esophageal positioning were identified. Although helpful, gastric pH measurement has limitations related to inability to obtain gastric aspirate, influence of feeding, drugs, and small bowel or esophageal positioning that may require chest radiograph confirmation [32, 33].

15.3.1 Prevention of Feeds Contamination

Incorrect feeds management can result in potentially harmful contamination. Currently, contamination from enteral formulas can be considered rare, since industrial preparations are usually administered. External sources of contamination can come from professionals' hands or water. The importance of correct handwashing and gloves utilization has been explored in Chap. 9. Water administration in enterally fed patients is common, both for dilution of formulas in order to reduce nutrients' concentration and therefore minimize the intolerance risk (diarrhea), administer drugs, and flush NG tube when nutrition is interrupted. For all of these purposes, bottled water should be preferred, and sterile water should be used with immunocompromised patients. Several studies documented infections from *Legionella pneumophila* and *Pseudomonas aeruginosa* from tap water. For this reason, reusable devices (such as tablet crushers) should be accurately dried after rinsing. When administering EN, feeding bags or bottles are connected to feeding sets. A recent retrospective observational study found a statistically significant reduction in diarrhea occurrence risk (HR = 0.27, 95% CI: 0.12–0.61, $p = 0.002$) when the

set hang time was reduced from 72–96 h to 24 h [34]. Feeds contamination might also occur due to retrograde microorganism migration from patient's GI tract toward NG tubes.

15.4 EN Complications

Up to 80% of patients receiving EN develop complications [35]. The term nutritional intolerance describes situations in which an increased gastric residual volume (GRV), together with vomiting, is detected, thus reducing the total nutrients amount administered [36]. To date, a definitive nutritional intolerance definition is not available, as underlined in a recent systematic review [37] reporting 43 different definitions of nutritional intolerance. The authors classified nutritional intolerance in three different categories, i.e., high gastric residual volume, presence of gastrointestinal (GI) symptoms, and inadequate enteral nutrition administration.

In a retrospective analysis [38], 30.5% of patients developed feeding intolerance, with a median occurring time of 3 days (range 1–12) from EN start. Feeding intolerance was associated with lower caloric and protein intake and significantly related with decreased median ventilator-free days (11.2 vs. 2.5; $p < 0.0001$), ICU-LOS (11.3 vs. 14.4; $p < 0.0001$), and days to discharge alive from hospital (20.3 vs. 23.8; $p = 0.0002$). Although nonstatistically significant, 60-day mortality was higher in patients with feeding intolerance.

15.4.1 High Gastric Residual Volume

Gastric residual volume (GRV) measurements are recommended to determine EN tolerance [39, 40], predict inhalation risk [41], and monitor the functional status of digestive tract. Delayed gastric emptying is common in enterally fed patients, involving up to

50% of MV patients, and comes from altered GI motility, drugs, surgery [42], altered state of consciousness, reduced coughing reflex, and indwelling ETT [43].

Ninety-seven percent of nurses measure GRV [35], to quantify and qualify [44] gastric content and identify intolerance to EN [45].

GRV measurement is normally performed by aspirating the stomach with a 50 mL syringe or connecting a collection bag to NG tube for at least 10 min [35]. Several factors, including tube diameter [46] and position [47] and fluid viscosity [45], influence the amount of detected GRV. High GRV (defined as gastric aspirates ≥200 mL) does not seem to be affected by continuous or bolus EN administration (13.3 vs. 20%, respectively, $p = 1$) [48].

Normally, GRV is classified as mild (<150 mL/6 h), moderate (251/350 mL/6 h), and severe (>350 mL/6 h). To date, the maximum tolerable GRV amount has still not been defined, so as the usefulness of this measurement. In fact, no statistically significant association was found between different GRV amounts and number of episodes of inhalation or regurgitation [41], and an increased GRV tolerance up to 500 mL did not influence diarrhea, abdominal distention, regurgitation, nor pneumonia [49].

Optimal timing to check GRV has also not been identified [50]. In many ICUs, GRV measurements are performed three times a day, after interrupting EN for 1 h [51]. Also, more frequent (every 6 h) GRV assessment is suggested during the first EN day, while a daily measurement can be adopted from the third, when no complications are detected [49]. Since higher GRVs are detected during the first EN hours [52], a more strict control is suggested within this period [29].

GRV < 250 mL should not be discarded but reintroduced. In fact, discarding gastric content seems to be associated to a higher delayed gastric emptying and hypokalemia incidence. When GRV is higher than 250 mL, the exceeding volume is discarded.

As high GRV is the main EN intolerance feature (61.6%) of observed patients, treatment with prokinetic agents can be adopted to facilitate nutrition admixtures proceeding through the GI tract [38].

15.4.2 Gastrointestinal Symptoms

Vomiting is defined as "an objective event that results in the forceful evacuation of gastric contents from the stomach, up and out of the mouth" [53]. In ICU patients, vomiting has been described as "any regurgitation," irrespective of the amount [54]. Several factors, including surgery, medications, CNS, and gut disorders, have been addressed as possible causes for vomiting. In ICU patients, vomiting and regurgitation represent, respectively, 12.2% and 5.5% of EN-associated complications [40]. Higher prevalence (38.2%) has been observed in a more recent observational study [54], without statistically significant difference in vomiting occurrence between survivors and non-survivors (37.3% and 40.9%, respectively; $p = 0.13$). In this study, vomiting was found to significantly reduce the mortality risk (OR 0.44, 95% CI: 0.29–0.68; $p < 0.001$). Vomiting rates do not relate with EN type of administration (continuous vs. bolus, 6.7% vs. 6.7%, $p = 1$) [48].

Vomiting is addressed as causing 6.8% of EN interruptions [52].

Abdominal distention is not clearly defined among studies exploring GI complications. It is generally assumed that abdominal distention can be diagnosed radiologically or clinically, and although less frequent when compared to vomiting (10.6%), it has been associated with a significantly higher risk of death (OR 1.64, 95% CI: 1.07–2.53; $p = 0.025$) [54].

Although not widely reported from the literature, vomiting and abdominal distention can lead to increased patient discomfort. Thus, proper assessment and treatment of these symptoms are required.

15.4.3 Inadequate EN Administration

Inadequate EN delivery is frequent in ICU patients. Currently, a homogeneous definition for inadequate EN administration does not exist, and findings from a literature review underlined how prescription goals for enterally fed patients vary from 70 to 110% [55].

According to a literature review, inadequate EN administration refers to:

- Patient's factors: age, sex, nutritional status, disease severity, and mechanical ventilation
- Feeding methods: feeding formula and tube location
- Feeding process: time to initiation, feeding underprescription, and EN interruption [55]

Patient-related factors do not seem to significantly affect EN delivery. Particularly, disease severity nor nutritional status influences the achievement of optimal caloric intake [56].

No clear benefit has been evidenced by nutrient-dense formulas administration. Particularly, a prospective study revealed a highest caloric intake with hypertonic formulas, but not adequate protein provision [57]. Use of hypertonic formulas should therefore balance potential risks (diarrhea) and benefits (administration of smaller volumes). Similarly, post-pyloric tubes did not demonstrate significant improvements in caloric and protein goals achievements [58].

A recent retrospective observational trial [59] examined process-related barriers to optimal EN volume administration. In this study, a high number of interruptions (49% of observed days, 198 total interruptions) were intercepted. Interruptions are also related to accidental device removal (ETT or enteral access) [59, 60] or need for device positioning [60], bedside or radiology procedures [59, 60], problems with small-bore feeding tubes [61], weaning [61], or presence of GRV [59, 61]. GRV ≥500 mL was related to

the largest EN loss (77%) and the longest interruption (18.5 h) [59]. EN interruptions seem to be a predisposing factor for underfeeding (OR, 2.89; 95% CI: 1.03–8.11) and prolonged ICU-LOS (IRR, 1.53; 95% CI: 1.41–1.67) [60]. Underfeeding is significantly predicted by delays in EN start after ICU admission, total amount of prescribed calories, and total interruption time [62]. Duration of interruptions varies between 1 and –24 h [63], thus compromising the final amount of calories and proteins received by the patient. In a prospective observational study, 62% of patients received lower caloric intake than required (according to Harris-Benedict equation requirement) [62].

When EN management is supported by a shared protocol, goals achievement in terms of use of more EN alone [20], earlier initiation [20, 64], and amount of prescribed and delivered EN [20, 65] significantly increases. Despite these considerations, a recent systematic review highlighted the need for more well-designed randomized studies, in order to ascertain the effects of protocol-driven EN on major outcomes (mortality, ICU-LOS, and hospital LOS) [66].

15.5 Drug Administration via Feeding Tubes

Oral and feeding tubes administration are often not interchangeable, and specific considerations concerning drug crushing and mixing, proper water-volume dilution, NG tube flushing, and compatibility with EN formulas should be highlighted.

15.5.1 Drug Crushing and Mixing

Oral medications can be available as solid or liquid form [33]. Solid forms include both products with immediate release (few minutes after reaching the stomach) both those with modified

release (extended or delayed) [33]. Oral medications form may impact on the possibility to crush them. Tablets can be provided with an enteric-resistant coat or be designed to slowly release the active medication or allow resistance to gastric pH. Crushing such medications may lead to altered drug effect, in terms of bioavailability, therapeutic effect, and toxicity, and should therefore be avoided. Moreover, coat chipping can be difficult and provoke aggregation between small particles, thus increasing the NG tube obstruction risk [33].

A recent randomized crossover study on 36 healthy volunteers demonstrated higher ticagrelor (and its metabolite) plasma concentrations when the crushed drug was administered orally or via NG tubes compared to whole tablet administration [67]. Although no relevant AEs were observed, caution should be used when transferring these results to the critically ill population.

Oral medications are crushed using dedicated crushers. Oral medication mixing occurs because of simultaneous prescription. Crushing together two or more medications might generate chemical reaction, with subsequent changes in drugs' properties, and similar considerations can be applied for liquid forms [33].

15.5.2 Proper Water-Volume Dilution

Oral suspensions and solutions osmolality can be up to 25-fold greater than the one in the GI tract [68]. When administering such drugs using a transpyloric tube, it is important to adopt adequate drug's dilution's volume to avoid intolerance [68], meaning that 150–250 mL of water could be required to achieve adequate osmolality [69]. Suspensions dilution might also be necessary to reduce their viscosity and facilitate proceeding through NG tubes [69], although adequate dilution volume can be difficult to establish. Immediate-release tablets, so as the content of immediate-release gelatine capsule, should be fine-crushed and then diluted in sterile water [69].

15.5.3 Compatibility with EN Formulas and Feeding-Tube Flushing

Limited informations about compatibility and stability of oral medications and EN formulas admixtures are available. Both drug's and EN formulas' characteristics may interfere with medication's stability. For this reason, admixture of oral medications and EN formulas is discouraged [70], and administration of EN formulas should be temporarily withheld when giving oral medications through NG tube [33, 70].

In a recent in vitro study, the compatibility between an EN formula and 62 suspensions and solutions has been tested [68]. Drugs with pH <4 can interact with diet proteins, leading to precipitate formation in NG tubes [70]. Acid pH is typical for oral liquid drugs (excluding antacid ones and potassium iodide), thus suggesting adequate NG tube flushing after medication's administration in order to avoid tube's occlusions [68]. Appropriate feeding tube flushing (before and after drug's administration) with at least 15 mL of sterile water is recommended to avoid interactions between drugs, drugs and EN, and drugs and feeding tubes (as for diazepam) [70]. Feeding tube's flushing may also prevent drug clotting (clonazepam, carbamazepine, phenytoin) within the tube [70]. Also, when administering drugs through a feeding tube, evaluation of tube diameter and tip positioning should be considered. Small-bore tubes are more likely to clog, although more comfortable for the patients [25]. Tip position (gastric, duodenal, or jejunal) could interfere with drug absorption, especially for those with gastric effect or absorption (lowered effect and absorption) or those with extended hepatic first-pass effect (increased absorption and effect) [25].

EN administration should be restarted not earlier than 30 minutes after drug's administration [33], but in case of drugs with well-established EN interaction (fluoroquinolones, hydralazine,

warfarin, carbamazepine, hydrochlorotiazide, theophylline, gabapentin), feeds should be withheld 1 and 2 h after administration (2 h for phenytoin) [25, 70].

15.5.4 Considerations About Nursing Practices

Noncompliant practices in oral medications administration through feeding tubes have been highlighted. Particularly, verification of tube position prior drug administration, proper medication preparation (including crushing only when appropriate and appropriate dilution), and tube's flushing were identified as susceptible for improvement, since nurses did not perform consistently with available evidences [71]. Moreover, lack of knowledge concerning pharmaceutical form and the importance of tip-tube position has been shown [72]. Nurses often refer to their experience (80%), while hospital policy, pharmacists, or more experienced nurses consult lightly influenced (40.9, 37.6, and 33.7, respectively) nursing practices [71]. Multidisciplinary interventions including pharmacy support and provision of detailed instructions for administration proved to be effective in reducing (although not statistically significant) the incidence of tube obstructions (HR 0.22, 95% CI: 0.047–1.05) and administration errors (23% before intervention; 82% after intervention) [73].

15.6 Bowel Management

Bowel care is no longer perceived as priority in ICU staff, and lack of knowledge has been highlighted during focus groups oriented to examine in depth staff's attitudes toward bowel care [74]. Implementation of a bowel management protocol in three Australian ICUs led to significant increase in knowledge concerning bowel

management, frequency of bowel function assessment, and proper decision (suppository or enema administration) to take following a *per rectum* exam [75]. Conversely, effects on patients in terms of duration and episodes of constipation and episodes of diarrhea did not change significantly after a bowel management protocol [76].

15.6.1 Diarrhea

Diarrhea has been defined as three or more loose bowel motions, or four or more bowel motions of any consistency, or more than 300 mL of stool on at least two consecutive days [77]; recently, the ESICM group on abdominal problems referred to diarrhea as three or more loose or liquid stools with a stool weight greater than 200–250 g/day (or 250 mL/day) [78]. A recently proposed definition [79] adds consideration of feces based on the Bristol Stool Chart (categories 5–7). The Bristol Stool Chart was originally developed to categorize stool according to consistency and form in seven different items [80] and later validated on a general population [81]. To our knowledge, no validation on the critically ill population has been conducted, and proper assessment of stool amount and characteristics in bedridden patients could be affected by loss or absorption of feces from bed linen. Similarly, estimation of stool volume/weight could represent a limit in the application of these definitions.

An observational study on MV patients documented loose stool (Bristol types 5–7) in 36.9% of study days, with diarrhea occurrence of 12% [82]. Nonetheless, the authors conclude that liquid stools are a common finding within critically ill patients due to common administration of EN and laxatives and should therefore not be considered a feature of diarrheic condition [82]. More recent observational studies reported a 12.9–14% prevalence of diarrhea on admitted patients [83, 84] or a 5.2% per 100 patient-days incidence [84].

Pathogenesis of diarrhea can be osmotic, motoric, secretory/inflammatory, or from altered absorption [22] (also deriving from reduction of intestinal surface). Two main underlying mechanisms can explain the pathogenesis of diarrhea, the action of osmotically active substances and the electrolyte imbalance, resulting in a larger amount of water in the intestinal lumen [85].

Previously described causes for diarrhea [77] have been revisited during the last 10 years. Well-recognized causes can nowadays be referred to:

- **Medications**: 20.0% of patients with diarrhea received laxatives prior to its occurrence, and 11.4% had enemas administered [83]. Diarrhea could also be referred to administration of liquid drugs containing sorbitol, saccharose, mannitol, lactose, and magnesium through a NG tube [70].
- **Enteral nutrition**: the role of EN in diarrhea onset is nowadays unclear; on one side, EN seems to have a protective effect on intestinal mucosa, but, on the other side, EN may have an osmotic effect; nonetheless, research findings suggest that EN per se does not increases the risk of diarrhea (RR 0.87%, 95% CI: 0.46–1.66), but EN delivery >60% of energy target does (RR 1.75, 95% CI: 1.02–3.01; $p = 0.042$). Administering continuous or bolus EN does not affect the incidence of diarrhea (13.3% vs. 33.3%, $p = 0.39$) [48].
- **Antibiotic and antifungal therapy** is associated with an incidence rate of 8.94/100 patient-days and 25.35/100 patient-days, respectively. Estimated RR for diarrhea significantly increases when antibiotics (RR 3.64, 95% CI: 1.26–10.51, $p = 0.017$) and antifungal drugs (RR 2.79, 95% CI: 1.16–6.70; $p = 0.022$) are administered [84]. Authors also reported that the administration of EN >60% of energy target together with antibiotics or antifungal drugs increases the incidence risk ratio for diarrhea by 4.8 or 5.0 times, respectively [84].

- **Intestinal infections**: the most commonly reported infectious agent for ICU is *C. difficile* (0.7 [84]–1% [83] of the ICU population); other agents can be intestinal viruses, *Salmonella* and *Campylobacter* [83].

Patients with diarrhea have longer ICU-LOS (9.5 vs. 1.7 days, $p < 0.001$) and higher mortality (22.5 vs. 8.7%, $p < 0.001$) [83].

The role of fiber administration to reduce diarrhea is still controversial. Fibers act both as bulking agents (insoluble fiber) and by increasing water absorption (soluble fiber) [22].

Recently published guidelines do not suggest routine use of fiber formulas, since no consistent evidence concerning diarrhea reduction with fiber use is currently available [11]. Hemodynamically stable patients might benefit from a 10–20 g/ fiber addition, as it helps maintain the intestinal flora [11]. Caution should be kept toward hemodynamically unstable patients, since increasing intestinal mass could impair bowel perfusion [22].

According to the findings of a recent systematic review and meta-analysis, administration of probiotics has no effect on diarrhea reduction (RR 0.97, 95% CI 0.82–1.15, $P = 0.74$) [86].

15.6.2 Bowel Constipation

Although frequent in ICU patients, bowel constipation (BC) is often ignored. Nonhomogeneous definition of BC is still available, and previously reported definitions refer both to need for laxatives or enemas and days between stool passage (3, 6, or 9 days, according to studies). Recently the Working Group on Abdominal Problems from the European Society of Intensive Care Medicine (ESICM) refers to the term "paralysis of the lower GI tract," meaning the absence of stool passage for three or more consecutive days without mechanical obstruction, regardless of bowel sounds [78]. Further observational studies

distinguished between early (3–5 days) and late (≥6 days) onset for constipation [87].

Recently, the concept of impaired gastrointestinal transit (IGT) has been introduced in enterally fed (for at least 3 days) and mechanically ventilated (for at least 2 days) patients; IGT bounds the absence of bowel movements for ≥days and BC treatment, together with at least other clinical criteria (radiological confirmation, feeding intolerance, abdominal distention, or need for gastric decompression) [88].

Prevalence of constipation in ICU population varies widely according to the setting and the definition used, thus leading to a difficult measurement of real impact of this problem. Nonetheless, constipation affects a significant proportion of ICU patients. Two observational studies revealed a constipation incidence (defined as "failure of bowel to function for 3 or more days") of 69.9% in surgical ICU patients [89] and of 83% in medical-surgical ICU patients. A more recent observational study investigating constipation in ICU patients found a global 51.9% incidence [87]. The abovementioned studies do not refer to patient's previous bowel habits.

Individual factors such as age and sex are not considered as predisposing factors for late defecation [90]. Table 15.3 summarizes predisposing factors for bowel constipation.

Constipation incidence is significantly reduced by early EN [89] and spontaneous breathing [87]. Therefore, attention to feeding and weaning from MV could also result in better GI outcomes. Interestingly, in a pseudo-randomized controlled trial [48], the incidence of constipation was significantly higher when EN was administered continuously compared to bolus (66.7% vs. 20%, $p = 0.025$).

Disease severity (measured by SOFA or APACHE II scores) has been addressed as responsible for delayed defecation [93]. Irrespective of stool-passage intervals considered (3–5 days or ≥6 days), constipation is significantly associated with invasive MV, use of vasopressors, continuous sedation, neuromuscular

Table 15.3 Predisposing factors for bowel constipation

Drugs	Exogenous opioids adhere to enteric opioid receptors, leading to altered motility and bowel dysfunction [91] and increasing water absorption from the GI tract, with consequent harder and drier feces [92]; moreover, opiates strongly impact on patient's LOC, leading to a reduced sensation of need for defecation
	Dopamine and norepinephrine can lead to reduced intestinal motility [93]
	Dehydration associated with diuretics can result in harder feces [94]
Environment	ICU environment often does not provide adequate privacy, leading to patient's embarrassment
	Reduced motility is common in ICU patients
Perfusion and oxygenation	Hypotension (SBP < 90 mmHg) and hypoxemia (PaO_2/FiO_2 ratio < 150 mmHg) impact on intestinal perfusion and oxygenation and are independently associated with late (≥ 6 days) passage of stool [95]
Surgery	Abdominal surgery per se [94, 96] and other site surgeries [90] can alter the brain-gut-microbiota axis
Late enteral nutrition	Delay in EN start could alter intestinal peristalsis [90]

blocking agents, enteral feeding, ICU-LOS, and mortality [87]. Although nonstatistically significant, MV duration increases in constipated patients [87]. Prolonged constipation (≥6 days) is significantly associated with increased MV duration, ICU-LOS [87, 93, 97], risk of VAP [87], and bacterial infections at any site [95]. Feces passing through the gut allow intestinal "cleaning" [98], thus contributing to reduced bacterial overgrowth and increased bacterial translocation.

The association between late constipation and mortality is controversial [87, 90, 97]. When considering severity of disease,

no clear assumption can be considered about which one is the causative agent and which one is the consequence [98].

Delay in stool passage has also been independently associated (adjusted HR 1.14, 95% CI 1.06–1.12; $p < 0.01$) with the onset of delirium [99].

Since bowel constipation is potentially life-threatening and causes discomfort to patients, maintenance of a regular intestinal function is essential to prevent potential complications. Correction of causative agents is the first step to manage the problem. Awareness of the problem so as proper consideration of risk factors (including daily review for opiates need) is crucial to keep adequate attention [94].

Constipation can be treated by administering laxatives, suppositories, or enemas. Laxatives include [91, 100]:

- Bulking agents (methylcellulose, psyllium): increase stool bulk
- Stimulant agents (senna, bisacodyl): stimulate peristalsis and increase water and electrolyte secretion at intestinal mucosa
- Osmotic agents (lactulose or polyethylene glycol (PEG)): increase water content in stool
- Emollient agents: create a slippery covering on stool, thus decreasing the amount of water absorbed at intestinal level

Currently, few data on effectiveness of laxatives in the critically ill population are available.

In a RCT on surgical and trauma ICU patients, lactulose administration during the first 3 days after ICU admission led to a statistically significant difference in patients with bowel movements (18% in the intervention group vs. 4% in the control group, $p < 0.05$) [101]. Daily administration of lactulose reduces time to first defecation (14.5 vs. 96.0 h, $p < 0.001$), days without defecation (33.1 ± 15.7 vs. 62.3 ± 24.5, $p < 0.001$), and number of patients affected by constipation (9.1% vs. 72.7%, $p < 0.001$); moreover, daily lactulose led to a greater reduction in SOFA score at discharge (−1.907; −3.683 to 0.13; $p = 0.036$) [102].

A less recent prospective RCT compared the effectiveness of two commonly administered laxatives (PEG and lactulose) and placebo in mixed ICU (including cardiac surgical patients). Both lactulose and PEG significantly reduced time to first defecation (36.0 vs. 75.0 h for lactulose versus placebo, $p = 0.001$; 44.0 vs. 75.0 h for PEG vs. placebo, $p = 0.001$). Also, a number of patients who had defecation during the study period statistically differed when comparing lactulose and placebo (69% vs. 31%, $p = 0.001$) and PEG and placebo (74% vs. 31%, $p = 0.001$) [97].

Other pharmacological agents can help resume GI motility. Metoclopramide and erythromycin both increase gastric emptying; however, their effect on small bowel movements [103] and in patients with postoperative ileus is limited [96]. Low doses (2–2.5 mg/24 h) of neostigmine help small bowel and colon motility [103], although potentially severe cardiovascular complications are described.

Enemas can be administered when oral laxatives are contraindicated, not tolerated, or not effective.

Bowel dysfunction related to opioids can be treated by administering methylnaltrexone (oral, intravenous, or subcutaneous) or naloxone. Methylnaltrexone acts as peripheral opiates antagonist, but its molecular structure does not cross the blood-brain barrier, thus avoiding side effects such as withdrawal syndrome or inadequate analgesia [103]. Methylnaltrexone can be administered orally, subcutaneously, and intravenously, without significant side effects or effect's reduction [100].

Take-Home Messages

- Assessment of nutritional status allows identification of patients at risk for malnutrition.
- Nutrition deficits increase the risk for major outcomes (mortality and LOS) and delay wound healing and recover of patients.
- Enteral nutrition is usually preferred, since it is more physiological and less costly.

- Complications of enteral nutrition refer both to the upper and lower gastrointestinal tract and may affect the delivery of required amounts.
- Special attentions are required when administering oral and liquid drugs through nasogastric tubes, both to avoid complications and reduced effect.
- Diarrhea and constipation commonly affect ICU patients; these complications relate with major outcomes.
- Protocols can be helpful to manage enteral feeding and to uniform the approach to gastrointestinal complications.

References

1. Marik PE. Enteral nutrition in the critically ill: myths and misconceptions. Crit Care Med. 2014;42(4):962–9. https://doi.org/10.1097/CCM.0000000000000051.
2. Lew CCh, Yandell R, Fraser RJl, Chua AP, Chong MF, Miller M. Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit: A Systematic Review. JPEN J Parenter Enteral Nutr. 2017;41(5):744–758. https://doi.org/10.1177/0148607115625638.
3. Roberts SR, Kennerly DA, Keane D, George C. Nutrition support in the intensive care unit. Adequacy, timeliness, and outcomes. Crit Care Nurse. 2003;23(6):49–57.
4. World Health Organization. BMI classifications. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed 28 Aug 2016.
5. CDC. Anthropometric reference data for children and adults: United States, 2007–2010. http://www.cdc.gov/nchs/data/series/sr_11/sr11_252.pdf. Accessed 06 Dec 2016.
6. Ruiz L, Colley JR, Hamilton PJ. Measurement of triceps skinfold thickness. An investigation of sources of variation. Br J Prev Soc Med. 1971;25(3):165–7.
7. Benítez Brito N, Suárez Llanos JP, Fuentes Ferrer M, Oliva García JG, Delgado Brito I, Pereyra-García Castro F, Caracena Castellanos N, Acevedo Rodríguez CX, Palacio Abizanda E. Relationship between mid-upper arm circumference and body mass index in inpatients. PLoS One. 2016;11(8):e0160480. https://doi.org/10.1371/journal.pone.0160480.

8. Frisancho AR. Triceps skinfold and upper arm muscle size norms for assessment of nutritional status. Am J Clin Nutr. 1974;27:1052–7.
9. Madden AM, Smith S. Body composition and morphological assessment of nutritional status in adults: a review of anthropometric variables. J Hum Nutr Diet. 2016;29(1):7–25. https://doi.org/10.1111/jhn.12278.
10. Simpson F, Early PN, Trial Investigators Group. Physical assessment and anthropometric measures for use in clinical research conducted in critically ill patient populations: an analytic observational study. JPEN J Parenter Enteral Nutr. 2015;39(3):313–21. https://doi.org/10.1177/0148607113515526.
11. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C, Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (a.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40(2):159–211. https://doi.org/10.1177/0148607115621863.
12. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321–36.
13. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care. 2011;15(6):R268. https://doi.org/10.1186/cc10546.
14. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying critically-ill patients who will benefit most from nutritional therapy: further validation of the "modified NUTRIC" nutritional risk assessment tool. Clin Nutr. 2016;35(1):158–62. https://doi.org/10.1016/j.clnu.2015.01.015.
15. Coltman A, Peterson S, Roehl K, Roosevelt H, Sowa D. Use of 3 tools to assess nutrition risk in the intensive care unit. JPEN J Parenter Enteral Nutr. 2015;39(1):28–33. https://doi.org/10.1177/0148607114532135.
16. Fung EB. Estimating energy expenditure in critically ill adults and children. AACN Clin Issues. 2000;11(4):480–97.
17. Walker RN, Heuberger RA. Predictive equations for energy needs for the critically ill. Respir Care. 2009;54(4):509–21.

18. Li B, Tang S, Ma YL, Tang J, Wang B, Wang JR. Analysis of bowel sounds application status for gastrointestinal function monitoring in the intensive care unit. Crit Care Nurs Q. 2014;37(2):199–206. https://doi.org/10.1097/CNQ.0000000000000019.
19. Breum BM, Rud B, Kirkegaard T, Nordentoft T. Accuracy of abdominal auscultation for bowel obstruction. World J Gastroenterol. 2015;21(34):10018–24. https://doi.org/10.3748/wjg.v21.i34.10018.
20. Heyland DK, Cahill NE, Dhaliwal R, Sun X, Day AG, McClave SA. Impact of enteral feeding protocols on enteral nutrition delivery: results of a multicenter observational study. JPEN J Parenter Enteral Nutr. 2010;34(6):675–84. https://doi.org/10.1177/0148607110364843.
21. Choi EY, Park DA, Park J. Calorie intake of enteral nutrition and clinical outcomes in acutely critically ill patients: a meta-analysis of randomized controlled trials. JPEN J Parenter Enteral Nutr. 2015;39(3):291–300. https://doi.org/10.1177/0148607114544322.
22. de Brito-Ashurst I, Preiser JC. Diarrhea in critically ill patients: the role of enteral feeding. JPEN J Parenter Enteral Nutr. 2016;40(7):913–23. https://doi.org/10.1177/0148607116651758.
23. Pearce CB, Duncan HD. Enteral feeding. Nasogastric, nasojejunal, percutaneous endoscopic gastrostomy, or jejunostomy: its indications and limitations. Postgrad Med J. 2002;78(918):198–204.
24. Scott R, Bowling TE. Enteral tube feeding in adults. J R Coll Physicians Edinb. 2015;45(1):49–54. https://doi.org/10.4997/JRCPE.2015.112.
25. Williams NT. Medication administration through enteral feeding tubes. Am J Health Syst Pharm. 2008;65(24):2347–57. https://doi.org/10.2146/ajhp080155.
26. Alkhawaja S, Martin C, Butler RJ, Gwadry-Sridhar F. Post-pyloric versus gastric tube feeding for preventing pneumonia and improving nutritional outcomes in critically ill adults. Cochrane Database Syst Rev. 2015;8:CD008875. https://doi.org/10.1002/14651858.CD008875.pub2.
27. Taylor SJ. Confirming nasogastric feeding tube position versus the need to feed. Intensive Crit Care Nurs. 2013;29(2):59–69. https://doi.org/10.1016/j.iccn.2012.07.002.
28. Lortie MA, Charbonney E. Confirming placement of nasogastric feeding tubes. CMAJ. 2016;188(5):E96. https://doi.org/10.1503/cmaj.150609.
29. Williams TA, Leslie GD. A review of the nursing care of enteral feeding tubes in critically ill adults: part II. Intensive Crit Care Nurs. 2005;21(1):5–15. https://doi.org/10.1016/j.iccn.2004.08.003.
30. Beghetto MG, Anziliero F, Leães DM, de Mello ED. Feeding tube placement: auscultatory method and x-ray agreement. Rev Gaucha

Enferm. 2015;36(4):98–103. https://doi.org/10.1590/1983-1447.2015.04.54700.
31. Turgay AS, Khorshid L. Effectiveness of the auscultatory and pH methods in predicting feeding tube placement. J Clin Nurs. 2010;19(11–12):1553–9. https://doi.org/10.1111/j.1365-2702.2010.03191.x.
32. Boeykens K, Steeman E, Duysburgh I. Reliability of pH measurement and the auscultatory method to confirm the position of a nasogastric tube. Int J Nurs Stud. 2014;51(11):1427–33. https://doi.org/10.1016/j.ijnurstu.2014.03.004.
33. Bankhead R, Boullata J, Brantley S, Corkins M, Guenter P, Krenitsky J, Lyman B, Metheny NA, Mueller C, Robbins S, Wessel J, A.S.P.E.N. Board of Directors. Enteral nutrition practice recommendations. JPEN J Parenter Enteral Nutr. 2009;33(2):122–67. https://doi.org/10.1177/0148607108330314.
34. Arevalo-Manso JJ, Martinez-Sanchez P, Juarez-Martin B, Fuentes B, Ruiz-Ares G, Sanz-Cuesta BE, Parrilla-Novo P, Diez-Tejedor E. Preventing diarrhoea in enteral nutrition: the impact of the delivery set hang time. Int J Clin Pract. 2015;69(8):900–8. https://doi.org/10.1111/ijcp.12645.
35. Kuppinger DD, Rittler P, Hartl WH, Rüttinger D. Use of gastric residual volume to guide enteral nutrition in critically ill patients: a brief systematic review of clinical studies. Nutrition. 2013;29(9):1075–9. https://doi.org/10.1016/j.nut.2013.01.025.
36. Davies AR. Gastric residual volume in the ICU: can we do without measuring it? JPEN J Parenter Enteral Nutr. 2010;34(2):160–2. https://doi.org/10.1177/0148607109357626.
37. Reintam Blaser A, Starkopf L, Deane AM, Poeze M, Starkopf J. Comparison of different definitions of feeding intolerance: a retrospective observational study. Clin Nutr. 2015;34(5):956–61. https://doi.org/10.1016/j.clnu.2014.10.006.
38. Gungabissoon U, Hacquoil K, Bains C, Irizarry M, Dukes G, Williamson R, Deane AM, Heyland DK. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. JPEN J Parenter Enteral Nutr. 2015;39(4):441–8. https://doi.org/10.1177/0148607114526450.
39. Metheny NA, Schallom L, Oliver DA, Clouse RE. Gastric residual volume and aspiration in critically ill patients receiving gastric feedings. Am J Crit Care. 2008;17(6):512–9; quiz 520
40. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The nutritional and metabolic working Group of the Spanish Society of intensive care medicine and coronary units. Crit Care Med. 1999;27(8):1447–53.

41. McClave SA, Lukan JK, Stefater JA, Lowen CC, Looney SW, Matheson PJ, Gleeson K, Spain DA. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. Crit Care Med. 2005;33(2):324–30.
42. Juvé-Udina ME, Valls-Miró C, Carreño-Granero A, Martinez-Estalella G, Monterde-Prat D, Domingo-Felici CM, Llusa-Finestres J, Asensio-Malo G. To return or to discard? Randomised trial on gastric residual volume management. Intensive Crit Care Nurs. 2009;25(5):258–67. https://doi.org/10.1016/j.iccn.2009.06.004.
43. Marshall A, West S. Nutritional intake in the critically ill: improving practice through research. Aust Crit Care. 2004;17(1):6–8, 10-5
44. Elke G, Felbinger TW, Heyland DK. Gastric residual volume in critically ill patients: a dead marker or still alive? Nutr Clin Pract. 2015; 30(1):59–71. https://doi.org/10.1177/0884533614562841.
45. Bartlett Ellis RJ, Fuehne J. Examination of accuracy in the assessment of gastric residual volume: a simulated, controlled study. JPEN J Parenter Enteral Nutr. 2015;39(4):434–40. https://doi.org/10.1177/0148607114524230.
46. Metheny NA, Stewart J, Nuetzel G, Oliver D, Clouse RE. Effect of feeding-tube properties on residual volume measurements in tube-fed patients. JPEN J Parenter Enteral Nutr. 2005;29(3):192–7. https://doi.org/10.1177/0148607105029003192.
47. Reignier J, Mercier E, Le Gouge A, Boulain T, Desachy A, Bellec F, Clavel M, Frat JP, Plantefeve G, Quenot JP, Lascarrou JB. Clinical research in intensive care and sepsis (CRICS) Group. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA. 2013;309(3):249–56. https://doi.org/10.1001/jama.2012.196377.
48. Kadamani I, Itani M, Zahran E, Taha N. Incidence of aspiration and gastrointestinal complications in critically ill patients using continuous versus bolus infusion of enteral nutrition: a pseudo-randomised controlled trial. Aust Crit Care. 2014;27(4):188–93. https://doi.org/10.1016/j.aucc.2013.12.001.
49. Montejo JC, Miñambres E, Bordejé L, Mesejo A, Acosta J, Heras A, Ferré M, Fernandez-Ortega F, Vaquerizo CI, Manzanedo R. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. Intensive Care Med. 2010;36(8):1386–93. https://doi.org/10.1007/s00134-010-1856-y.
50. Moreira TV, McQuiggan M. Methods for the assessment of gastric emptying in critically ill, enterally fed adults. Nutr Clin Pract. 2009;24(2):261–73. https://doi.org/10.1177/0884533609332176.

51. Soroksky A, Lorber J, Klinowski E, Ilgayev E, Mizrachi A, Miller A, Ben Yehuda TM, Leonov Y. A simplified approach to the management of gastric residual volumes in critically ill mechanically ventilated patients: a pilot prospective cohort study. Isr Med Assoc J. 2010;12(9):543–8.
52. Elpern EH, Stutz L, Peterson S, Gurka DP, Skipper A. Outcomes associated with enteral tube feedings in a medical intensive care unit. Am J Crit Care. 2004;13(3):221–7.
53. Steele A, Carlson KK. Nausea and vomiting: applying research to bedside practice. AACN Adv Crit Care. 2007;18(1):61–73; quiz 74-5
54. Reintam A, Parm P, Kitus R, Kern H, Starkopf J. Gastrointestinal symptoms in intensive care patients. Acta Anaesthesiol Scand. 2009; 53(3):318–24. https://doi.org/10.1111/j.1399-6576.2008.01860.x.
55. Kim H, Stotts NA, Froelicher ES, Engler MM, Porter C. Why patients in critical care do not receive adequate enteral nutrition? A review of the literature. J Crit Care. 2012;27(6):702–13. https://doi.org/10.1016/j.jcrc.2012.07.019.
56. Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. Chest. 2003;124(1):297–305.
57. Reid C. Frequency of under- and overfeeding in mechanically ventilated ICU patients: causes and possible consequences. J Hum Nutr Diet. 2006;19(1):13–22. https://doi.org/10.1111/j.1365-277X.2006.00661.x.
58. Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. Crit Care. 2003;7(3):R46–51. https://doi.org/10.1186/cc2190.
59. Kozeniecki M, McAndrew N, Patel JJ. Process-related barriers to optimizing enteral nutrition in a tertiary medical intensive care unit. Nutr Clin Pract. 2016;31(1):80–5. https://doi.org/10.1177/0884533615611845.
60. Peev MP, Yeh DD, Quraishi SA, Osler P, Chang Y, Gillis E, Albano CE, Darak S, Velmahos GC. Causes and consequences of interrupted enteral nutrition: a prospective observational study in critically ill surgical patients. JPEN J Parenter Enteral Nutr. 2015;39(1):21–7. https://doi.org/10.1177/0148607114526887.
61. O'Meara D, Mireles-Cabodevila E, Frame F, Hummell AC, Hammel J, Dweik RA, Arroliga AC. Evaluation of delivery of enteral nutrition in critically ill patients receiving mechanical ventilation. Am J Crit Care. 2008;17(1):53–61.
62. Kim H, Stotts NA, Froelicher ES, Engler MM, Porter C, Kwak H. Adequacy of early enteral nutrition in adult patients in the intensive care unit. J Clin Nurs. 2012;21(19–20):2860–9. https://doi.org/10.1111/j.1365-2702.2012.04218.x. Epub 2012 Jul 30

63. Ramakrishnan N, Daphnee DK, Ranganathan L, Bhuvaneshwari S. Critical care 24 × 7: but, why is critical nutrition interrupted? Indian J Crit Care Med. 2014;18(3):144–8. https://doi.org/10.4103/0972-5229.128704.
64. Doig GS, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, Dobb G, Nutrition Guidelines Investigators of the ANZICS Clinical Trials Group. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA. 2008;300(23):2731–41. https://doi.org/10.1001/jama.2008.826.
65. Compton F, Bojarski C, Siegmund B, van der Giet M. Use of a nutrition support protocol to increase enteral nutrition delivery in critically ill patients. Am J Crit Care. 2014;23(5):396–403. https://doi.org/10.4037/ajcc2014140.
66. Lottes Stewart M. Nutrition support protocols and their influence on the delivery of enteral nutrition: a systematic review. Worldviews Evid-Based Nurs. 2014;11(3):194–9. https://doi.org/10.1111/wvn.12036.
67. Teng R, Carlson G, Hsia J. An open-label, randomized bioavailability study with alternative methods of administration of crushed ticagrelor tablets in healthy volunteers. Int J Clin Pharmacol Ther. 2015;53(2):182–9. https://doi.org/10.5414/CP202202.
68. Klang M, McLymont V, Ng N. Osmolality, pH, and compatibility of selected oral liquid medications with an enteral nutrition product. JPEN J Parenter Enteral Nutr. 2013;37(5):689–94. https://doi.org/10.1177/0148607112471560.
69. Boullata JI. Drug administration through an enteral feeding tube. The rationale behind the guidelines. Am J Nurs. 2009;109(10):34–42; quiz 43. https://doi.org/10.1097/01.NAJ.0000361488.45094.28.
70. Matysiak-Luśnia K, Lysenko Ł. Drug administration via enteral feeding tubes in intensive therapy - terra incognita? Anaesthesiol Intensive Ther. 2014;46(4):307–11. https://doi.org/10.5603/AIT.2014.0050.
71. Phillips NM, Endacott R. Medication administration via enteral tubes: a survey of nurses' practices. J Adv Nurs. 2011;67(12):2586–92. https://doi.org/10.1111/j.1365-2648.2011.05688.x.
72. Mota ML, Barbosa IV, Studart RM, Melo EM, Lima FE, Mariano FA. Evaluation of intensivist-nurses' knowledge concerning medication administration through nasogastric and enteral tubes. Rev Lat Am Enfermagem. 2010;18(5):888–94.
73. van den Bemt PM, Cusell MB, Overbeeke PW, Trommelen M, van Dooren D, Ophorst WR, Egberts AC. Quality improvement of oral medication administration in patients with enteral feeding tubes. Qual Saf Health Care. 2006;15(1):44–7. https://doi.org/10.1136/qshc.2004.013524.

74. McPeake J, Gilmour H, MacIntosh G. The implementation of a bowel management protocol in an adult intensive care unit. Nurs Crit Care. 2011;16(5):235–42. https://doi.org/10.1111/j.1478-5153.2011.00451.x.
75. Knowles S, Lam LT, McInnes E, Elliott D, Hardy J, Middleton S. Knowledge, attitudes, beliefs and behaviour intentions for three bowel management practices in intensive care: effects of a targeted protocol implementation for nursing and medical staff. BMC Nurs. 2015;14:6. https://doi.org/10.1186/s12912-015-0056-z.
76. Knowles S, McInnes E, Elliott D, Hardy J, Middleton S. Evaluation of the implementation of a bowel management protocol in intensive care: effect on clinician practices and patient outcomes. J Clin Nurs. 2014;23(5–6):716–30. https://doi.org/10.1111/jocn.12448.
77. Ferrie S, East V. Managing diarrhoea in intensive care. Aust Crit Care. 2007;20(1):7–13.
78. Reintam Blaser A, Malbrain MLNG, Starkopf J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 2012;38(3):384–94. https://doi.org/10.1007/s00134-011-2459-y.
79. Reintam Blaser A, Deane AM, Fruhwald S. Diarrhoea in the critically ill. Curr Opin Crit Care. 2015;21(2):142–53. https://doi.org/10.1097/MCC.0000000000000188.
80. O'Donnell LJD, Heaton KW. Pseudo-diarrhea in the irritable bowel syndrome: patients' records of stool form reflect transit time while stool frequency does not. Gut. 1988;29:A1455. https://doi.org/10.1136/gut.29.10.A1429.
81. Heaton KW, Radvan J, Cripps H, Mountford RA, Braddon FE, Hughes AO. Defecation frequency and timing, and stool form in the general population: a prospective study. Gut. 1992;33(6):818–24.
82. Bishop S, Young H, Goldsmith D, Buldock D, Chin M, Bellomo R. Bowel motions in critically ill patients: a pilot observational study. Crit Care Resusc. 2010;12(3):182–5.
83. Tirlapur N, Puthucheary ZA, Cooper JA, Sanders J, Coen PG, Moonesinghe SR, Wilson AP, Mythen MG, Montgomery HE. Diarrhoea in the critically ill is common, associated with poor outcome, and rarely due to Clostridium difficile. Sci Rep. 2016;6:24691. https://doi.org/10.1038/srep24691.
84. Thibault R, Graf S, Clerc A, Delieuvin N, Heidegger CP, Pichard C. Diarrhoea in the ICU: respective contribution of feeding and antibiotics. Crit Care. 2013;17(4):R153. https://doi.org/10.1186/cc12832.
85. Baldi F, Bianco MA, Nardone G, Pilotto A, Zamparo E. Focus on acute diarrhoeal disease. World J Gastroenterol. 2009;15(27):3341–8.

86. Manzanares W, Lemieux M, Langlois PL, Wischmeyer PE. Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis. Crit Care. 2016;19:262. https://doi.org/10.1186/s13054-016-1434-y.
87. Prat D, Messika J, Avenel A, Jacobs F, Fichet J, Lemeur M, Ricard JD, Sztrymf B. Constipation incidence and impact in medical critical care patients: importance of the definition criterion. Eur J Gastroenterol Hepatol. 2016;28(3):290–6. https://doi.org/10.1097/MEG.0000000000000543.
88. Nguyen T, Frenette AJ, Johanson C, Maclean RD, Patel R, Simpson A, Singh A, Balchin KS, Fergusson D, Kanji S. Impaired gastrointestinal transit and its associated morbidity in the intensive care unit. J Crit Care. 2013;28(4):537.e11–7. https://doi.org/10.1016/j.jcrc.2012.12.003.
89. Nassar AP Jr, da Silva FM, de Cleva R. Constipation in intensive care unit: incidence and risk factors. J Crit Care. 2009;24(4):630.e9–12. https://doi.org/10.1016/j.jcrc.2009.03.007.
90. Fukuda S, Miyauchi T, Fujita M, Oda Y, Todani M, Kawamura Y, Kaneda K, Tsuruta R. Risk factors for late defecation and its association with the outcomes of critically ill patients: a retrospective observational study. J Intensive Care. 2016;4:33. https://doi.org/10.1186/s40560-016-0156-1.
91. Poulsen JL, Brock C, Olesen AE, Nilsson M, Drewes AM. Evolving paradigms in the treatment of opioid-induced bowel dysfunction. Ther Adv Gastroenterol. 2015;8(6):360–72. https://doi.org/10.1177/1756283X15589526.
92. Thomas J. Opioid-induced bowel dysfunction. J Pain Symptom Manag. 2008;35:103–13. https://doi.org/10.1016/j.jpainsymman.2007.01.017.
93. van der Spoel JI, Schultz MJ, van der Voort PH, de Jonge E. Influence of severity of illness, medication and selective decontamination on defecation. Intensive Care Med. 2006;32(6):875–80. https://doi.org/10.1007/s00134-006-0175-9.
94. Vincent JL, Preiser JC. Getting critical about constipation. Pract Gastroenterol. 2015;15
95. Gacouin A, Camus C, Gros A, et al. Constipation in long- term ventilated patients: associated factors and impact on intensive care unit outcomes. Crit Care Med. 2010;38:1933–8. https://doi.org/10.1097/CCM.0b013e3181eb9236.
96. Behm B, Stollman N. Postoperative ileus: etiologies and interventions. Clin Gastroenterol Hepatol. 2003;1(2):71–80. https://doi.org/10.1053/cgh.2003.50012.

97. van der Spoel JI, Oudemans-van Straaten HM, Kuiper MA, van Roon EN, Zandstra DF, van der Voort PH. Laxation of critically ill patients with lactulose or polyethylene glycol: a two-center randomized, double-blind, placebo-controlled trial. Crit Care Med. 2007;35(12):2726–31. https://doi.org/10.1097/01.CCM.0000287526.08794.29.
98. van der Spoel JI. Oudemans-van Straaten Ubi poop, ibi evacua? HM. Crit Care Med. 2010;38(10):2064–5. https://doi.org/10.1097/CCM.0b013e3181f1789b.
99. Smonig R, Wallenhorst T, Bouju P, Letheulle J, Le Tulzo Y, Tadié JM, Gacouin A. Constipation is independently associated with delirium in critically ill ventilated patients. Intensive Care Med. 2016;42(1):126–7. https://doi.org/10.1007/s00134-015-4050-4.
100. Chappell D, Rehm M, Conzen P. Opioid-induced constipation in intensive care patients: relief in sight? Crit Care. 2008;12(4):161. https://doi.org/10.1186/cc6930.
101. Masri Y, Abubaker J, Ahmed R. Prophylactic use of laxative for constipation in critically ill patients. Ann Thorac Med. 2010;5(4):228–31. https://doi.org/10.4103/1817-1737.69113.
102. de Azevedo RP, Freitas FG, Ferreira EM, Pontes de Azevedo LC, Machado FR. Daily laxative therapy reduces organ dysfunction in mechanically ventilated patients: a phase II randomized controlled trial. Crit Care. 2015;19:329. https://doi.org/10.1186/s13054-015-1047-x.
103. Fruhwald S, Holzer P, Metzler H. Intestinal motility disturbances in intensive care patients pathogenesis and clinical impac. Intensive Care Med. 2007;33(1):36–44. https://doi.org/10.1007/s00134-006-0452-7.