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REVIEW

Enteral Nutrition in Clinical Practice

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Enteral nutrition has, at long last, found its place in the modulation of disease. Because of its importance in terms of both anabolic and catabolic processes, today's clinician must have a working knowledge of the types of enteral formulations, their delivery and the therapeutic considerations (particularly concomitant medications) that impact on the safety and efficacy of enteral nutrition. The advantages and disadvantages of this therapeutic intervention must be carefully weighed by the clinician, in concert with sound medical principles. Despite the widespread belief that enteral nutrition is superior to parenteral nutrition in humans, data does suggest that there is little difference between the two. Also, associated costs of enteral nutrition in contrast to parenteral nutrition need to be reappraised based on more invasive enteral access and falling parenteral nutrition prices. Although the enteral route is presumed to be the best feeding modality, the clinician must be ever vigilant about the shortcomings of using the gut, especially in the setting of severe inflammation, stenosis or sepsis. The best feeding modality, then, must blend a knowledge of the patients' anatomy, physiology, and disease with considerations of enteral access, timing of delivery, complications, and a myriad of other therapeutic variables (to include concurrent medication administration) that impact on the enteral feeding regimen. This article reviews the basic principles of enteral nutrition in clinical practice. It describes nutritional assessment, routes of administration, selection of feeding formulas based on nutritional needs, interactions with medications, as well as possible complications of enteral feeding.

Key words: *enteral nutrition; food, formulated; food-drug interactions; intubation, gastrointestinal; nutrition disorder; nutritional requirements*

Enteral nutrition is provided either as a supplemental modality or for complete nutrition support for patients who are unable to ingest enough of any nutrient. Macrosubstrates and micronutrients must be provided by the diet in adequate amounts, otherwise deficiency signs and syndromes will surface and, in turn, adversely affect health. Often, the impact of insufficient nutrition on well being is difficult to appreciate prior to the manifestation of overt signs or symptoms.

Malabsorption and maldigestion must be recognized early in the decision-making process in the use of enteral nutrition. Weight loss, signs of macronutrient (i.e., decreased visceral protein status, hypoglycemia, and steatorrhea) and micronutrient (electrolytes, trace elements, and vitamins) abnormalities suggest that the intestine may not be optimally functioning. Upper gastrointestinal structure and function can be assessed using xylose absorption, upper endoscopy with biopsies, motility/emptying studies, and radiological procedures. Breath tests, Shilling's test, flexible sigmoidoscopy and colonoscopy with biopsies, motility, and microbiologic and radiological studies can be used to distinguish lower bowel abnormalities. The Bern- stein test to identify esophageal acid sensitivity, gastric secretory tests, secretin infusion for gastrin- oma workup, secretin testing and serum trypsin for diagnosis of pancreatic insufficiency, and abdominal paracentesis have been used to identify more specific issues. In addition, qualitative and quantitative testing of stool and bowel secretions also play roles in better defining bowel absorptive processes.

Enteral nutrition, as well as the use of the enteral route for the administration of medications can be life saving but also lethal. Aside from the potential problems associated with receiving inadequate or excessive nutrition or medication therapy, additional injury to the patient may result from using the gut that is at risk for bacterial or candidal translocation. For example, in mechanically ventilated blunt trauma patients, endoscopic transpyloric tube placement and feeding have a substantial failure rate (36%). Additionally, intolerance to duodenal feeding in this patient population also has an impressive mortality (100%), where intestinal dysfunction may be a manifestation of injury severity and directly af-

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fect survival (1). Therefore, enteral nutrition should be started only if the potential benefits outweigh the risks.

Nutrient Stores and Nutritional Balance

Approximately 1600 mL/m^2 of water will be needed to meet maintenance requisites, whereas an additional 70 mL/kg will be needed for replacement (extraordinary) needs. After water needs, protein and caloric requirements must be met. Daily needs may draw from storage depots and depletion of the storage depot depends on the fractional clearance rate of the nutrient (determined by the nutrient balances and size of the depot). Persistent negative balance or ongoing pathologic processes (e.g., iron deficiency may suggest chronic gastrointestinal blood loss) may culminate in significant morbidity or mortality. The urgency of nutrient repletion and the route delivery depends on the actual or anticipated degree of storage compartment depletion. For example, some vitamins and minerals have minimal daily requirements but relatively large body stores (e.g., cobalamin) and supplementation may be unnecessary during an average hospitalization. However, if the storage reservoir has been sufficiently depleted prior to institutional admission, the depletion may have reached a life threatening level and nutritional replacement may even represent a disease-modulating strategy (2).

Table 1. Monitoring parameters of enteral nutrition

1. Age
2. Race
3. Sex
4. Chief complaint/diagnosis
5. Admission date
6. TPN/volume date start
7. TPN/volume stop
8. Enteral tube/charge
9. Enteral charge/volume date start
10. Enteral charge/volume date stop
11. Different enteral/volume start
12. Different enteral/volume stop
13. Weight change since admission
14. HR
15. RR
16. Temperature (maximum)
17. WBC
18. Bands
19. Organism/site/date
20. Enteral tube location (distal tip)
21. Fat (mL/day)
22. BUN/Cr
23. TP/alb
24. UUN
25. Prealbumin
26. Transferrin
27. Arterial blood gas
28. Phosphate
29. Ionized calcium
30. Glucose level
31. Dextrose mg/kg/minute
30. Triglyceride
31. Amylase
32. Lipase
33. Prothrombin time/INR
34. Medication implications

Nutritional Assessment

Many issues need to be considered before and during enteral feeding (Table 1). The patient's gastrointestinal tract must be studied and the most appropriate (short or long-term) route must be selected. Decisions must be made as to whether the delivery should be intermittent, continuous, or cyclic (Table 2). The formula selection must, then, deal with formula complexity, type (i.e., renal, pulmonary, and immune), and volume (Table 3).

Enteral Administration

Tube Placement

Transnasal, transoral, jejunostomy or gastro- stomy feeding tube position must be documented radiographically before feeding is initiated. Prokinetic agents such as erythromycin, metoclopramide, or cisapride may be used to promote tube transit through the gastrointestinal tract. Caution should be exercised, however, not to combine the prokinetic cisapride with erythromycin derivatives, fluconazole and itraconazole, to avoid interactions through the P450 system and subsequent arrhythmias (3). The most important cardiac effects are QT-interval prolongation and ventricular arrhythmias. Cisapride metabolism is also inhibited by the antifungals ketoconazole, fluconazole, itraconazole, and miconazole, and by the antibac- terials troleandomycin and clarithromycin. Therefore, cisapride should not be coadministered with these drugs. If prokinetic agent use is unsuccessful, endoscopic or fluoroscopic guidance may be needed to position the feeding tube (4). If four or more weeks of tube feeding are anticipated, gastrostomy, jejunostomy, or combination G-J tubes should be considered.

Time Schedule of Food Delivery

Intermittent (generally thought to include a fasting period of at least eight hours) or continuous feeding regimens each have positive and negative aspects. Intermittent feeding is reserved for gastric feeding. Initially, 100-150 mL is used and increased to 200-300 mL every 4-6 hours as tolerated. It is important to periodically check residuals; the frequency will depend on the bolus volume and the patient. Continuous infusion is generally used in conjunction with a feeding pump to maintain a constant infusion rate, which is especially important if the distal catheter tip is in the jejunum (the area of most risk for dumping syndrome). Cyclic (i.e., only part of the day) feeding may be appropriate in some patients, but the risk of increased calciuria, magnesuria, and phosphaturia needs to be appreciated, particularly in patients at risk for osteoporosis (5).

Several authors have found that intermittent administration of enteral formulas is associated with more bloating, cramps, diarrhea, and thermo- genesis (6,7). In addition, broader swings in hormonal regulation are associated with intermittent administration of nutrition; however, these are associated with increased serum protein synthesis. In sum, intermittent administration is more physiological and transition from continuous feeds should be done over several days to avoid complications.

Table 2. Considerations in decision making in enteral nutrition

Gastrointestinal tract entry point	nasal/oral-gastric/duodenal/jejunal tubes percutaneous endoscopically-placed gastrostomy/jejunostomy surgical jejunostomy
Bowel function	atrophy inflammation ischemia surgical insult edema (in the setting of hypoalbuminemia) fistulas ileus increased transit time (motility disease, opioids, anticholinergics) decreased transit time (motility disease, laxatives, antacids) translocation risk (particularly in the setting of sepsis) hemorrhage malabsorption peritonitis pancreatic or bile acid insufficiency
Formula type	elemental polymeric organ-specific immunomodulating
Formula volume	hourly tolerance daily needs
Delivery	intermittent continuous cyclic
Metabolic monitoring parameters	See Table 1

Initiation of Feeding

It is common clinical practice to initiate enteral nutrition using low flow rates or diluted formula. These adjustments are made in an effort to minimize patient's intolerance. In well-nourished patients, studies do not support the common clinical practice of initiating alimentation with low flow rates (<25 mL/h) or diluted formula. Complex and elemental enteral formulas have been investigated to determine whether various flow rates or osmola- lities affected clinical intolerance or carbohydrate malabsorption in 20 healthy volunteers (8). Infusion rates have ranged between 50 and 150 kcal/h and the osmolalities between 325 and 690 mOsm/kg of water. Even at the maximal flow rate and osmo- lality, results have shown that both types of enteral formulas are well tolerated as assessed by the frequency of abdominal pain, bloating, passage of rectal gas, and stooling. No carbohydrate malabsorption has been detected as measured by breath hydrogen.

Osmolality

Other findings have shown that undiluted hypertonic diet results in significantly better nitrogen intake and balance, that starter regimens reduce nutrient intake but not symptoms, and that diarrhea is significantly related to treatment with antibiotics and not to administration of an undiluted hypertonic polymeric diet. One hundred and eighteen patients with normal gastrointestinal function were randomly allocated to one of three feeding regimens in a double blind study to determine the relation between the tonicity of the diet and gastrointestinal side effects related to the diet and to evaluate the efficacy of "starter" regimens in reducing gastrointestinal side effects during enteral nutrition (9). Patients received a hypertonic diet with an osmolality of 430 mmol/kg (group 1), the same diet but with the osmolality increasing from 145 to 430 mmol/kg over the first four days (group 2), or an isotonic diet (300 mmol/kg) (group 3). All diets were prepared aseptically and administered by 24-h nasogastric infusion. The mean daily nitrogen intake in group 1 was significantly greater than that in both groups 2 and 3, and the mean overall daily nitrogen balance was significantly better in group 1 than groups 2 and 3. The incidence of side effects related to the diet was similar in all three groups, but diarrhea was significantly associated with concurrent treatment with antibiotics.

Formula Selection

Consideration of a number of different enteral formula attributes must be made prior to use of one or a combination of formulas. These include lactose content, osmolality, amount of formula needed to meet the Recommended Dietary Allowances (RDA), amount of residue produced, disease or organ compromise, and delivery considerations (i.e., closed system administration, size of enteral tube required, and timing). Unfortunately, commercially available products with fixed nutrient content may be undesirable and result in significant morbidity and mortality if not appropriately monitored. Minimal daily volumes of about 1-2 L are needed to provide the RDA's for nutrients and additional nutrients may be needed beyond this for patients with identified deficiencies (see information on specific enteral formula packages).

Nutritional Considerations

Protein

After denaturation in the stomach, protein presents to the duodenum as large polypeptides and to a lesser extent as amino acids. Subsequent to the digestion of polypeptides to glycopeptides (two to eight amino acids), amino-oligopeptidases in the brush border membrane

Table 3. Types of enteral nutrition formulas

By molecular composition	elemental monomeric polymeric
Disease-specific	kidney liver lung immunomodulating
Modular additives	protein carbohydrate lipid electrolytes

generate dipeptides and tripeptides. Membrane translocation of the resultant peptides occurs via a peptide-transport system and free amino acids are carried via specific amino acid transport systems. Amino acids and dipeptides then proceed to the portal vein. Virtually all protein made of a combination of approximately 20 amino acids, half of which are essential) in the human is labile or serves as a structural component. Negative protein balance for even short periods of time can be clinically significant. If one loses two kg of the six kg protein that is found in a 70 kg male, death is quite predictable. Approximately 15-16% of protein is alpha-nitrogen, the nitrogen group on the end of the chain, which is principally responsible for anabolism. About 80-85% of protein is excreted as urea in the urine (12-16 g nitrogen or 80-100 g protein/day) resulting in 2-3 kg of protein losses in several weeks. An estimate of the enteral protein requirement for the average healthy adult to preserve protein depots (assuming no excessive losses) is 0.75-0.9 g/kg body weight/day. Increased requirements occur with excessive losses from the gastrointestinal tract (enteropathies, fistulas, diarrhea, nasogastric suction, exudation), skin (exfoliative diseases, burns) and draining wounds. Disease conditions, such as burns or nephrotic syndrome, will increase nitrogen excretion (10,11).

Non-urea urine nitrogen such as creatine, creatinine, ammonia, or uric acid can also be measured using chemilluminescence technology to obtain more complete nitrogen accountability, however, rarely is this kind of definition clinically necessary. If nitrogen intake equals output, the patient is said to be in nitrogen balance. The period of anabolic measurement (i.e., the so-called flow phase of injuries) is generally about 3-4 weeks after initiating adequate feeding. Assessment of nitrogen balances weekly thereafter may provide useful information about protein status. Without a good history, measurements of nitrogen balance early in therapy do not provide useful information. Each gram of negative nitrogen is multiplied by 6.25 to obtain the number of grams of protein replacement. Each gram of nitrogen is found in 25-30 g of lean body mass. The number of calories required to incorporate one gram of nitrogen into lean body mass is generally between 100-150 kcal regardless of route. The caloric need is related, of course, to metabolic demands and excretory organ function. Enteral formulas contain a variety of protein sources that include whey, egg white, casein- ates, delactosed lactalbumin, soybean, soy isolates, and free amino acids.

Body weight is a reliable nutritional measure if there is no unusual fluid retention or excretion. Skeletal muscle protein depots (midarm muscle circumference, creatinine excretion for height), and other proteins associated with different physiologic functions (i.e., prealbumin, albumin, transferrin, tests of immune competency) are used to evaluate protein status. Cytokines, in addition to other moieties, are known to regulate changes in plasma protein synthesis (12).

Although there are approximately 100 different proteins in the intravascular compartment, only three categories of protein (albumin, globulins and fibrinogen) are measured in the blood as total protein. In essence, total protein can be used as a measure of colloidal oncotic pressure. A low serum albumin concentration has also been linked to intolerance to enteral feedings. However, two prospectively controlled trials have failed to demonstrate improved tolerance to enteral feeding in hypoalbuminemic patients receiving exogenous albumin. Therefore, evidence to date is insufficient to support the routine administration of exogenous albumin to hypoalbuminemic patients receiving nutrition support (13). The use of serum albumin to evaluate nutritional status in individual patients has low sensitivity and specificity and data indicates that serum albumin is a better nutritional status indicator in epidemiological surveys (14).

The University Hospital Consortium has developed guidelines, as determined by the Delphi method (i.e., expert opinion) for the rational use of colloidal expanders in clinical nutrition. Patients with diarrhea (greater than 2 L/day), albumins less than 2 g/dL and previous trials of short-chain peptide and elemental diets and who have had other causes of diarrhea (i.e., motility, secretory or absorption disorders) ruled out, may benefit from the administration of exogenous albumin (15).

Energy (Carbohydrates and Lipids)

There are barely one day of glucose stores in the form of glycogen in muscle and liver (300 g), but lipid stores can approach 15,000 g in a 70 kg male.

Carbohydrate and lipid constitute the caloric entities needed to incorporate alpha nitrogen from protein sources into lean body mass. Energy requirements must be met in some way every day. Bartlett et al (16) have shown that patients meet their demise if their cumulative negative caloric balance is greater than 10,000 kcal prior to surgery. Of 17 patients who had a cumulative negative balance of at least 10,000 calories, 13 died. The incidence of multiple organ failure was also higher in patients with large caloric deficits.

Part of the daily caloric needs come from either exogenous sources (enteral and parenteral nutrition), or endogenous metabolism of energy stores. Energy intake should equal the energy requirement unless weight loss or gain is desired. Using 20-25 kcal/kg/day or calculating resting energy expenditure using an energy equation with age, weight, and height (least important) will provide energy need approximations. These can be empirically increased as necessary to meet anabolic or maintenance requirements. The basal metabolic rate is the energy requirement at rest and correlates with body surface area.

Carbohydrate sources in enteral formulas are sugar, hydrolyzed cornstarch, guar gum, oat and soy fibers, fructose, and maltodextrin. Carbohydrates present to the small intestine as starches (polysaccharides) and oligosaccharides (sucrose and lactose). Once enzymatically digested, simple sugars are translocated across the brush border membrane via active and passive transport mechanisms on their way to the portal vein. Bacterial hydrolases, disaccharidases, and enzymes that deal with short-chain fatty acids work within the colon to digest cellulose complexes and other fibers. Short-chain fatty acids then stimulate sodium and water reabsorption, and serve as an energy source to the intestinal mucosa.

The brain and liver consume the greatest amount of oxygen in the body. Approximately 20% of basal energy expenditure will be needed to provide energy for the brain, which prefers glucose. The brain will use ketones,

however, if glucose is not available. The heart on the other hand, prefers fat. If fat calories are severely reduced or eliminated, hepatic metabolism will be significantly curtailed (up to 34% Phase I oxidative/reductive falloff). Essential fatty acid deficiency (EFAD) can also be appreciated in as little as five days without lipid supplementation. Others, however, have suggested that biochemical evidence of EFAD can manifest in as little as one day (17).

Major omega-6 lipid sources that are used in enteral formulas include soybean oil, corn oil, sunflower and safflower oils. These all contain approximately 50-60% linoleic acid and precurse even-numbered icosanoids. Although linolenic acid, an omega-3 lipid, is found in much lower quantities in these lipids, omega-3 laden manhaden and canola oils precurse odd-numbered icosanoids and are used in several enteral formulas. In addition to these long chain fatty acids, several products also contain medium chain triglycerides that do not prevent essential fatty acid deficiency. Medium-chain triglycerides containing 8-12 carbons do not require luminal lipolysis and can be absorbed intact by the mucosal membrane. Within the enterocyte, medium-chain triglycerides are digested by intracellular lipases and the resultant free fatty acids pass directly into the portal vein. The long-chain triglycerides contain 14-24 carbons and their digestion includes lipolysis and the formation of mixed bile salt micelles. Within the enterocyte cytosol, triglycerides are re-esterified and packaged into chylomicrons for release into the lymphatic system. Chylomicrons are transported through the thoracic duct into the venous system.

Micronutrients

There are approximately a dozen electrolytes, as well as vitamins, and half a dozen trace elements that are used in enteral formulas. Commonly assessed micronutrients include major minerals (Na, K, Ca, P, Mg, and Cl), trace elements (Fe, Znc) and vitamins (B_{12} and folic acid). Although biochemical assessment of other micronutrients is possible, the clinical appreciation of mineral and vitamin deficiencies usually requires the recognition of corresponding signs and symptoms.

Trace elements that are included in enteral formulations include the ones with Recommended Daily Dietary Allowances (i.e., iodine, iron, selenium, and zinc) and Estimated Safe and Adequate Daily Dietary Intakes (i.e., chromium, copper, fluoride, manganese, and molybdenum).

Vitamins included are the fat solubles (vitamins A, D, E, and K), the semi-water solubles (cyanocobalamin and folic acid) and the water solubles (thiamine, riboflavin, niacin, pyridoxine, and vitamin C). Another semi-water soluble vitamin, biotin, and water soluble pantothenic acid are included to meet Estimated Safe and Adequate Daily Dietary Intakes recommendations.

The metabolic impact of an acid or alkaline ash or residue diets (Table 4) has been studied. If the anionic nature of an enteral diet exceeds the cationic content, the diet will be absorbed as an acidic ash. Subsequently, the acidic ash can acidify urine and cause the retention of acidemic entities and the excretion of alkalemic moieties. Quini- dine, for example, is a basic medication whose excretion can be reduced with urine alkalinization using orange juice (18). Enteral formulas are generally in the range of 6.5- 6.8 pH and the slightly acidic nature may be of benefit since it has been suggested that acidified enteral feedings have been effective in eliminating and preventing gastric bacterial colonization in critically ill patients (19).

Complications

The provision of a complete initial assessment of the gastrointestinal tract and factors related to its successful use can minimize the incidence of complications (Table 5).

Mechanical Obstruction and Motility Disturbances

Mechanical obstruction and motility disturbances are possible complications. Common associated causes include duodenal ulcer, pyloric channel ulcer, ileus, anticholinergic medications, opiates, central nervous system disturbances, metabolic derangements, and severe protein deficiency. Treatment must be directed at the cause; use of a small intestine feeding tube (nasoduodenal or jejunostomy) may overcome the problem. All medications should be provided in liquid form, and the use of crushed tablets should be avoided when possible (20). Aluminum-containing antacids or su- cralfate may interact with some nutritional formulas to produce plugs or bezoars. Once a clog occurs, it may not be possible to dislodge it. Perforation and trans-section of tubes may occur if excessive pressure is applied. A stylet may also perforate the tube and cause gastrointestinal damage.

Table 4. Acid, alkaline, and neutral foods[a]

Potentially acid or acid-ash foods (anionic)	meat, fish, fowl, shellfish, and eggs cheese peanut butter and peanuts fat – bacon, nuts (brazil nuts, filberts, walnuts) starch – all types of bread (especially whole wheat), cereals, crackers, macaroni, spaghetti, noodles, and rice vegetable – corn and lentils fruit – cranberries, plums, and prunes dessert – plain cakes and cookies
Potentially basic or alkaline-ash foods (cationic)	milk and milk products nuts – almonds, chestnuts, coconut vegetable – all types (except corn and lentils), especially beets, swiss chard, dandelion greens, kale, mustard greens, spinach, and turnip greens fruit – all types (except cranberries, prunes, and plums) sweets – molasses
Neutral foods	fats – butter, margarine, cooking fats, and oils sweets – plain candies, sugar, syrup, and honey starch – arrowroot, corn, and tapioca beverages – coffee and tea

[a]If there are more anions (i.e., anion minus cations = net anions) then acid ash will prevail and acid will then be absorbed; that, in turn, leads to acidified urine.

Appreciating where the distal tip of the feeding tube will likely lie will be of benefit to the enterally-fed patient (21). For example, duodenogastric reflux is less likely if feeding ports are located beyond the ligament of Treitz but may still occur, even with jejunostomy feeding. Esophagitis may result from nasogastric or nasoduodenal tubes (22). Dumping syndrome is of greatest risk when large volumes are delivered to the jejunum. In particular, patients having a high risk for aspiration (Table 6) should be meticulously appraised.

Lipoid Pneumonia

Although lipoid pneumonia is commonly appreciated, oil-based products may still be inappropriately used to lubricate enteral tubes for placement. This practice must be abandoned. Water or a vehicle with an aqueous external phase should be used to lubricate tubes. Lipoid pneumonia has also been reported with baby oil inhalation (23), intranasal application of petroleum jelly (24), and throat gargles containing lipoid paraffin (25). Interestingly, pneumonia has even resulted from the use of WD-40 spray lubricant as a liniment for sore back and neck muscles (26).

Diarrhea

The average amount of stool production is 200g/day. Increases in frequency or volume define diarrhea. Decreased transit time from enteral feeding is treated by reducing formula concentration or amount of infusion rate as a first step. A change to another formula may be useful, even if specific nutrient offenders are not identified. Judicious use of antidiarrheal agents should be a last resort after infectious, motility, secretory, osmotic causes and malabsorption have been ruled out as possible etiologies for diarrhea. The most common reason for decreased gastrointestinal transit time in patients receiving enteral nutrition is medications (e.g., antibiotics and associated flora disturbance). In the absence of a standard definition for diarrhea, clinicians have developed their own descriptions, such as an increased frequency of stools, an increased quantity of water in the stool, an increased weight of the stool, or a change in the consistency of the stool. The clinician should first determine whether the diarrhea is osmotic or secretory. Diarrhea in patients who receive enteral nutrition is often caused by such conditions as diabetes, malabsorption syndromes, infection, gastrointestinal complications, or concomitant drug therapy instead of the enteral formula. Factors related to the enteral nutrition that may contribute to diarrhea include the composition of the formula, the manner of administration, or bacterial contamination. To ensure that the nutritional requirements of patients are met and the appropriate treatment is administered, all possible causes of diarrhea should be considered before discontinuing or reducing the amount of formula delivered (27). Osmotic diarrhea is often a result of the medication regimen, whereas secretory diarrhea includes both motility and absorption problems that are frequently associated with infection, malignancy, or obstruction.

Infections

Enteral formulas are a risk factor for infection in intensive care patients if microbial growth is not prevented. Earlier in vitro studies suggested that sterile tubings require change with each eight- hour dose of food (28). Much of this work is presently being challenged in the climate of cost containment and addressed with the development of closed systems for enteral administration (29). Using sterile water in the preparation of enteral solutions may be prudent with those patients who are immunocompromised since the use of tap water seeding nosocomial legionellosis has been described (30).

Continuous enteral feeding is widely practiced in intensive care units. It has been found that pneumonia developed in 54% of 24 ventilated patients on continuous enteral feeding for more than 3 days. This appeared to affect only patients with a persistently high morning (7:00 AM) gastric pH, with 12 of 13 (92%) patients developing pneumonia. In 11 patients, the causative organisms were cultured initially from the stomach, oropharynx, and trachea before pneumonia supervened. This effect was distinct from that found with the prophylactic use of antacids or H_2-receptor antagonists. The mortality (46%) of this group of patients was 1.6 times greater than the expected mortality predicted by the Apache II Severity of Disease Classification System (31). Sucralfate successfully prevented gastric colonization with potentially pathogenic microorganisms. However, the efficacy was markedly decreased when continuous enteral feeding was administered simultaneously (32).

The relationship of pneumonia and increased gastric pH is, however, unclear. At least two meta- analyses investigating the role of gastric pH and nosocomial pneumonia and several individual studies have shown that raising gastric pH does not increase the incidence of nosocomial pneumonia. Importantly, those clinical trials that purport to show that raising gastric pH increases the

Table 5. Assessment and management of enteral nutrition complications

Delivery assessment and managment	Clinical assessment
Aspiration • pH • dye addition • prevention – head elevation	Diarrhea • infectious (*C. difficile*) • fluid assessment • enteral formula contamination • other (vehicles, medications)
Delivery site • check gastric residuals for gastroparesis • jejunum – consider dumping syndrome	Infection • bacterial translocation • aspiration

Table 6. Risk factors for aspiration

Artificial airway
Aspiration pneumonia history
Consciousness level decline
Cough reflex absent
Delayed gastric emptying
Gag reflex impairment
Gastroesophageal reflux history
Weakness or debilitation

incidence of nosocomial pneumonia have not been blinded studies and have failed to control for sites of enteral feeding and volume. Taken together, analysis of several clinical trials finds no compelling evidence for the concept that gastric alkalini- zation increases the incidence of nosocomial pneumonia (33). Acidified enteral feedings have been found to be effective in eliminating and preventing gastric colonization in critically ill patients. Further investigation is needed, however, to assess its effect on nosocomial infection rates (34).

The effect of continuous intraduodenal enteral nutrition on gastric pH was compared with the effects of fasting, parenteral, and standard nutrition control regimens containing equal amounts of carbohydrate, protein, and lipid. Continuous enteral nutrition produced gastric pH values similar to those seen with fasting or standard nutrition, suggesting that, under most physiological conditions, gastric acidity is subject to close feedback control. Parenteral nutrition increases gastric pH, suggesting that systemic nutrients may influence this feedback mechanism (35).

Special Considerations

Use of Medications

As a general rule, no medications should be directly added to enteral nutrition formulas. The addition of medications to enteral formulations must address matters of both physical and chemical stability. However, much of the challenge to the clinician involves sorting out the maze of therapeutic variables and their relationship to enteral nutrition and medicinal use. The most common way to administer medications in an enteral regimen is to flush the administration tubing, administer the drug, and reflushing. The size of the medication versus the size of the internal catheter diameter is generally not as important as other physical, chemical, or therapeutic compatibility.

The prevention of vomiting is important to avoid aspiration of medications or enteral nutrition during delivery. The use of antiemetics, particularly serotonin antagonists, play a major role in addressing these kind of problems. Most of the 5-hydroxytryptamine (5-HT) present in the adult human body is located in the gastrointestinal tract. The vast majority is contained in enteroendocrine cells, while the rest exists mainly in myenteric interneurons separated from the mucosa by an intraenteric barrier. Physiological studies suggest that 5-HT plays a vital role in mediating both sensory and reflex responses to gastrointestinal stimuli and, thus, this transmitter is closely implicated in intestinal reactions (36).

Use of Dyes for Leak and Aspiration Detection

The addition of dyes to enteral solutions is frequently used to detect aspiration or leaks in the gastrointestinal tract in spite of decolorization that may occur in the lower bowel or hypersensitivity reactions (37). Further, the detection of blue discoloration of tracheal secretions has been shown to be unreliable. Glucose oxidase test strip methods have been used as an alternative to blue dye visualization for detecting aspiration of enteral feedings in intubated adults, but this too deserves more investigation (38).

Tube Dynamics

Routine transpyloric placement of feeding tubes has been shown to reduce aspiration in intensive care unit patients. Early on, mercury- weighted enteral tubes were designed to move tubes through the bowel. A variety of materials to weight the distal tip of the tube (frequently teflon beads or mercury) and prokinetic medications are now used to promote transit in the bowel because spontaneous passage of the radiopaque catheter may eliminate the cost of radiologic or endoscopic intervention. The occurrence of transpyloric passage and the rapidity at which it occurred has been shown to be significantly greater for unweighted tubes (39). Erythro- mycin, metoclopramide, and cisapride improve symptoms of patients with gastro-esophageal reflux disease, diabetic gastroparesis and idiopathic gastroparesis, but only cisapride has been shown to be capable of maintaining a gastrokinetic effect under chronic administration (40). The successful use of erythromycin as a prokinetic agent has been shown to be a viable alternative therapy for diabetic gastro- paresis (41). More definitive studies must be done to ascertain whether the addition of a weight to the end of the tube or the use of certain prokinetic agents will reliably improve spontaneous transpyloric placement and minimize the need for endoscopic procedures.

The Role of Gastrointestinal Peptides and Interventions at Their Level

Where (e.g., the distal tip of the catheter) and how (e.g., liquid or crushed) nutrients or medications enter the gastrointestinal tract will determine the relative extent of absorption or excretion. An appreciation of many variables needs to be emphasized. These include pH (an extremely important predictor of medication stability), volume, administration rate, and gastrointestinal peptides. These peptides, each having unique functions, are distributed throughout the gastrointestinal tract. For example, gastrin is principally responsible for gastric hydrogen ion secretion and trophic action to the mucosa. CCK will cause gallbladder contraction and pancreatic secretion, to include secretin, will promote pancreatic bicarbonate secretion. Both macronutrients and micronutrients play roles in stimulating these hormonal peptides within the gastrointestinal tract (Table 7).

There is much work that remains to be done to fully appreciate the role that gastrointestinal peptides may play as therapeutic agents. Numerous neuropeptides and hormones are involved in the regulation of intestinal transit and, in general, these peptides are available only in parenteral dosage forms. Many gastrointestinal hormones known to act on smooth muscle influence muscle contractility. Other hormones, like CCK8, insulin, gastrin (which regulates both the production and release of histamine as well as the growth of the entero- chromaffin-like or ECL cell), and neurotensin, trigger the development of an intestinal feed pattern. Gastrointestinal transit may be altered in physio- pathological situations in which corticotropin-releasing factor, thyrotropin-releasing hormone, and some cytokines (interleukin-1β, tumor necrosis factor-α) play important roles. Motilin is thought to be the major hormone involved in triggering the gastric migrating motor complex while somatostatin (SST) and enkephalins are

Table 7. Nutritional stimuli of gastrointestinal peptide secretion and actions of gastrointestinal peptides and enzymes

Enzyme/hormone	Nutritional stimulus for release	Main actions
Amylase		converts carbohydrates, starch, and glycogen to simple disaccharides
Cholecystokinin	amino acids, fat calcium	stimulates pancreatic enzyme secretion and gallbladder contraction
Chymotrypsinogen		breaks down proteins into proteases and peptides
Enteroglucagon		inhibits pancreatic enzyme secretion and bowel motility
Gastric inhibitory peptide	carbohydrates, fat	decreases gastric motility and stimulates insulin secretion
Gastrin	amino acids	stimulates gastric acid secretion and mucosal growth
Glucagon		stimulates hepatic glycogenolysis and inhibits motility fat absorption
Lipase		hydrolyzes SCT and MCT, involved in fat absorption
Pancreatic polypeptide		inhibits gallbladder contraction and pancreatic/biliary secretion
Pepsinogen		converts large proteins into polypeptides
Secretin	calcium, gastric acid	stimulates hepatic and pancreatic water and bicarbonate
Trypsinogen		breaks down proteins into proteases and peptides
Vasoactive inhibitory peptide		vasodilator; stimulates water and bicarbonate secretion, release of insulin and glucagon, and production of small intestinal juice

implicated in its propagation along the small intestine (42). SST probably inhibits pancreatic exocrine secretion by a variety of mechanisms which depend on the species and the type of secretion studied (postprandial vs. interdigestive secretion, protein vs. bicarbonate secretion): SST may act via inhibition of the release of circulating hormones such as cholecystokinin (CCK) and secretin or via intrapancreatic inhibition of the release or action of CCK. SST may inhibit acetylcholine release from nerve terminals, which express specific SST receptors or directly affect the secretory response of the acinar cells via specific SST receptors by a reduction of intracellular cAMP. SST may also indirectly alter the pancreatic response to a meal by its extrapancreatic effects, e.g., inhibition of gastric secretion, gastric emptying, gallbladder emptying and gastrointestinal motility (43). Octreotide, an analogue with a longer half-life and higher potency, has greatly facilitated the clinical application of SST effects (44). SST peptides may act very differently at different sites, as hormones, paracrine substances, or neurotransmitters. Because of this complexity of action, very little is known about the physiological effects of SST in the gastrointestinal tract. The SST analogue exerts a long-lasting inhibitory action on gastric acid, pancreatic enzyme, bicarbonate secretion, and on bile flow. It also inhibits stimulated intestinal secretion, i.e., the release of neuropeptides from the intestine and pancreas. It can also prolong orocecal transit time and prevent gallbladder contraction. It inhibits absorption of nutrients and exerts inhibitory effects on splanchnic hemodynamics. It is because of these actions that SST has attracted so much attention in the treatment of different gastrointestinal disorders (45).

Gastric acid secretion is precisely regulated by neural (acetylcholine), hormonal (gastrin), and paracrine (histamine, SST) mechanisms. The sti- mulatory effect of acetylcholine and gastrin is mediated via increase in cytosolic calcium, whereas that of histamine is mediated via activation of adenylate cyclase and generation of cAMP. The prime inhibitor of acid secretion is SST. Its inhibitory paracrine effect is mediated predominantly by receptors coupled via guanine nucleotide binding proteins to inhibition of adenylate cyclase activity. All the pathways converge on and modulate the activity of the luminal enzyme, H^+,$K(^+)$-ATPase, the proton pump of the parietal cell. Precise information on the mechanisms involved in gastric acid secretion and the identification of specific receptor subtypes has led to the development of potent drugs capable of inhibiting acid secretion. These include competitive antagonists that interact with stimulatory receptors (e.g., muscarinic M_1-receptor antagonists and histamine H_2-receptor antagonists) as well as noncompetitive inhibitors of H^+,$K(^+)$-ATPase (e.g., omeprazole, lansoprazole). The histamine H_2-receptor antagonists (cimetidine, ranitidine, famo- tidine, nizatidine and roxatidine acetate) continue to be used by lay people for peptic ulcer disease since they are available without prescription and are effective in preventing relapse. Nonetheless, histamine H_2-receptor antagonists may cause untoward CNS, cardiac and endocrine effects, as well as interfering with the absorption, metabolism and elimination of various drugs. The dominance of the histamine H_2-receptor antagonists is now being challenged by omeprazole. Omeprazole reaches the parietal cell via the bloodstream, diffuses through the cytoplasm and becomes activated and trapped as a sulfonamide in the acidic canaliculus of the parietal cell. Here, it covalently binds to H^+,$K(^+)$- ATPase, the hydrogen pump of the parietal cell, thereby irreversibly blocking acid secretion in response to all modes of stimulation. The main potential drawback to its use is its extreme potency, which sometimes leads to virtual anacidity, gastrin cell hyperplasia, hypergastrinemia and, in rats, to the development of carcinoid tumors (46).

Intestinal delivery is important not only for drugs that act locally but also for those with systemic activity. In particular, there is considerable interest in the oral delivery of peptides and it is felt that the colon may provide an advantageous absorption site for such molecules. The different targeting mechanisms available to the pharmaceutical scientist to provide site-specific delivery in the gastrointestinal tract are now being appreciated. Delivery systems and targeting agents, which are being developed for the delivery of drugs, may also be exploited for the delivery of vaccines, since many of the delivery problems are common to both areas (47).

Management of Constipation

Although constipation is rarely found in patients receiving enteral feeding it is nonetheless important to recognize that fecal impaction, bowel distention or stenosis can complicate the feeding effort. The diagnosis of constipation is based on history, physical examination, and laboratory tests (48). Constipation is a collective term for different manifestations of different etiology, pathology and treatment. It can be a symptom of organic disease or may disclose a colonic or anorectal functional disorder of unknown etiology – this is called chronic idiopathic constipation (CIC). CIC can be due to colonic or anorectal dismotility. The latter presents as rectal inertia or outlet obstruction, which is characterized by excessive straining although stools are soft and bulky. The treatment of CIC is problematic and controversial. However, the patient should be given the chance to try pharmacological treatment at the start before embarking on surgery. Biofeedback may be helpful, especially in outlet obstruction constipation. Sphincter myotomy and myectomy, partial rectal resection and colec- tomy have been used, with variable results. Medical treatment with a fiber-rich diet or orally or rectally administered laxative agents may be indicated in the treatment of constipation, especially when a cause can not be identified. While long- term fiber therapy is safe, it is important to stress that the untoward effects, which may result from laxative abuse, could be greater than those of constipation (49).

The treatment of constipation with intermittent use of laxatives is relatively safe. Bulking agents may diminish absorption of some minerals and drugs, but this is not usually clinically significant. The chronic ingestion of stimulant laxatives has been blamed for the development of the "cathartic colon", but there are no definitive studies which have demonstrated this. Senna would appear to be the stimulant laxative of choice during pregnancy and lactation. Bisacodyl is the polyphenolic derivative of choice. Lactulose, sorbitol, or lactilol rarely cause significant adverse effects. Magnesium salt laxatives and phosphate enemas can cause serious metabolic disturbances in babies and young children. Liquid paraffin, as indicated earlier in this discussion, is contraindicated if there is a risk of aspiration. Interference with the absorption of fat soluble vitamins would not appear to be clinically significant. Docusate sodium may potentiate the hepatotoxicity of other drugs, but reports of this are rare. The role of cisapride in constipation has not been established.

Management of Diarrhea

Treatment of diarrhea should be directed to the cause. A randomized, double-blind, placebo-controlled trial of patients on tube feeding was performed to uncover the etiologies for diarrhea (>200 g of stool, or three or more liquid stools, in any 24-h period). Factors other than tube feeding, mainly drugs administered through the tube were found to be responsible for decreased transit time (50). Lactobacillus treatment did not alter the risk of diarrhea. Diarrhea occurred more commonly in tube-fed patients who had low serum albumin levels and had been treated with antibiotics for long periods, but these associations were generally not causal. Hypertonic feeding formulas are not associated with increased risk of diarrhea. It was concluded that most cases of diarrhea in tube-fed patients were caused by factors extraneous to the tube feeding.

Excipients in pharmaceuticals usually are considered inert, and may be overlooked in the differential diagnosis of diarrhea. Sorbitol-containing medicinal liquids are capable of inducing osmotic diarrhea. A total of 129 products (98 chemical entities) were reviewed (51). Fifty-four (42%) of the products examined contained sorbitol. The frequency of sorbitol presence by liquid type was: solutions (33%), suspensions (43%), syrups (59%), elixirs (43%), concentrates (67%), drops (33%), tinctures (none), and emulsions (none). The percentage of listings indicating the presence of sorbitol was: manufacturer's product information (79%), Facts and Comparisons (52%), and American Hospital Formulary Service Drug Information 91 (13%). Only three of the 54 products had the exact sorbitol content stated in any source.

Antidiarrheal drugs are second line drugs whose use is aimed at minimizing inconvenience and discomfort. No antidiarrheals should be recommended for children under 4 years of age. Loper- amide is the drug of choice in older children and adults. The atropine component of diphenoxylate/ atropine combinations can cause significant adverse effects. Bismuth salicylate is an inconvenient treatment for travelers' diarrhea, as large frequent doses of the liquid formulation are needed. Some bismuth can be absorbed and there is the potential to cause encephalopathy. Octreotide, methy- sergide, and cholestyramine have roles for specific causes of diarrhea. Octreotide is effective in high output states from the small or large bowel, with few adverse effects. Finally, Clonidine may have a role in the treatment of chronic diabetic diarrhea (52). The clinician must always be aware of decreased absorption of nutrients and medications when agents that are used that increase bowel transit. For example, octreotide may be indicted in organ rejection if immunosuppression agents are not absorbed.

Drug Administration and Bioavailability

Drug or nutrient bioavailability is estimated by measuring increases or decreases in the k_a (rate of absorption) or F (amount absorbed). Gastric emptying is delayed with oral and intravenous lipid. As a rule, the longer the time in stomach, the better F in the small intestine (if the drug is not acid labile); the less the ionization, the better the absorption; and medications or foods with pKa's (pH at which 50% of a substance is ionized) of 3-8 will be affected by the gastrointestinal pH (gastric pH=1-2; colonic pH= 6-8). Duodenal pH is not related to the gastric pH in either fed or fasted states. Other effects on absorption include extensive enzymatic metabolism and presystemic metabolism (First Pass Effect). Specific amino acids at the absorption sites may be needed to optimally absorb the medication. Active transport moieties can be affected by agents that disrupt normal cell metabolism (i.e., NaF which inhibits energy to the active transport system). Villous atrophy (isoniazid, aspirin, chloramphenicol), radiation (digoxin), celiac disease (propranolol), and complexation (ciprofloxacin) are still other influences on drug absorption (53).

The hypertonicity of liquid medications must be evaluated in conjunction with the required dosage volume. Some medications require a minimal dosing volume and can be adequately diluted in gastric fluids or tube-flush volumes to a tolerable osmotic load. Other

medications such as dipheno- xylate, loperamide, and paregoric have a pharmacologic influence on motility and can be administered undiluted into the small bowel. Still others can require dilution to a final volume of 4 to 10 oz to reduce osmolality to a level tolerable by the gastrointestinal tract. Bolus administration of a large volume of medication is impractical for many patients, especially if it must be administered three or four times a day. For these patients, an alternate route of drug administration is often preferable. In some instances, the iv. route is most appropriate. In others, crushing the appropriate oral form, mixing it in a slurry with a suitable diluent, and administering the slurry through the feeding or naso- gastric tube can be an acceptable alternative. Regardless of the method of drug delivery, one must be cognizant of the limitations of the administration strategy, the potential for complications that can result from the administration of a medication by the enteral route, and alternative means of medication administration, should complications ensue. A vast number of pharmaceutical products are marketed in a wide array of dosage forms. For these reasons, a pharmacist or other knowledgeable healthcare provider should be consulted for information regarding product availability, bioavailability, compatibility, and potential for drug-nutrient interactions when drugs are given in conjunction with enteral feeding (54).

Absorption from the gastrointestinal tract is a first-order process described by its rate and extent. Gastrointestinal surgery changes the anatomy of the gastrointestinal tract and alters important variables in the absorption process. In the wake of procedures, which diminish small bowel surface area, the extent of absorption of phenytoin, digoxin, cyclosporin, acyclovir, hydrochlorothiazide, and certain oral contraceptives is reduced. The underlying cause of the reduction is unknown. When gastric emptying time or pH is altered by surgery, the rate of drug absorption appears to be reduced. However, it is not clear which variable is more important in determining therapeutic effects. The effects of celiac and inflammatory bowel diseases on the distribution and clearance of drugs must be considered before attributing abnormal serum concentrations of drugs to malabsorption. Gastrointestinal disease may slow gastric emptying and delay the complete absorption of drugs when their rate of absorption depends on gastric emptying time. Other inflammatory gastrointestinal diseases such as graft-versus-host disease of the intestine, Behcet's syndrome and scleroderma involving the gastrointestinal tract may directly reduce absorption of drugs such as cyclosporin, amitripty- line, benzodiazepines, anticonvulsants, paracetamol (acetaminophen) and penicillamine. Gastrointestinal diseases, which alter intestinal pH, affect the absorption only of drugs with limited water solubility and pH-dependent dissolution such as ketocon- azole. Clinicians should be aware of the variable absorption seen after gastrointestinal disease as well as surgery and monitor their patients accordingly (55).

Since many patients with a wide variety of diseases are nowadays stimulated to adopt a physically active lifestyle, the question of the influence of exercise on the pharmacokinetics of drugs has become more and more relevant. It is also not uncommon to have a physical therapist or occupational therapist providing range and motion exercises to bedridden patients, which can move both nutrients and medications to target sites up to thirty times faster. Because exercise influences a large number of physiological factors that also determine the pharmacokinetics of drugs, including hemodynamics, metabolism, pH, temperature and gastrointestinal function, it can be expected to have an effect on the pharmacokinetic parameters (absorption, distribution, elimination) of certain agents. However, only a very limited number of studies has been directed towards this issue, and only a very few drugs have been studied. Nevertheless, it is clear that exercise does influence the pharmacokinetics of certain drugs, although the magnitude and direction of the effects vary. This is not surprising in view of the widely differing physicochemical properties of drugs, the many possible, often opposing effects of exercise on the parameters affecting drug pharmacokinetics and the different types of exercise performed. The chance of a clinically relevant effect of exercise on the pharmacokinetics of a particular drug is largest in those with a steep dose-response curve, a narrow therapeutic range, a need for continuity of therapeutic effectiveness and a relatively short half-life, in combination with intensive exercise of long duration. If untoward drug effects occur during or after exercise, a change in the pharmacokinetics of the drug related to the exercise should be seriously considered as a possible cause (56).

Administration of medications to patients with nasogastric tubes has traditionally been done in a bolus fashion. An alternative, that should generally be avoided, is to admix the medications to the continuous drip enteral feeding (with subsequent continuous administration). The addition of theophylline, phenytoin suspension, or methyl- dopa, however, to three enteral products (Ensure®, Ensure Plus® and Osmolite®, all made by Ross Products Division, Abbott Laboratories, Columbus, OH, USA), cannot be recommended (57).

Phenytoin is, perhaps, of most concern with regard to interaction and therapeutic impact. Much has been written about proposed phenytoin administration plans. Inadequate drug plasma levels have been associated with the administration of phenytoin with enteral feedings through nasogastric tubes. It is demonstrated in this study that loss of phenytoin to tubing is a function of pH. Nonionized phenytoin is irreversibly bound to nasogastric tubing from solution at the pH of enteral nutrient solutions while this is not the case for anionic phenytoin in unbuffered water or saline. The sodium salt converts to practically insoluble phenytoin in the gastrointestinal pH range of 1 to 8. Due to such a conversion inside or at the surface of slow-release dosage forms, the release of drug in this pH range was incomplete. Although several phenytoin sodium products might have similar dissolution rates in water, the extents of drug release under gastrointestinal pH conditions (pH 1-8) could differ greatly, thus supporting the FDA recognition that the similarity in dissolution profiles in water does not assure that the products are bioequivalent. The reported lower steady-state level of phenytoin in human plasma following oral administration of a slow-release dosage form may be related to incomplete drug release (58).

Finally, guidelines for diet planning and counseling of patients on monoamine oxidase inhibitor (MAOI) drug regimens are widely available. Small amounts of normally

harmless pressor amines in foods can lead to a hypertensive crisis, which is often termed the "cheese reaction". Initial recognition of the problem led to reduced usage of MAOIs and overzealous food restrictions. Recently, confidence in handling such reactions and in MAOI usage has increased. MAOIs treat anxiety and depression by supposedly inhibiting the inactivation of neurotransmitters. A side effect is the concurrent failure to inactivate the potent vasopressor amine, tyramine. Consumption of 6 mg of tyramine may produce a mild crisis whereas 10 to 25 mg may produce severe headaches with intracranial hemorrhage and its sequelae. Any food rich in aromatic amino acids can become high in tyramine if aging, contamination, prolonged storage, or spoilage occurs. Rational guidelines for dietary counseling in MAOI usage include: keep tyramine intake below 5 mg, begin diet counseling before drug therapy, monitor patient compliance, recommend preparation and consumption of only fresh foods, and continue the diet four weeks beyond drug therapy (59).

The many medicinals that have been investigated with regard to the issue of enteral formula interaction is much too lengthy for this review. However, the more popular medications that are being investigated include quinolones (60-70), digoxin (71-76), and omeprazole (77,78). Evaluation of their interaction with enteral regimens present a formidable challenge to the clinician.

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