Clinical practice review

Nutrition in the Critically Ill Patient: Part III. Enteral Nutrition

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ABSTRACT

Objective: To review the human nutrition in the critically ill patient in a three-part presentation.

Data sources: Articles and published peer-review abstracts and a review of studies reported and identified through a MEDLINE search of the English language literature on enteral nutrition.

Summary of review: Enteral nutrition is indicated in the critically ill patient when there is an inability to ingest adequate nutrients by mouth and where the gastrointestinal tract is otherwise normal. The commonly used polymeric feeding solutions provide a mixture of nutrients similar to that encountered in the normal diet, usually as an iso-osmolar low residue solution. Because lactose intolerance may be encountered during critical illness, most formulations are lactose free. Special glutamine formulations and immune enhancing enteral formula (e.g. enriched with Ω fatty acids, arginine and ribonucleic acids) have been used in critically ill patients. However there have been few studies to indicate that these diets are of greater benefit compared with normal enteral formulations.

The daily nutritional requirements are often not met in critically ill patients largely due to delayed gastric emptying or diarrhoea. Prokinetic agents, special formulations containing fibre and probiotics, have been used in an attempt to improve the tolerance to the formulations, although there have been no comparative studies that allow firm recommendation to be made. In general, a standard enteral solution is usually prescribed first and instilled into the stomach using a fine bore nasogastric tube. If gastric emptying is delayed prokinetic agents are tried before a transpyloric tube or enterostomy tube feeding is considered.

Conclusions: Nutritional requirements for the critically ill patient should be delivered enterally in patients who have a normally functioning gastrointestinal system. A standard formulation is usually prescribed and instilled into the stomach using a fine bore tube. If gastric emptying is delayed prokinetic agents are tried before a transpyloric tube or enterostomy tube feeding is considered. Diarrhoea caused by enteral pathogens may require specific treatment. If pathogens are excluded then fibre and probiotics may be considered. Motility reducing agents (e.g. opiates) may cause abdominal bloating. (Critical Care and Resuscitation 2003; 5: 207-215)

Key words: Nutrition, parenteral nutrition, enteral nutrition, critically ill

Short term starvation in normal hospital patients, in the order of several days, has not been shown to adversely affect outcome. In critically ill patients, however, normal feeding may not be possible for many days or weeks and delays in commencing nutrition may lengthen hospital stay. In certain subsets of patients (e.g. burns, renal failure, head injury), the early institution of feeding has a positive benefit. In one recent review of 15

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prospective and randomised studies, enteral feeding within 36 hours of ICU admission resulted in a decreased infection rate and a reduction in length of stay by 2.2 days.  

Nutrition can be administered enterally or parenterally. Parenteral nutrition has been discussed in an earlier review. This article will consider the indications, provision and problems encountered with enteral nutrition.

**Indications**

Tube feeding is indicated when there is an inability to ingest adequate nutrients by mouth and where the gastrointestinal tract is otherwise normal. While enteral nutrition is often associated with fewer complications, reduced sepsis, requires less monitoring and is cheaper than parenteral nutrition, it has not yet been shown to be associated with a reduction in mortality when compared with parenteral nutrition.

It has been suggested that part of the reduced sepsis seen with enteral nutrition, compared with parenteral nutrition, may be due to preserved gut mucosa as villous atrophy can be demonstrated when enteral nutrition is not maintained. This is associated with atrophy of Peyer’s patches within the gut and gut associated lymphoid tissue (GALT). Studies in animals have shown bacterial translocation across such mucosa, with resultant portal bacteraemia. Heavy reliance is then made upon the immune function of Kupffer cells within the liver to control the bacterial load. Without up-regulation of such immune function from the atrophic GALT, it is postulated that systemic bacteraemia can result in sepsis.

Nevertheless, in one study comparing enteral with parenteral nutrition in postoperative gastrointestinal cancer patients without renal, hepatic, cardiac or pulmonary failure, no significant differences were found between the two groups in nutritional, immunologic or inflammatory parameters and that the complication rates were similar.

The disorders in which enteral nutrition are often indicated include those listed in Table 1.

**Table 1. Indications for enteral nutrition**

<table>
<thead>
<tr>
<th>Coma</th>
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<tbody>
<tr>
<td>Dysphagia</td>
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<tr>
<td>Pharyngitis</td>
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<td>Oesophagitis</td>
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<tr>
<td>Bulbar palsy</td>
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<tr>
<td>Upper gastrointestinal obstruction</td>
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<tr>
<td>Pharyngeal carcinoma</td>
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<td>Oesophageal carcinoma</td>
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<td>Burns</td>
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**Feeding tubes**

While large bore naso-gastric ‘sump’ tubes may be used for enteral feeding, their long-term use is often associated with an increased incidence of sinusitis, and fine-bore (internal diameter 1.5 mm) nasoenteric tubes should be used where available.

The tubes are inserted into the stomach, duodenum or jejunum often by the use of a wire stylet, and their position is confirmed both clinically (e.g. a 20 mL bolus of air is inserted into the tube while listening over the gastric fundus), radiologically or even by capnometry. Post-pyloric placement of the tube may be performed using fluoroscopy, endoscopy, or using an electrocardiogram trace or blindly with an infusion of erythromycin (3 mg/kg) and confirmed by demonstrating high amplitude and low frequency (3/min) gastric electromyogram waves changing to low amplitude high frequency (11 - 13/min) duodenal electromyogram waves, or following gastric air sufflation (to open up the pyloric outlet and stimulate gastric contraction) and tube rotation (‘cork-screw’ technique).

The latter technique has a 75% - 90% success rate and involves placing the patient in the supine position and rotated 45° onto their right side. The stomach is emptied using a nasogastric tube which is then removed. A 10 - 12 French weighted feeding tube containing a metal stylet is inserted into the stomach. The stylet is removed, bent at an angle of 30°, approximately 2 - 3 cm from the end, and reinserted into the feeding tube. The bend allows the tip of the tube to ‘hook’ the pyloric outlet during tube rotation and advancement. A 50 - 60 mL syringe is used to pump 10 mL/kg of air into the stomach (500 - 800 mL of air in an adult). Following insertion of air into the stomach the feeding tube is rotated using the 60 mL syringe attached to the proximal end of the feeding tube and slowly advanced in short 4 - 5 cm bursts, until the tube is inserted to a length compatible with small bowel placement (approximate distances in the adult being nose-to-cardia 45 cm, stomach 55 cm, pylorus 65 cm, duodenum 75 cm, small bowel 85 - 90 cm). The tube is taped in place and its position is confirmed using aspiration (small bowel fluid the aspirate is bile with a pH >7; stomach aspirate has a pH < 4), auscultation with insertion of 20 mL air (if the tube is in the stomach the bubbling heard loudest over the upper left quadrant, if the tube is in the duodenum the bubbling is heard best over the midline radiating to left upper quadrant, if the tube is in the jejunum, bubbling is heard best over the right upper quadrant and radiates to the left flank area) or an abdominal X-ray.

If the patient requires enteral access for longer than 1 month then gastrostomy, duodenostomy or jejuno-stomy tubes may also be used, and are inserted either percutan-
Feed formulae

The commonly used polymeric feeding solutions provide a mixture of all nutrients similar to that encountered in the usual diet, usually as an iso-osmolar low residue solution (Table 2). To reduce the solution’s osmolality, glucose is replaced by glucose polymers. Because lactose intolerance may be encountered (often acquired because of impaired gut integrity during critical illness), lactose is often excluded from these formulations.

The elemental diets differ from the standard polymeric feeding solutions by containing oligosaccharides, oligopeptides, amino acids and medium-chain triglycerides and therefore are able to be absorbed without further modification by gastrointestinal fluids.

Table 2. Listed composition of enteral tube feeding diets

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<tr>
<th></th>
<th>Vol (mL)</th>
<th>Carbohydrate (g/L)</th>
<th>Protein (g/L)</th>
<th>Fat (g/L)</th>
<th>Na⁺ (mmol/L)</th>
<th>K⁺ (mmol/L)</th>
<th>Osmol (mosmol/L)</th>
<th>lactose (g/L)</th>
<th>fibre (g/L)</th>
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<td>16</td>
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<td>36</td>
<td>375</td>
<td>-</td>
<td>4.2</td>
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* low carbohydrate, high fibre (for glucose intolerance), ** high protein, high carbohydrate (for trauma), *** high medium chain triglyceride formulation (for fat intolerance), † high fat, low carbohydrate (for respiratory failure), †† low volume, low sodium, low potassium (for renal failure), ††† glutamine enriched (14.2 g/L), ‡ arginine, fish oil and RNA enriched (to enhance immune function), HN = higher nitrogen, g = grams of powder
These ‘predigested’ mixtures are often used in malabsorptive states (e.g. in patients who have short-gut syndrome or exocrine pancreatic insufficiency). Peptides are absorbed faster than their equivalent amino acids and are a better nitrogen source in the elemental diet. Lipisorb® contains a high content of medium-chained triglycerides.

**Hypercatabolic states**

Many critically ill patients, such as those with burns or sepsis, have hypercatabolic states. The metabolic response to sepsis is different to that seen in starvation. The normal response is one of glycogenolysis and glycolysis for the first twenty-four hours. Protein is then the substrate for gluconeogenesis with lipolysis providing acetyl moieties for oxidative phosphorylation. This is associated with a reduction in basal metabolic rate. Over the next few days to weeks, vital organs switch to the metabolism of ketone bodies. In hypermetabolic states, this adaptive process does not occur and there is no decrease in metabolic rate. Proteolysis and gluconeogenesis continue, and a state of prolonged negative nitrogen balance occurs. Hyper-alimentation, with energy provision in excess of demand does not affect this negative nitrogen balance.

Glutamine plays an important role in hepatic gluconeogenesis. It is one of the most abundant amino acids, constituting up to 60% of free skeletal muscle intracellular amino acid. During times of stress, a net flux of glutamine from muscle to splanchnic areas has been shown to occur, and glutamine requirements increase during acute illness. In addition to gluconeogenesis, glutamine acts as a nitrogen donor for DNA and RNA synthesis. It may also have important effects in mediating immune function. While special glutamine formulations have been used in critically ill patients, there have been few studies to indicate that these diets are of greater benefit compared with normal enteral solutions. In one study of critically ill patients, where glutamine-enriched enteral tube feeds were compared with standard low-glutamine tube feeds, skeletal muscle catabolism (as assessed from the arterial plasma phenylalanine/tyrosine ratio) was reduced by day five in the glutamine-enriched group compared with the low-glutamine group, although there was no increase in the plasma glutamine (due to splanchnic conversion of glutamine to alanine with some conversion to arginine and citrulline) and no difference in the nitrogen balance (c.f. parenteral glutamine). In another study of critically ill trauma patients, five days of glutamine-supplemented enteral nutrition was associated with a lower incidence of pneumonia, sepsis and bacteraemia when compared to a control (i.e. low-glutamine enteral nutrition) group. Other amino acids, particularly tyrosine and cysteine may become conditionally essential in times of stress.

The use of growth hormone has been shown to limit the nitrogen loss, stimulate protein synthesis and reduce the requirement for dietary protein, allowing lower energy requirements, which can be given predominantly as carbohydrate. One prospective, randomised, controlled study in 12 adult home parenteral nutrition dependent patients with small bowel syndrome (remnant length 48 ± 11 cm) who were on an unrestricted hyperphagic diet, low-dose growth hormone (0.05 mg/kg/day) for two three week periods, separated by one week, increased intestinal absorption of nitrogen, carbohydrates and fat. However, growth hormone has been associated with increased mortality in intensive care patients. This may be due to impaired glycemic control. In a small, but well conducted study in paediatric burns patients, the provision of high carbohydrate feeding was shown to result in improved catabolism, compared with a diet rich in lipid. Nevertheless, caution is required with high glucose loads, as poor glycemic control has also been associated with worse outcome in critically ill adults.

**Immunonutrition.** In addition to gluconeogenesis, glutamine is utilised at high rates by lymphocytes for the synthesis of nucleic acids. Indeed, lymphocyte and macrophage proliferation has been shown to be dependent upon glutamine concentration in vitro. Glutamine is a precursor for glutathione. T cells have been shown to have diminished glutathione in patients with acquired immunodeficiency syndrome (AIDS), and compounds which can replenish glutathione have been suggested to improve T cell function in vitro.

Triglycerides are the substrate for phospholipase A<sub>2</sub>, which cleaves arachidonic acid. Arachidonic acid can be further metabolised by cyclo-oxygenase to a variety of inflammatory eicosanoids such as prostaglandins, leukotrienes and thromboxanes. Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) can suppress immune function, and is present at high concentration in burns patients. Lipids rich in ω-6 polyunsaturated fatty acids provide such precursors. Omega-3 fatty acids have been shown to block PGE<sub>2</sub> production as well as that of thromboxane A<sub>2</sub>. In the experimental model, lipid infusions enriched with ω-3 fatty acids (e.g. fish oils) suppress the generation of pro-inflammatory cytokines by mononuclear leukocytes and are amplified during ω-6 lipid infusions. Enteral feeds containing glutamine, arginine, omega-3 polyunsaturated fatty acids and nucleic acids are commercially available as ‘immune enhancing’ feed preparations.

A prospective, multicentre, double-blind, randomised controlled trial in patients with acute respiratory distress syndrome found that, compared with a standard isonitrogenous enteral diet, a low-carbohydrate, high-fat
enteral diet containing fish-oil (with eicosapentaenoic acid), borage oil (with γ-linolenic acid), extra vitamin E and ascorbic acid and added L-carnitine, taurine and β-carotene (i.e. ‘immunonutrition’), had reduced the requirement for mechanical ventilation, decreased new organ failures and intensive care unit stay, although there was no significant difference in mortality.27 While 12 of the 13 currently reported prospective randomised trials comparing an immune enhancing enteral formula (e.g. enriched with ω3 fatty acids, arginine and ribonucleic acids) with standard formula diets in preoperative or trauma patients reported improved outcomes (e.g. reduce the length of stay, number of acquired infections, etc), overall mortality was not affected.28,29

In critically ill patients with sepsis, enteral immune enhanced diets, when compared with parenteral nutrition, have been associated with an increase in mortality, with one prospective multi-centre, randomised controlled trial being abandoned at the first planned interim analysis.30,31 Also another multicentre, prospective, randomised, controlled trial found that immunonutrition increased mortality in critically ill patients with pneumonia compared with an isonitrogenous and isocaloric control diet.32

Organ failure

In patients who have respiratory failure, preparations are available with high lipid content and low carbohydrate composition. Pulmocare®, for example, is a 1.5 kcal/mL feed which provides 56% of calories from fat, with only 28% of calories derived from carbohydrate. Metabolism of lipid evolves less carbon dioxide than glucose metabolism. Such feeds are marketed to reduce carbon dioxide retention and whilst this is biochemically true, the difference in CO₂ evolution is not likely to significantly change the outcome of patients with end-stage respiratory disease.

Special formula have also been suggested for patients with hepatic and renal failure and although low sodium and low potassium mixtures may be useful, the effects of an alteration in fat, carbohydrate and protein ratios have not been shown to be superior to standard preparations.

Enteral feed administration

The enteral nutrition solution is usually instilled continuously through a nasoenteric tube, using a pump or gravity feed. Starter regimens in which enteral feeding is initiated with a low flow rate or diluted formula, which is then increased to the prescribed feed over a 3 - 4 day period to minimise possible gastrointestinal side effects,33 have not altered the incidence of side effects when either polymeric feeding solutions34,35 or elemental diets35,36 are prescribed.

While the advantages of the enteral route compared with the parenteral route for the delivery of nutrition during critical illness are generally accepted, the timing of nutrition support remains controversial. Enteral feeding is generally administered within 2 - 5 days after injury. However, very early enteral feeding (e.g. 4 - 8 hr after injury, particularly when jejunal instillation can be performed) has been used in some centers with benefit.37

With one systematic review of early enteral feeding in seriously injured patients reporting fewer infections and a shorter hospital stay (although no significant difference in mortality).38 Post-pyloric feeding is generally considered if there is anatomical gastric outlet obstruction (such as duodenal oedema associated with pancreatitis, aortic aneurysm repair or superior mesentric artery syndrome), or if there are persistently high gastric residual volumes in the presence of an otherwise normal gut.

Impaired gastric emptying is often seen in the critically-ill patient and contributes to high residual volumes. Causes are multi-factorial and include sepsis, head-injury, sedative agents (particularly opioids), catechol requirements, anatomical reasons, electrolyte abnormalities and drugs (e.g. anticholinergeric agents). Pharmacological agents may be used to improve gastric emptying (see later), reducing the requirement for post-pyloric feeding. Whilst post-pyloric feeding has been associated with lower gastric volumes, and therefore presumed improved caloric intake, a recent multi-centre randomised single-blind prospective study showed no difference in feeding duration, ICU length of stay, incidence of sepsis, incidence of pneumonia, or mortality between gastric and jejunal feeding.39 In another randomised study comparing nasojejunal feeding and nasogastric feeding, there was better tolerance of feed for those patients in whom feeding was post-pyloric, though this was not statistically significant. Sepsis rates between the two groups were similar.40

Other randomised studies have reported no benefit from transpyloric feeding when compared with gastric feeding,41 and recent reviews of the early enteral feeding studies conclude that the benefits of fewer infections and shorter hospital stay have not been supported by the data.42,43

While, some studies have reported that reflux, aspiration and infection rates could be reduced by placing the patient in a semi-recumbent position,44,45 there is in general little data on the effects of patient position on enteral feeding. In one small cross-over study, there was no difference in gastric residual volume in patients fed whilst in the supine or prone positions.46

Prokinetic agents

A variety of pharmacological agents to improve gastric
emptying in critically ill patients have been used, including:

Metoclopramide. Metoclopramide is a dopamine antagonist that prevents the inhibitory effects of dopamine on gastrointestinal contraction. It also sensitises the gut to acetylcholine, the major neurotransmitter propagating the myoelectric complex, and has been shown to improve gastric emptying. The dose usually ranges from 10 mg 4 - 6 hourly.

Cisapride. Cisapride is a 5-hydroxytryptamine agonist which activates intrinsic sensory neurones and initiates peristalsis. While oral cisapride (10 mg 6-hourly) increases gastric emptying in the critically ill patient and can be used to improve enteral feeding tolerance, in some countries it has been withdrawn because of its proarrhythmic side effects. The proarrhythmic effect may also be enhanced by drugs that compete for the cytochrome P450 mixed-function oxidase system involved in the metabolism of cisapride (e.g. erythromycin, ketoconazole).

Erythromycin. Erythromycin is a macrolide antibiotic that activates enteric motilin receptors, potentiating the myoelectric complex of proximal bowel, resulting in gastrointestinal smooth muscle contraction. Erythromycin (250 mg 6-hourly) has been reported to improve gastric emptying of enteral nutrition in acutely ill patients, as well as facilitating feeding tube placement within the small bowel. Most studies, however, suffer from having only small patient numbers. Erythromycin also has proarrhythmic side effects.

Naloxone. Opioid receptors within the myenteric plexus inhibit descending pathways and prevent smooth muscle contraction. Opioid sedation, often used in intensive care patients, is associated with impaired gut motility. Recently, a small study of predominantly neurosurgical patients, evaluated the opioid antagonist naloxone given enterally on enteral feeding and pneumonia rate. Gastric residual volumes were less in those patients receiving naloxone and pneumonia rates were significantly lower.

Nevertheless, many studies that report beneficial effects of prokinetic agents compared with placebo often enrol small numbers of patients. As there are no studies that have directly compared the different agents, and as differences in study methodology make it difficult for comparisons between studies to be made, no recommendations can be made concerning the best motility agent.

Even with the use of prokinetic agents, delayed gastric emptying in critically ill patients is often the main reason for an inability to achieve the desired daily nutritional intake, with some studies reporting, in practice, that patients typically receive only 2/3 of their estimated daily requirements.

Dietary fibre
‘Fibre’ is a complex group of plant substances, which resist hydrolysis within the digestive tract. Polysaccharides, oligosaccharides, cellulose, pectins and gums are some of the diverse compounds which can be classified as ‘fibre’. The different fibre types can loosely be classified into soluble and insoluble fibres, which have different effects within the gut.

Soluble fibre, such as that found in oat bran, forms a gel when combined with water within the stomach and small bowel. This results in delayed gastric emptying and a decreased small bowel transit time, decreasing the glycaemic index of food, resulting in a slower, more sustained rise in blood glucose and improved blood glucose control.

Insoluble fibres, such as wheat bran, have a greater effect in the colon, with little fermentation occurring within the gut. They result in water absorption and bulking of stool, with beneficial effects in combating both constipation and diarrhoea. Recently, enteral feeds such as Jevity®, Fibresource® and Nutrison multifibre® have become available which contain both soluble and insoluble fibre and have been suggested to manage enteral feed associated diarrhoea.

Probiotics
Diarrhoea can be a common occurrence in the critically ill and can have adverse effects including abnormal fluid loss, electrolyte disturbance and skin disruption with pressure sores. As there is an association between diarrhoea and antibiotic use, due to alterations in normal gut flora, probiotics have been suggested to ameliorate this.

Probiotics are microorganisms (e.g. lactobacilli, yeasts) which have a symbiotic relationship with the host and have beneficial effects on the gastrointestinal tract absorption following their ingestion. They have been used for the management of diarrhoea associated with antibiotic use, traveller’s diarrhoea, gastrointestinal tract infection and inflammatory bowel disease. The exact mechanisms of their beneficial effects have not been fully elucidated, although alterations in the resident gut flora at the endoluminal surface, with increased mucin production preventing pathogenic bacteria reaching and binding to epithelial receptors, are thought to play a role. Modulations of the GALT (with increased immunoglobulin A levels) may also play a role.

In a recent study of intensive care patients who were randomly assigned to receive placebo or the yeast, Saccharomyces boulardii, those who received the yeast in addition to tube enteral feeding, had significantly less diarrhoea.

While probiotics are safe to use in the general population, the confirmation that administration of...
bacteria or yeast to immunocompromised, critically ill patients is without hazard has not yet been evaluated.

In general, gastric feeding should be tried first in critically ill patients who have a normally functioning gastrointestinal system. A standard formulation (see General Table 2) enteral feeding is usually prescribed up to a volume of 80 mL/hr. If the feeding tube is placed into the stomach it is aspirated 2-hourly. If the volume is less than 150 mL this volume is replaced and enteral feeding is continued. If the residual volume is greater than 150 mL, the volume is not replaced and the feed is discontinued for 2 - 4 hours, and is usually recommencing at 20 mL/hr until tolerated (i.e. aspirate no greater than 150 mL at 2 hours) and increased up to the prescribed value (i.e. 40 - 80 mL/hr) in 20 mL/hr increments.\textsuperscript{63} If gastric emptying is delayed prokinetic agents are tried before a transpyloric tube or entero-stomy tube feeding is considered.

**Complications**
The complications associated with enteral nutrition include those listed in Table 3.\textsuperscript{64-66}

<table>
<thead>
<tr>
<th>Table 3. Complications of enteral feeding</th>
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<tbody>
<tr>
<td><strong>Mechanical</strong></td>
</tr>
<tr>
<td>Tube malposition</td>
</tr>
<tr>
<td>Tracheal intubation (pneumonia,</td>
</tr>
<tr>
<td>hydrothorax, pneumothorax)</td>
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<tr>
<td>Intravenous administration of enteric</td>
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<tr>
<td>feeds</td>
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<tr>
<td>Tube trauma</td>
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<tr>
<td>Nasopharyngeal ulceration, sinusitis</td>
</tr>
<tr>
<td>Oesophagitis, erosions, stricture</td>
</tr>
<tr>
<td>Gastric ulceration</td>
</tr>
<tr>
<td><strong>Regurgitation and aspiration</strong></td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
</tr>
<tr>
<td><strong>Nausea, vomiting, cramps</strong></td>
</tr>
<tr>
<td><strong>Gastric dilation</strong></td>
</tr>
<tr>
<td><strong>Hyperglycaemia</strong></td>
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<tr>
<td><strong>Hypernatraemia</strong></td>
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REFERENCES


