CHAPTER THREE

Gastrointestinal obstruction by solidification of enteral nutrition: a result of impaired digestion in critically ill patients

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ABSTRACT

Objective Solidification of enteral nutrition may cause gastrointestinal obstruction with severe complications. The effect of the composition of enteral nutrition on the tendency of casein to coagulate is increasingly acknowledged and new formulas may prevent solidification. To identify patients in need for specific enteral nutrition, we need to know the clinical risk factors for the development of gastrointestinal obstruction by the solidification of enteral nutrition.

Methods The 58 cases summarized in this review were identified through a PubMed search.

Results Critically ill patients have several risk factors, including an impaired digestion, and treatment with medication that interfere with gastrointestinal function. Surgery of the upper gastrointestinal tract is thought to be the most important risk factor, leading to changes in anatomical structure, secretion of digestive enzymes, and neurohormonal function of the gastrointestinal tract.

Conclusion Awareness of risk factors in critically ill patients may help intensivists and surgeons take appropriate measures to prevent this complication. Critically ill patients with an impaired digestion (e.g. Whipple surgery), should be considered for alternative enteral nutrition formulas with non-coagulating proteins or hydrolysed proteins.

INTRODUCTION

Use of enteral nutrition (EN) is a well-established method to provide a complete nutrition with necessary calories and proteins to minimize catabolism, diminish suppression of immune competence and decrease septic complications in the critically ill (1). EN is preferred over parenteral nutrition, because it preserves the intestinal integrity and prevents mucosal atrophy and bacterial translocation (1). There are various routes of access to administer EN, including gastric feeding and jejunal feeding. Surgical patients and critically ill are frequent candidates for jejunal feeding due to their underlying illness and gastro-paresis (2). EN is usually well-tolerated; however, an underestimated complication of tube feeding is the solidification of EN causing gastrointestinal (GI) obstruction. Solidification of EN can lead to serious complications such as small bowel obstruction, mural abscesses, hemorrhages, ulcers, pancreatitis, small bowel necrosis, bowel perforation, and even death (3).

It is increasingly acknowledged that the coagulating properties of EN depend on the composition of the formula. Solidification of undigested milk located in the GI tract, also known as a lactobezoar, was first mentioned in 1959 by Wolf and Bruce (4). Lactobezoars are mainly observed in premature infants. Schreiner ***et al.*** reviewed 665 formula fed infants, and reported that the lactobezoars only evolved from the casein-predominant formulas and not from the whey-predominant formula (5). Another study showed that formulas with hydrolyzed proteins may be better tolerated by infants with gastric emptying problems than intact protein formulas (6). Van den Braak ***et al***. reported that casein-predominant EN had a greater tendency to coagulate than EN containing soy, pea and whey proteins (7).

In our experience a large number of intensivists and surgeons are familiar with the impaction of EN from their own patients. Awareness of this phenomenon and potential risk factors is of utmost importance for diagnosing GI obstruction caused by the solidification of EN. Now that there seem to be new opportunities in selection of the composition of EN to avoid the solidification in patients with an increased risk, it is important to define the predisposing factors. Due to the potential severe complications and limited therapeutic possibilities, we aimed to identify the predisposing factors for development of this complication and to discuss the underlying mechanism.

METHODS

A literature search for reports published from 1948 to 2012 was conducted in the PubMed databases, MEDLINE (1966 - 2012) and OLD MEDLINE (1948 - 1966). The following key words were entered: gastrointestinal obstruction, enteral nutrition, solidification, coagulation, and bezoar. Additionally, a search for GI obstruction by the solidification of EN in critically ill patients and infants was performed. Finally, 58 adult cases reported in 33 articles were identified and are summarized in this review.

SUMMARY OF ALL CASE REPORTS

Solidification of EN in the GI tract was first reported in literature in 1981. From this point on this complication is reported regularly in literature, as illustrated in Figure 1. We found 33 articles describing 58 cases of critically ill patients with GI obstruction due to the solidification of EN

(3, 8-39). A summary of the diagnosis on admission is given in Table 1. The medical history was mentioned in 31 patients and is summarized in Table 2. Fourteen patients had a history of upper GI surgery; 9 patients underwent upper GI surgery upon admission and 5 had a past history of upper GI surgery. The solidification of EN was seen in the esophagus in 44 patients, in the stomach in 1 and in the small intestine in 13. Solidification of EN was more likely to occur in the esophagus when patients were fed directly in the stomach; this was seen in 35 out of 37 patients. Patients fed directly in the small intestine were more likely to develop a GI obstruction due to solidified EN in the small intestine; this occurred in 12 out of 17 patients. In the other 5 cases, the GI obstruction occurred in the esophagus, possibly caused by intra gastric dislocation of the jejunal tube or a tear in the jejunal tube at this level. The location of the tube and the location of the GI obstruction by solidification of EN is summarized in Table 3. In 4 cases, the administration route was not mentioned. Most patients were mechanically ventilated and received medication such as opiates and sedatives that can cause GI motility disorders. Sucralfate, a stress ulcer prophylaxis associated with this complication, (chapter 4.2) was administered in 15 patients.

FIGURE 1. *Timeline of all 33 published articles reporting 58 cases of solidification of enteral nutrition.*

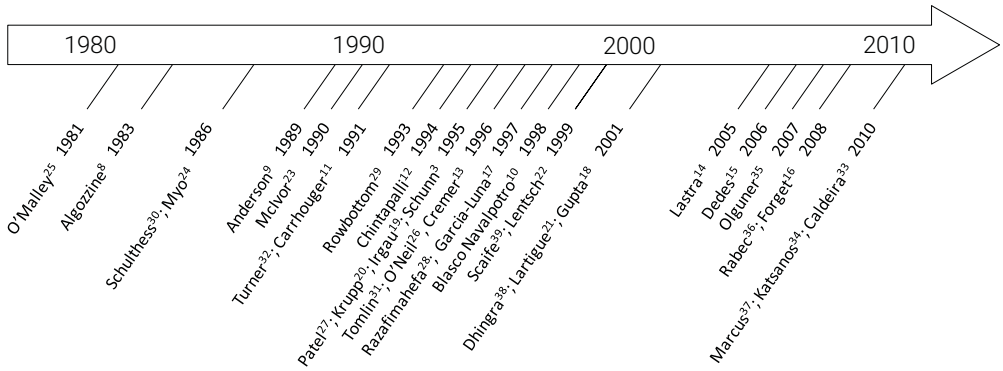

TABLE 1. *Diagnosis on admission for 58 cases of solidification of enteral nutrition in the gastrointestinal tract.*

Diagnosis on admission	n
Surgery	**15**
Upper gastrointestinal surgery	9
Roux-en-Y	5
Subtotal gastrectomy and Billroth II	2
Pancreatoduodenectomy	1
Cholecystectomy	1
Other surgery	6
Hartmann procedure	1
Aorto-bifemorale bypass	1
Coronary bypass surgery	2

Diagnosis on admission	n
Laryngectomy	2
Neurological	**12**
Cerebral haemorrhage	3
Guillain-Barré	3
Head trauma	3
Encephalitis seizures	2
Stroke	1
Other	**29**
Critically ill, nos	8
Respiratory failure	6
Major burns	6
Cardiac arrest	2
Multi trauma	2
Femoral fractures	2
Gastrointestinal bleeding	1
Pharyngeal cancer	1
Microangiopatic haemolytic anemia	1
Toxic epidermal necrolysis syndrome	1
Not mentioned	**1**
TOTAL	**58**

TABLE 2. *Medical history of 58 cases describing gastrointestinal obstruction by solidification of enteral nutrition. Medical history was mentioned in 31 patients; together they had 38 diseases. Seven patients were previously healthy. In 27 cases the medical history was not mentioned.*

Medical history	n
Previous surgery	**5**
Partial gastrectomy	5
Neurological	**4**
Guillain Barre	1
Neuropathy	1
Myasthenia gravis	1
Vascular dementia	1
Other	**29**
Diabetes mellitus	5
Hypertension	5
Chronic obstructive pulmonary disease	3
Coronary artery disease	3

Medical history	n
Renal insufficiency	2
Hiatal hernia	2
Reflux oesophagitis	1
Achalasia	1
Oesophageal stricture	1
Zenckers diverticulum	1
Small cell lung carcinoma	1
Thalassemia	1
Alcohol abuse	1
Wolff-Parkinson White	1
Tuberculosis	1
Previously healthy	**7**
Medical history mentioned for 31 patients	**38**
Medical history not mentioned for 27 patients	

TABLE 3. *Location of the tube and the location of the gastrointestinal obstruction by solidification of enteral nutrition.*

Location	Location of the obstruction		
Location of the tube	Esophagus (n = 44)	Stomach (n = 1)	Small intestine (n = 13)
Stomach (n = 37)	35	1	1
Small intestine (n = 17)	5	-	12
Not mentioned (n = 4)	4	-	-

PRE-DISPOSING FACTORS

Impaired digestion

Surgery of the upper GI tract is thought to be the most important risk factor; it changes both the anatomical structure and the neurohormonal function of the GI tract, and it alters the secretion of digestive enzymes. Examples of pre-disposing upper GI surgeries are the (partial) gastrectomy, pyloroplasty, gastric banding, Roux en Y, and the pancreaticoduodenectomy (Whipple procedure). After pancreatic surgery, reduced production of pancreatic enzyme is predisposing for solidification of EN. Vagotomy, which is often executed during these operations, decreases the receptive capacity of the fundus, reduces the evacuation of indigestible solids, and decreases chlorhydropeptic secretion which impairs digestion (40).

The majority of reported cases of GI obstructions by solidification of EN involve critically ill patients with an alteration in the GI tract; this seems to be a common denominator. The etiology of the altered upper GI motility in the critically ill remains unclear, although several

predisposing factors such as admission diagnosis, inotropic support, sedative agents, narcotics, electrolyte abnormalities, shock, mechanical ventilation, and inflammatory cytokines have been implicated (41). Theoretically, a low cardiac output state, vasopressor use, or mechanical ventilation predisposes alone or in combination for the solidification of EN by splanchnic hypoperfusion. This hypoperfusion may lead to ischemia, reduced bicarbonate secretion, decreased upper GI motility, and acid back-diffusion (42).

Neurological diseases are also associated with this complication. Guillain-Barré affects the bulbar region which could affect oesophageal motility, lower oesophageal sphincter pressure and gastric emptying (8, 9). Traumatic brain injury may cause gastro-oesophageal reflux (GER) and gastroparesis, predisposing for the solidification of EN in the esophagus (16). Spinal cord injury impairs GI motility as a result of interruption of sympathetic outflow. Interruption of the spinal cord above the level of sympathetic outflow to the GI tract disturbs the normal interdigestive antral-duodenal motor coordination and may delay postprandial gastric emptying (43).

Diabetes mellitus and associated gastropathy are also possible risk factors. Gastroparesis is thought to occur in 20-30% of diabetics (44). Dehydration, in renal failure patients or patients with major burns, is also considered to be a risk factor (17, 38).

Medication and interference with gastrointestinal function

Sucralfate is thought to be associated with the solidification of EN. Sucralfate is given as a stress ulcer prophylaxis; it protects ulcers from acid by acting as a barrier. There are no data available on the chemical interaction between EN and sucralfate, but considering its protein-binding properties sucralfate may bind to EN to form insoluble complexes. Physicians should therefore be cautious when sucralfate is administrated in combination with EN.

Assuming that impaired digestion is a major risk factor for solidification of EN in the GI tract, it has been suggested that drugs which interfere with digestive enzymes may contribute to the solidification of EN. Antacids, for example H_2-receptor antagonists, might be involved, due to their role in decreasing the secretion of gastric acid (9). An increased pH influences pepsin, which is a proteolytic enzyme produced by the stomach. Pepsinogen is converted into pepsin in an acid environment, and is inactive when gastric pH is maintained above 6. It is possible that pepsin is less active when H_2-receptorantagonists are administered, causing a lower capacity for pepsin to degrade food proteins into peptides. In our opinion, the digestion and absorption of casein-based EN may be improved by antacid administration. Casein coagulates in an acidic environment such as the stomach, decreasing its digestibility. Maintaining gastric pH above 6 through the use of antacids may result in less coagulation, and may therefore improve digestion and absorption. Coagulation of casein-based EN is further discussed in chapter 6.4.

Drugs can also impair GI motility. There are three main factors that govern gastric emptying and motility: (1) the composition and physico-chemical properties of the ingested meal, (2) neural control, and (3) hormonal control. Drugs can influence neural control and, to a far lesser degree, hormonal control of the stomach. Anticholinergic drugs and adrenergic agonists inhibit gastric contractility and emptying (13). Dopaminergic agents, such as dopamine, are

the most important neurotransmitters involved in gastric relaxation (45). Narcotics, such as opiates, can also influence GI motility. In healthy subjects, even at low dose, morphine markedly inhibits gastric emptying due to enhanced proximal gastric relaxation, increased pyloric tone and increased retrograde duodenal contractions (41). All above mentioned medication is often used in the critically ill. This medication, in combination with the already impaired GI function in the critically ill, might increase the risk of the solidification of EN.

TREATMENT

GI obstruction by solidification of EN can be treated by several modalities, dependent on the location in the GI tract. Therapeutic interventions are summarized in Table 4. In 34 out of 58 cases, the solidified EN was removed in multiple sessions by endoscopic breakdown, combined with suction and flushing with saline, gastrografin, N-acetylcysteine or Coca-Cola®. The mechanism by which Coca-Cola® dissolves the EN is not fully clarified, although it may be linked to its pH of 2.6, due to phosphoric acid (H3PO4), which is close to the pH of gastric juice. This acidification may contribute to the disintegration of the solidified EN. Sodium bicarbonate (NaHCO3) in Coca-Cola® has a mucolytic effect and carbon dioxide (CO2) bubbles penetrate the surface of the solidified EN; this combination may soften the mass, improving digestion. (46) N-acetylcysteine is thought to exert its mucolytic activity on solidified EN by attacking disulfide bonds in mucopolysaccharides (47). Two patients were treated with a pancreatic enzyme and papain, an enzyme with peptidase activity. These enzymes were administered in several sessions through a nasogastric tube (NGT) positioned proximal to the obstruction, which dissolved the solidified EN (18). In 3 patients, no treatment was necessary because the solidified EN encircled the tube and was removed by pulling out the tube. In 3 other cases, the solidified EN disappeared of its own accord when EN was stopped. Endoscopic treatment of the solidified EN was not successful in 16 patients, resulting in surgical interventions varying from enterotomy to partial small bowel resection.

Solidification of EN in the small intestine is a serious problem, resulting in laparotomy in 11 out of 13 cases. Patients can develop a small bowel obstruction and even necrosis of the small bowel when the solidified EN causes high pressure on the bowel wall, which may even result in resection of the necrotic part of the bowel.

Improving GI motility has been mentioned as a possible contributor to the treatment or prevention of solidification of EN in the critically ill. GI prokinetics mentioned in literature are erythromycin, metoclopramide, cisapride and neostigmine (1).

TABLE 4. *Conservative therapy was sufficient in 42 cases; 16 patients needed surgery. NGT, nasogastric tube; TPN, total parenteral nutrition.*

Treatment	n
Endoscopic breakdown and lavage	**34**
Saline	28
Gastrografin and N-acetylcysteine	2
Coca-Cola®	4
Lavage through NGT proximal of obstruction	**2**
Pancreatic enzyme	1
Papain	1
Encircled the tube, removed by pulling out tube	**3**
Resolved spontaneously by starting TPN	**3**
Surgery	**16**
Enterotomy	13
Small bowel resection	3

DISCUSSION

GI obstruction by solidification of EN in critically ill patients is still a clinical entity. However, insight into the potential risk factors and treatment is still lacking. An extensive search of literature revealed 58 cases and we found that this complication is seen exclusively in critically ill patients. Despite the improved formulation of EN during the last decade, this is still a regularly reported complication in literature. In this review, we attempted to identify a common denominator to increase the understanding of this serious condition amongst physicians and hopefully contribute to the prevention of GI obstruction caused by solidification of EN.

Surgery

We recently observed several cases of solidification of EN after pancreatic surgery in our hospital; this resulted in an ileus and in one case, ischemia of 20 cm of the small bowel. Our policy at this moment is to give a hydrolysed EN for 10 days following Whipple surgery. Surgery of the upper GI tract is thought to be the most important risk factor; it changes anatomical structure, as well as the neurohormonal function of the GI tract, and it alters the secretion of digestive enzymes. After major upper GI surgery, e.g. pancreaticoduodenectomy (Whipple procedure), disturbances of intraluminal pH levels may occur due to the lack of acid secretion, which could contribute to solidification of the EN. The remaining portion of the pancreas produces little or none of the enzymes that would normally digest carbohydrates, proteins and fats. A predigested EN with hydrolysed protein should be considered in these patients. Furthermore, an increased flow rate may lead to intraluminal accumulation of EN and solidification may then occur in the absence of intestinal fluid. Therefore, a stepwise approach to reaching required caloric need should be mandatory, especially following Whipple procedures.

Impaired gastrointestinal function

One of the recurrent topics in literature is an impaired GI function. An altered GI motility and digestion may be due to previous surgery, but may also be caused by neurological disease, shock, mechanical ventilation and many of the other previously mentioned pre-disposing factors. This, in combination with medication administered in the intensive care unit (narcotics, sedatives, anticholinergic drugs and dopaminergic drugs) leads to an even more impaired GI motility. Prevention of duodenal ulcers can be realized by H_2-receptorantagonists, but sucralfate is still used in some countries. It is known that simultaneous administration of EN and sucralfate may cause solidification, something that should be taken into consideration when other risk factors are involved.

Location

The location of the GI obstruction by solidification of EN, as mentioned in Table 3, is remarkable. When fed directly in the stomach, the GI obstruction was most likely to occur in the lower third of the esophagus. Several explanations are suggested here. In general, the pH of the stomach is 2 and the pH of the lower third of the esophagus is much higher. The critically ill have predisposing factors for gastroesophageal reflux (GER). NGT's cause mechanical irritation of the mucosa and interfere with normal oesophageal motility and sphincter function. A poorly functioning lower oesophageal sphincter may become even less competent with passage of a NGT. Patients with large-bore NGT also have a higher incidence of GER compared to those with a small-bore NGT (48). When GER occurs, acidified EN reaches the lower third of the esophagus. In one case report by Schulthess et al., the solidified EN was fixed around the NGT, and in section it appeared to consist of several layers, comparable to an onion (30). This suggests that several episodes of GER caused a multilayered EN plug. Another explanation may be polymicrobial colonization of the esophagus with fermentation of the carbohydrate in the EN, which could than have resulted in a local decrease of the intra oesophageal pH. Yeast colonization has also been associated with clogged feeding tubes (49).

When gastric feeding is not tolerated, EN is administered through a nasojejunal tube in the small intestine. The authors wish to emphasize that patients fed directly in the small intestine underwent a Whipple procedure and thus have an altered GI function that should be carefully monitored. An increased flow rate may lead to intraluminal accumulation of EN, and solidification of EN may then occur in the absence of intestinal fluid. The solidification of EN in the small intestine might be attributed to intestinal acid-base levels. GI obstruction by solidified EN in the small intestine may cause major complications such as small bowel necrosis and perforation. The incidence of this complication is not widely known, as few cases have been reported. However, we consider the incidence to be underestimated.

Casein

Suggested causes of solidification of undigested milk in infants were high caloric and casein-predominant formulas. Older formulas showed a great difference to human breast milk. Formulas have now changed to whey-predominant, which resulted in a reported decrease in the incidence of GI obstruction by solidification of undigested milk. Therefore, it is important

to know whether adjusting the composition of EN can also contribute to the prevention of the solidification of EN in adults. EN mainly based on casein tends to precipitate in an acidic environment such as the stomach, a process known as coagulation of casein (37). During the acidification of EN, the solubility of the casein molecules changes, particularly around the isoelectric point (pH 4.6) where the casein micelles coagulate (50). In the stomach, the pH of EN is lowered from ± 7 to ± 2. Casein is insoluble around a pH of 4.6, whereas it again becomes soluble at pH 2. In patients with a (partial-) gastrectomy, the production of gastric acid and pepsin is reduced. The pH in the stomach may possibly remain around 4.6, the point at which casein is the least soluble. The reduced production of pancreatic enzymes following pancreatic resection may possibly contribute to the coagulation of casein based EN.

Van den Braak *et al.* showed that casein-based EN coagulates after artificial gastric digestion, whereas soy, pea and whey protein, described as non-coagulating proteins, do not coagulate after artificial gastric digestion (7). Interestingly, an EN formulation with a combination of casein, soy, pea and whey protein does not coagulate. In our opinion, critically ill patients with an impaired digestion (e.g. after Whipple surgery), should be considered candidates for alternative EN formulas with non-coagulating proteins or hydrolysed proteins.

Fibre

Another factor mentioned in literature in the solidification of EN is the presence of insoluble fibres. Fibres are added to EN to improve GI tolerance (e.g. prevention of diarrhoea and constipation), for glycaemic and lipid control and for their pre-biotic effect (1). Scaife *et al.* presented 4 cases of GI obstruction by solidification of EN enriched with soy polysaccharide, an insoluble bulk fibre.(39) Based on these case reports, guidelines for parenteral and EN recommend avoiding insoluble fibres in all critically ill patients (1). Although essential, Scaife *et al*. do not provide us with information on the protein source used in the EN, which is in our opinion the major contributor to EN coagulation. The impact of fibres on the coagulation of EN has been studied in an artificial gastric model. EN based on non-coagulating proteins enriched with soluble and insoluble fibre does not coagulate after artificial gastric digestion (7); this strengthens our hypothesis that fibres have a minor impact on the coagulation of EN compared to the protein source, e.g. casein. To strengthen our hypothesis, it is important to have more information on the coagulating properties of EN and how fibres can interact with the casein. Therefore, future studies should investigate the influence of soluble and insoluble dietary fibres on the coagulating properties of EN.

CONCLUSION

The current review represents the most comprehensive examination of GI obstruction caused by solidification of EN in critically ill patients to date. Several mechanisms have been described in literature. Critically ill patients may have potential risk factors for solidification of EN, including an impaired GI function. They are also treated with medication that interferes with GI digestion and motility. Awareness of risk factors in critically ill patients may help intensivists take appropriate measures to prevent the solidification of EN. Moreover, considering the composition of EN may also contribute to prevention. EN based on non-coagulating proteins, or hydrolysed proteins, may lead to less complications in critically ill. We conclude that a combination of factors lead to GI obstruction due to the solidification of EN.

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