Nutritional Support in Gastrointestinal Disease

Module 12.1

Compromised Gut

Learning Objectives

- To learn the anatomy of the gastro-intestinal tract;
- To learn the physiology of the gastro-intestinal tract especially with regard to nutrition;
- To learn the consequences of critical illness on the function of the gastro-intestinal tract;
- To learn the causes of disturbances in the balance between intestinal bacteria spp and their effects on the function of the bowel;
- To learn the consequences of anatomical pathology on the integrity and function of the intestinal tract;
- To appreciate the connections between intestinal inflammation and liver disease;
- To learn medical, surgical and nutritional interventions beneficial to the integrity and function of the gut.

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Key Messages

- Metabolic and digestive functions of the intestine reside predominantly in the proximal part of the small bowel (duodenum and jejunum). The distal part of the bowel has especially important functions in the resorption of bile acids and electrolytes. Apart from resorption of water and electrolytes the colon resorbs short chain fatty acids derived from fermentation of soluble fiber;
- The degree of malfunction of the intestine in trauma and diseases depends on the severity of the disease and of the trauma. Several anatomical and functional abnormalities (stenoses, blind loops, pouches, constipation, severe disease) and lead to inflammation and interfere with adequate absorption of nutrients;
- Bacterial overgrowth is an important cause of malfunction of the intestine;
- Compromised bowel (short bowel or and bacterial overgrowth) may have deleterious effects on the liver. This happens in neonates and less often in adults;
- The fat component in parenteral nutrition may induce of aggravate compromised bowel-associated hypertriglyceridemia, cholestasis and steatohepatitis;
- Correction of anatomical abnormalities (stenoses, defunctionalized small bowel segments, stagnant or dilated loops) and activation of the gut by enteral nutrition improves bowel function;
- Immunonutrition may have beneficial effects (Module 7.2).
1. Physiology of the gut

1.1 Anatomy
The length of the GI-tract depends on body size and on the way the intestine is measured. Consequently only a rough estimate can be given for its true length and size. The intestine appears to be substantially shorter than measured at autopsy when measured during surgery when the intestine has a normal muscle tonus. Rough estimates are that the distance from mouth to the entrance to the stomach (cardia) measures 40 cm. At endoscopy the origin of the esophagus is located 15 cm from the oral orifice (teeth) and the end (the cardia) at 40 cm. After resection the 25 cm of esophagus measured at endoscopy shrinks to much less than 20 cm after resection due to its tonus.

The length of the stomach depends on whether it is measured along the minor or greater curvature of the stomach. The measurement is also unreliable when the shape of the stomach is taken into account. The esophagus enters the stomach approximately halfway between the pylorus and the top of the fundus. This is the reason that when the esophagus and the vessels entering the stomach proximally are disconnected the top of the fundus can be brought up all the way to the basis of the oral cavity to bridge the gap arising from resection of the oesophagus. An average estimate of the length of the stomach therefore varies between 25 and 50 cm.

The duodenum derives its name from the fact that in medieval times it was considered to measure 12 fingers, which amounts to roughly 30 cm. This is also dependent on the state of the duodenum and where the transition between the duodenum and the jejunum is located. According to the definition this is at the ligament of Treitz which however not a very clearly defined rather broad attachment to the intestine.

Measurement at surgery is not very well defined but the jejunum and ileum together do not measure more than 4 meters, which is less than generally described. Often mistakenly measures of 6 meters are described but this probably refers to the total length of the GI tract. A sharp transition between jejunum and ileum is not present. Rather there is a gradual decrease in thickness of the small bowel. The jejunum is at least twice as thick and more than twice as heavy per centimetre as the ileum, which is also reflected in its function.

There is a sharp transition between ileum and colon at the ileocecal valve (Valvula Bauhini). The colon and rectum measure approximately 150 cm. The transition between colon and rectum again is not very well defined. The last 15 cm to the anus are usually defined as rectum.

1.2 Physiology
Already in the passage from mouth to stomach important digestion takes place. Saliva contains proteases, lipases and amylases which help to pre-digest the three macronutrients already during its stay in and passage through the stomach. The oral cavity and the esophagus are resistant to hypertonic foods due to their (multi-layered) squamous epithelia. In the stomach and especially in the duodenum the partly solubilized and fragmented food bolus is made isotonic by diluting hypertonic solubilized food components by allowing the passage of water from the mucosal layer into the intestinal lumen. The most important functions of the stomach are that it can contain a large meal with differing composition, which is after predigestion gradually released into the duodenum and that its acidity creates a hostile environment for ingested bacteria or for bacteria from the distal bowel. The duodenum and especially the jejunum are much less resistant against bolus feeding. This is exemplified by surgery induced situations, where after ingestion food immediately reaches the jejunum (postgastrectomy, gastric bypass). This leads to dumping, which forces the individual to stop eating. The symptoms of “dumping” probably arise from the effects of sudden and substantial release of hormones by “dumping” of un-predigested food into the jejunum. This is a major reason why after gastrectomy or gastric bypass patients lose a substantial amount of weight.

Further digestion and subsequent resorption of the macro-nutrients takes predominantly place in the duodenum and jejunum (Fig. 1).
Figure 1 Location and absorption of macronutrients, bile acids, Ca, Fe, Folic acid, vit B12 in different parts of the intestine (Boron/Boulpaep, Medical Physiology, Saunders 2003)

Also intermediary metabolism of amino acids, carbohydrates and lipids is much more active in the proximal small bowel than in the ileum and colon. Especially glutamine degradation and conversion to glutamate, alanine, citrulline and ammonia take predominantly place in the jejunum. Water and electrolytes are in varying amounts released into the lumen and simultaneously absorbed again. Hypertonic solutions are diluted by water secretion into the lumen and absorbed again. Hypotonic solutions are made isotonic by secretion of kations (especially Na) and are subsequently reabsorbed. In this manner, a fluid flux across the GI tract occurs of approximately 8-10 liters. This flux leads in the healthy bowel to the net uptake of the quantity of fluid ingested orally and loss of negligible amounts of fluid in the stools. Absorption of water and electrolytes takes place in the complete small bowel and in the colon, which explains that after resection of substantial parts of the small and large bowel the first components insufficiently absorbed, consist of electrolytes (Ca++, K+, Mg++, Cl-) and water, and not of the macronutrients. Apart from the absorption of water and electrolytes the small bowel and especially the ileum plays also an important role in the re-absorption of bile acids. Loss of bile acids and subsequent shrinking of the bile acid pool diminishes the emulsification of fat in the duodenum and jejunum leading to loss of fat in the stools and fat soluble vitamins and kations like Ca2+ and Mg++ bound to fatty acids. The only vitamin that is significantly absorbed in the ileum is vitamin B12. In the colon the 1000-1500ml of fluid bowel contents coming from the ileum is largely absorbed, producing a solid stool. Net absorption of water and electrolytes in the small and large bowel is largely driven by active ion-pumping of the Na+-K+ pump, which induces transmembrane concentration differences and electro-chemical gradients which drive Na+ linked co-transport of important luminal components including amino acids, glucose, bile acids and others. This process is easily disturbed in infectious or inflammatory states where the electro-chemical gradient across the cell wall of the enterocyte cannot be maintained and where co-transporters and exchangers are internalized, leading to diarrhea (1).

2. Severe inflammatory illness

Severe inflammation or infection has distinct influences on the whole organism, regardless of the location of the infectious/inflammatory focus. Recent views are that inflammatory activity causes opening of tight junctions in the lung, kidney, liver, intestine and other organs which leads to
passage of cells, proteins and fluid into the interstitium (2, 3). This process interferes with normal digestion and absorption of water and electrolytes. These processes of absorption depend to a high degree on active ATP-driven ion-transport, which is disturbed in severe inflammatory states (1). Disturbed ion-transport also interferes with several other crucial functions like bile secretion but similar disturbances also occur in the kidney. As a consequence bile secretion and electrolyte/bile acid handling in the intestine (and other functions) are disturbed, leading to loss of fluid and electrolytes in fluid stools.

This also happens in the presence of inflammatory masses due to infectious foci in the abdomen like appendicitis, Crohn’s disease, diverticulitis. The healthy bowel, walling off the infectious organ or abscess exhibits “collateral” inflammation in turn interfering with active water and electrolyte transport. This explains the intra-luminal fluid levels encountered around the inflammatory mass on plain abdominal X-rays and the diarrhea in these patients.

Not only absorption is disturbed. Also digestion and motility are compromised in either generalized inflammatory states or in local inflammatory masses in the abdomen. This is the result of release of cytokines elicited by infection or inflammation. Endotoxin challenge in experimental animals clearly interferes with normal progression of migrating motor complexes and peristalsis (4). As a consequence of these disturbances patients with severe localized or generalized inflammatory illness have diarrhea or no passage of stools at all.

Consequently, the feasibility of enteral nutrition varies depending on the severity of inflammatory illness. Endeavors to institute enteral nutrition in patients exhibiting multiple organ failure (MOF) should be carefully initiated with small amounts of iso-osmolar nutrition, containing adequate amounts of sodium. Great care should be taken that passage is adequate, that bowel distension does not increase in severity. It is not likely that motility disorders are limited to the stomach or colon. Gastric residuals are unlikely to arise exclusively from gastroparesis but originate from generalized motility disorders in the whole gastro-intestinal tract (5). Disturbances in passage can be restricted to the proximal digestive tract however when there are local impediments (necrotizing pancreatitis with a “locked-in” duodenum, and other local inflammatory or mechanical barriers in the proximal digestive tract. In these situations thin feeding tubes may be threaded through the impediment to a distal position where passage in uninhibited. Nutritional support into the jejunum should be isotonic and no bolus injections should be given. Nor does it seem advisable to infuse water. The jejunum is less resistant to hypertonic or hypotonic feedings than the stomach and does not tolerate bolus feeding. In critical illness perfusion of the bowel is restricted which may be further aggravated by the challenge of enteral nutrition (6). In severe inflammatory illness full enteral nutrition is due to the aforementioned disturbances not always feasible (7), and in such patients, requiring long term artificial nutritional support, combinations of enteral and parenteral nutritional support are therefore sometimes necessary to cover nutritional requirements (see page/subchapter).

The composition of the nutritional regimen is more critical in severe (infectious) illness than in metabolically stable patients. Metabolic instability includes insulin resistance and glucose intolerance as well as hypertriglyceridemia. Severely and chronically ill patients do often suffer from these abnormalities and need very careful monitoring (see Topic 18: Nutritional Support in ICU).

The goal of nutritional support in severely ill patients is to limit muscle breakdown on the one hand but on the other hand and more importantly to support host response. This includes the immune response (synthesis of acute phase proteins, complement factors, immune globulins, white cells, macrophages etc.) and wound repair. As long as inflammatory activity persists, net catabolism (more protein breakdown than synthesis) will persist. Nevertheless in chronically ill patients nutritional support is necessary to survive (see Topic 18: Nutritional Support in ICU).

3. Conditions associated with bacterial overgrowth

3.1 Starvation/malnutrition

Rats exclusively fed with parenteral nutrition have low bile flow and low biliary and enteric secretion of sIgA, leading to increased adherence and pathogenicity of bacterial strains normally
belonging to the gut flora (8-10). Especially the enterobacteriaceae (Klebsiella, E.Coli, Pseudomonas spp.) are disreputable in this respect. Not only an increase in these strains, but also a decrease in “protective” bacterial strains (Lactobacilli, Bifidobacteria spp) are part of a syndrome of “bacterial overgrowth” in which bacterial strains that normally are commensal and not pathogenetic, cause mucosal inflammation, including increased permeability (11). It has been suggested that the “stressed” condition of the host promotes virulence factors, allowing these bacteria to become pathogenetic. An alternative hypothesis might be that opportunistic pathogens actively sense alterations in host immune function and respond by enhancing their virulence phenotype (12, 13). In the following paragraphs disease states will be discussed that alter host immune function specifically at the level of the intestinal mucosa. In areas with malnutrition a high prevalence of parasitic infection is present which has been attributed to bad hygiene. It is also possible however that the malnourished intestine increases virulence of parasites which would act as commensals in well-nourished children. This chicken-egg question is difficult to resolve.

3.2 Stenosis/Dysmotility
There are several relatively rare conditions causing intestinal stenosis and dysmotility. An important cause is Crohn’s disease in which longstanding inflammation ultimately leads to fibrosis, scarring and contraction both in the transverse and in the longitudinal direction. Other reasons are postsurgical stenoses, stenoses due to radiation enteritis and stenoses due to malignancies. This last category is characterized by a subacute and progressive course, whereas the first category may develop over years and rarely leads to complete obstruction. Motility disorders are encountered in diabetes, some dysmotility syndromes, scleroderma, but also in radiation enteritis, where the lumen often is widely patent but where dysmotility interferes with normal passage and absorptive function. All these conditions lead to stasis and a situation in which virulence factors of commensal bacteria will be stimulated, leading to bacterial overgrowth.

3.3 Defunctionalized bowel
Apart from evidence in experimental setting, in many clinical situations intestinal starvation often leads to mild but relevant inflammation. Exclusion enteritis is a clinically often diagnosed entity, especially detected at endoscopy in excluded colo-rectal segments. It also is present and probably more deleterious in the small bowel. Excluded small bowel segments due to high fistulae or deviating stomata also show macroscopic and microscopic inflammatory signs. This is even more outspoken in patients undergoing jejuno-ileal bypass for morbid obesity. Not only do they show inflammatory activity in the excluded small bowel segment but evidence supporting the relevance of this inflammatory process is derived from the fact that these conditions respond favorably to treatment with antibiotics directed against potentially harmful strains (14). The benefit is not only achieved in conditions where intestinal segments are surgically excluded, but also in pure starvation, e.g. during long term total parenteral nutrition (15, 16). Inflammatory signs and symptoms are often mild, and the benefit of treatment therefore modest and temporary, in view of the fact that the anatomical situation causing bacterial overgrowth is not relieved. A clinically much more relevant interaction may exist between intestinal bacterial overgrowth and the liver. This will be discussed in sub-section Gut/Liver axis (see paragraph 4.).

3.4 Pouchitis
Approximately 30% of patients with ileal pouches develop pouchitis. The inflammatory signs are generally mild, but lead to an increase in stool frequency and sensations of abdominal discomfort. Its pathogenesis is not completely resolved but bacterial overgrowth very likely plays an important role. Disturbances in the balance between Clostridia spp and Lactobacilli/Bifidobacteria (17) have been reported and increases in the concentrations of secondary bile acids (18, 19). In the mucosa of the pouch generally mild inflammatory signs are detected and pouchitis generally responds favourably to antibiotics like Metronidazole or Ciproxin. One might speculate that the disruption of the ecological balance is caused by the relative obstruction that is caused by the pouch. Defecation is initiated only because the patient feels bowel distension as mild cramps and knows by experience that this is caused by a full pouch. Deliberate straining is then required to defecate. The low grade obstruction and recurrent distension of the small bowel pouch may lead to changes in bacterial flora in a similar manner as in true stenosing lesions. Alternative explanations include lack of nutrients like glutamine and butyrate (20). The inflammation leads especially to a largely secretory diarrhea in which much fluid and electrolytes are lost, and possibly to some mild steatorhea.
4. Gut-Liver axis

4.1 Intestinal inflammation and liver disease

4.1.1 Pathophysiological sequelae of a non-functional gut
Whereas the data regarding the relevance of the specific influence of bacterial translocation on the occurrence of MOF are not very convincing, there is strong evidence that gut dysfunction is related to liver abnormalities (21). In present day surgical practice surgeons often have to deal with primary or secondary (after surgery) abdominal catastrophe.

The patient shown (figure) has suffered a bowel wall disruption and a jejunal fistula opening into the wound as a double barrel stoma. In this patient the proximal output of the fistula was collected and re-infused into the distal part of the small bowel. Such patients require total parenteral nutrition and develop overt or discrete cholestasis (increased Alk. Phosphatase, γGT and Bilirubin), often accompanied by hypertriglyceridemia and fatty liver. However, after re-infusion into the distal defunctionalized part of the small bowel these values normalize (21). Refunctionalisation of the gut relieves the liver abnormalities, implying that a non-functioning gut has toxic effects on the liver.

Figure 2 Proximal jejunal fistula in the midline of the abdomen
Suction drain brown yellow. Infusion drain white.

4.1.2 Secretory IgA and gut starvation
More than a decade ago several groups have demonstrated that parenteral nutrition and gut starvation significantly reduced slgA secretion in the bile of rats (22). Also enteral administration of the parenteral nutrition solution significantly decreased bile flow and its slgA content (22). It is generally acknowledged that slgA constitutes a major defense mechanism against bacterial invasion of the gut mucosa. This is supported by the observation that a highly significant inverse correlation between slgA concentration and bacterial adherence was found in the rat cecum (23). Gut starvation is therefore a major factor in the loss of mucosal defense and the proliferation of enterobacteriaceae. This is confirmed indirectly by a classical study in which it was demonstrated that treatment with Metronidazole relieved TPN associated cholestasis occurring in Crohn’s disease patients requiring artificial nutritional support (15). Although this finding may not be overly relevant for long term treatment of parenteral nutrition associated liver disease it confirms that bacterial overgrowth and subsequent mucosal inflammation in the non-functioning gut is one of the causal factors in inducing intrahepatic cholestasis.

4.1.3 Bacteria and bile acids
Bile acids can play a prominent role in the genesis of intrahepatic cholestasis in many of the clinical conditions described in this chapter. Bacterial dehydroxylation of primary bile acids yields secondary bile acids, some of which are cholestatic (24, 25). One would expect that in short bowel
syndrome with accelerated transit of luminal contents transit time would be too short to generate these secondary bile acids. Bile acid metabolism is changed however in short bowel syndrome and patients with bile acid malabsorption are more prone to develop diarrhea and cholestasis. The exact mechanism is not fully elucidated but bile acids are cytotoxic both for the biliary tree and for the colon. Normally hepatotoxicity is carefully prevented by intricate mechanisms, including a balanced bile acid composition, effective secretory pathways depending on hepatocyte nuclear receptors, cytokines and ileal peptides (26). Adequate phospholipid secretion may also protect against bile acid toxicity (27). Although data are not fully unequivocal, several reports demonstrate beneficial effects of ursodeoxycholic acid on cholestasis (26, 28). Ursodeoxycholic acid is viewed as a “good” bile acid and its benefit is considered to be derived from relative normalization of the bile acid pool (29).

4.2. Pathological states and the gut-liver axis

4.2.1 Short bowel syndrome
In neonatology necrotising enterocolitis is a potential complication of premature birth. A proportion of these babies loses much of their small bowel and develops a short bowel syndrome, requiring parenteral nutrition. A dreaded complication of this clinical state is severe steatohepatitis and cholestasis, progressing to fibrosis, cirrhosis and liver insufficiency. The proportion of premature babies developing this complication is decreasing due to better post-natal care, including tailored nutritional support, but there is still a number of children ultimately requiring liver and intestinal transplantation to prevent a fatal outcome. This disease state also proves the existence of an active gut-liver axis (28, 30, 31), where the same mechanisms may play a role as partly described earlier. Depletion of body mass, glutamine lack, bacterial overgrowth, a diminished bile acid pool and the production of secondary cholestatic bile acids may contribute to intestinal inflammation and liver damage. Also the parenteral feeding regimen itself may be an important factor (32) (see further).

4.2.2 Bypass operations for morbid obesity; other blind loops
The existence of an active Gut-Liver axis is also supported by the severe liver insufficiency that may arise in patients undergoing bypass surgery for morbid obesity. In the last decade a number of reports in the literature mentions liver transplantations performed for this condition (33, 34). This pathological state proves that in the iatrogenic “short bowel” situation parenteral nutrition is not required to develop liver disturbances. The functional short bowel situation itself that is created and the presence of a blind loop are important causative factors for liver disease. Evidence supporting the last contention comes from the observation that treatment with Metronidazole relieves part of the fatty liver component of the disease in patients (14). Similarly removal of the blind loop in dogs has been shown to be beneficial (35).

4.2.3 Kwashiorkor
Children in the third world suffering from Kwashiorkor obviously suffer from a multitude of deficiencies, derived from a diet that is generally deficient both in micro- and in macronutrients. Originally much emphasis has been put on protein lacking in the diet. More recently observations have been put forward that show that the Kwashiorkor clinical syndrome is derived from malnutrition on which inflammatory activity/infection is superimposed, whereas the Marasmic picture is expressed as a result of malnutrition with less severe inflammation/infection (36). These forms of malnutrition are part of a gliding scale and Kwashiorkor babies are subject to more inflammatory activity or infection than Marasmic babies. In the last decennia it has become evident that in the Western world adult intensive care patient that are seriously infected develop symptoms that are identical to the Kwashiorkor symptoms. A striking distinction between these two extremes of the scale between Kwashiorkor and marasmus is that the Kwashiorkor babies have more severe steatosis. This parallels the observations in morbid obesity and bypass surgery (14) and suggests that infection underlies the different phenomenology, including steatosis hepatitis. In other studies hepatomegaly (37) and cholestasis (38) was observed significantly more often in children dying from Kwashiorkor.
4.2.4 Extrahepatic cholestasis; primary sclerosing cholangitis; primary biliary cirrhosis
The presence of a normal bile acid pool and normal composition of bile acids and content of slgA is important for the resistance of the gut and the liver against bacterial actions. The absence of normal bile and slgA during extrahepatic cholestasis may therefore lead to a vicious circle and aggravate the situation by adding to the extrahepatic component an intrahepatic component. In clinical practice it may be advisable if possible to administer bile enterally when bile can be drained in case of extrahepatic biliary obstruction.

Primary Sclerosing Cholangitis (PSC) is an enigmatic disease accompanying Inflammatory Bowel Disease. Experts in this field deny a close causative correlation between the intestinal pathology and the hepatic symptomatology. The argumentation is that PSC sometimes precedes overt inflammatory bowel disease, but also that PSC symptoms are not relieved and sometimes aggravate after resection of inflamed bowel segments. Also the question is why the main focus of inflammation is directed to the bile ducts instead of the secretory process in the hepatocytes.

Recently circumstantial (epidemiological) evidence has been presented that patients with primary biliary cirrhosis have leakier guts than control patients. It is debatable whether the hepatic inflammatory process is the result or the cause of the diminished mucosal barrier function. Stronger support can be derived from the observation that patients with celiac disease have an increased risk to develop liver cirrhosis. The inflammatory signs in the liver are alleviated by strict adherence to a gluten-free diet and improvement of gut morphology and function. An important question is why in IBD specifically the bile ducts are affected whereas this is not the case in celiac disease. Several potential explanations can be offered. New epidemiological data suggest that IBD may also coincide with PBC, implying that IBD is not specifically or exclusively related to PSC (39). Secondly the severity of the inflammatory process in the gut may be a determinant of the inflammatory process in the liver. Furthermore there may be a genetic heterogeneity in the pro-inflammatory and anti-inflammatory effects of the cytokine cascade. Different inflammatory diseases of the intestine are associated with or lead to a variety of liver abnormalities. However, the type of liver abnormality is not tightly linked to a specific intestinal disease. This suggests that the process is aspecific, but that the phenomenology may be dependent on other factors including the severity of disease or patient related genetic factors. Polymorphisms of cytokine responses offer likely explanations.

4.3 Parenteral nutrition and liver disease
In the previous section it has been shown that compromised bowel, inflammatory activity and infectious states are associated with liver abnormalities also in patients that do not receive parenteral nutrition. Unfortunately however these clinical conditions are often also encountered in patients receiving parenteral nutrition which makes it difficult to specify the role of parenteral nutrition per se.

On the other hand parenteral nutrition is sometimes associated with liver abnormalities when there are no obvious other precipitating factors (32). Especially liver steatosis and cholestasis are often encountered and hypertriglyceridemia occurs relatively often. In the past this was clearly induced by hyperalimentation and parenteral regimen in which as caloric source exclusively carbohydrates were used. In addition defective glucose control was not known to have such dismal effects on infectious complications but also on steatosis. Another potential factor contributing to disturbances in fat clearance and bile secretion may be the type and structure of fat included in the regimen. In a blind but not randomized experiment we found two fat emulsions, both consisting of long chain fatty acids derived from soy, with an emulsifier egg lecithin, but from two different companies, caused different degrees of cholestasis and hypertriglyceridemia.

It is uncertain but possible that this is due to differences in emulsion stability and particle size. In this (unpublished) study we also found that there is a correlation between plasma triglyceride levels and bilirubin levels. The literature on this subject is not of high quality, but there is evidence suggesting that the LCT part of the emulsion is the culprit. Therefore different producers of these lipid emulsions have tried to develop new compositions, containing either less LCT with more MCT fats, or to produce structured lipids in which the glycerol backbone is esterified randomly with LCT and MCT fats. Presently claims have been made that omega-3 fatty acids may be cleared better than other fatty acids and interfere less with bile secretion (40).
5. Nutritional measures to improve gut integrity

5.1 Enteral Nutrition
The deleterious effects of starvation on the entero-hepatic cycle of bile acids, the production of sIgA, bacterial overgrowth and potentially other factors inducing inflammatory activity in the bowel wall and subsequently in the liver, have been discussed in paragraph “Conditions associated with bacterial overgrowth/Starvation”. It follows that enteral nutrition alleviates these abnormalities (32). In general restoration of the normal passage of food and of the entero-hepatic cycle of bile acids has beneficial effects on the enteric flora and inflammatory activity in the gut wall. For this purpose it is necessary to normalize the bile acid pool and the composition of the enteric flora. Normalization of normal gut physiology is not only nutrition dependent but may also require surgery to refunctionalise blind loops, to resect or narrow dilated diverticula or intestinal loops, to remove or widen stenosing bowel segments leading to proximal obstruction, bowel distention and bacterial overgrowth. Antibiotics are often necessary to delete potentially pathogenic flora. Supplementation with bile acids (Ursodeoxycolic Acid) helps to normalize the size and composition of the bile acid pool (29). In the recent decade much energy has been invested in nutritional formulas containing glutamine, pre- and probiotics or special fatty acids that may have beneficial effects on the bowel wall, passage and flora.

5.2 Specific enteral formulas
In this paragraph only a limited summary will be given regarding the different enteral nutrition modalities. For this purpose we refer to Module 7.1 and Module 7.2. Claims have been put forward however that several specific adaptations of the enteral nutrition regimen may have beneficial effects on the gut flora and consequently on intestinal inflammation.

These adaptations especially regard adaptations of the amino acid composition, the fat content, and the pre- and probiotic composition of the enteral nutrition regimen. Although much speculation exists with regard to the use of pre- and probiotics to the benefit of a healthy gut flora, very little definitive data are available. Nor has the “compromised gut” as described in this part of the module been the focus of randomized trials.

5.2.1 Amino acid composition
Arginine has been part of multimodality adaptations of enteral nutrition formulas, also including omega-3 fatty acids and RNA. Benefit is likely to be achieved in patients undergoing elective surgery (41). The multimodality character of the adapted formula has precluded identification of the specific component in the intervention responsible for the benefit. Nor is it possible to identify the mechanism underlying the benefit. In view of the fact that most of these patients do not have a “compromised bowel” and the claims as to why the feed is effective, it is not likely that the mechanism operates by improving the integrity of the intestine.

It has become more and more accepted that glutamine has beneficial effects on bowel integrity and outcome of surgery and critical illness [42, 43]. Infectious morbidity has been demonstrated to be beneficially influenced by enteral route in trauma and burns (42), and by parenteral route in critically ill patients and in surgical patients (44).

5.2.2 Pre- and probiotics (see for detailed information Module 1.4 and Module 1.5)
The inclusion of pre- and probiotics in the enteral nutrition regimen is receiving much attention, both in clinical nutrition as well as in chronic IBS and in constipation. Although a beneficial trend can be identified, the multitude of different pre- and probiotic-mixtures precludes specification of a particular pre- and probiotic mixture achieving the highest benefit. Especially Oligofructoses and Inulin have been shown to have specific effects in IBS (in combination with probiotics) (45) and pouchitis (46-48) respectively. These soluble fibers are normal food constituents and non-toxic, and therefore prescription of moderate amounts may also be considered when bacterial overgrowth is diagnosed.
In pouchitis inulin decreased the concentration of secondary bile acids and improved the balance between potentially pathogenic enterobacteriaceae, and beneficial bifidobacteria and lactobacilli species (49). Beneficial effects have also been described of glutamine containing enemas in pouchitis patients. These studies are anecdotal, so that no definitive conclusions can be drawn.

Similar recommendations can be given regarding probiotics. There is a multitude of potentially beneficial strains, which makes definitive conclusions impossible at this stage.

Examples are Lactobacillus spuriu, Lactobacillus acidophilus, Lactobacillus plantarum 299V, Lactobacillus GG, Bifidobacterium lactis, Lactobacillus lactis, Streptococcus thermophilus and many others. In practice varying benefit can be observed from prescription of commercially available yoghurts containing probiotics, for instance in pouchitis, as well as in other conditions. Promising results are available with a probiotic mixture (8 different strains) for prevention and treatment of refractory pouchitis (50). A word of caution should be expressed regarding the use of probiotics in critically ill patients. Recently probiotics given twice daily (1010 bacteria total/day) to patients with severe pancreatitis receiving a fiber containing enteral formula proved to cause non occlusive small bowel necrosis in a high proportion of cases (51). At present is therefore not advisable to use probiotics in critically ill patients.

A very interesting development consists of the genetic modifications of Lactobacillus lactis strains with human genes producing IL 10 (52, 53). At present the focus of this research is Crohn’s disease, in which a continuing disbalance between pro-inflammatory cytokines (TNF-alpha, IL 1) and anti-inflammatory cytokines (IL 10) is considered to be the cause of ongoing inflammation. Other applications in some of the disease states, described in this module may also be considered.

5.2.3 Fatty acids

The multimodality treatment with enteral nutrition containing omega-3 fatty acids, RNA and Arginine appears to be beneficial in elective surgical patients, but noxious in critically ill patients (41). It is possible (but impossible to prove) that the benefit of the combination is derived from the inclusion of omega-3 fatty acids, down regulating but not completely inhibiting a too strong stress response. It has also been considered that the noxious effect of the multimodality enteral formula in critically ill patients is derived from the inclusion of Arginine. The mechanism of the action of omega-3 fatty acids very likely consists of changing the composition of pro- and anti-inflammatory mediators. It is unknown at present whether this has effects on bacterial overgrowth in the compromised bowel. The future will witness the exploration of enteral fat on gut integrity. Recent experimental evidence has identified a vagal/brain/vagal loop, protecting the integrity of the bowel, and enhanced by inclusion of fat in the feed (54).

5.3 Specific parenteral formulas

5.3.1 Glutamine

At present the conclusion of meta-analyses is that addition of glutamine to the parenteral feeding regimen (approximately 20 g in adults/day) has beneficial effects in some studies in surgical patients and in other patients not receiving enteral nutrition, improving mucosal barrier function (ref), and in critically ill patients for less well explored reasons (44, 55). The non-critically ill patient population with compromised bowel is not specifically studied for obvious ethical reasons. Effects of parenteral glutamine on pouchitis have not been investigated.

6. Summary

Most of the digestion and absorption of macronutrients occurs in the proximal part of the intestine (oral cavity to jejunum) whereas electrolytes and fluid are absorbed in the whole gut. The distal ileum absorbs bile acids and vitamin B12. In the colon soluble fiber is fermented and short-chain fatty acids produced and absorbed. Many surgical or disease related anatomical abnormalities (stenoses, blind loops, bypasses, motility disorders, pouches) lead to bacterial overgrowth, inflammation of the gut wall and malabsorption of nutrients. All aspects of gut function (motility, digestion, absorption) are disturbed in critical illness due to inflammatory activity, induced in the gut (as well as in all other tissues/organs in the body). The role of increased permeability as a sign of intestinal inflammation, in translocation of bacteria and in the genesis of multiple organ
dysfunction syndrome is uncertain, but there is a clear pathogenetic connection between inflammatory activity in the intestine and cholestasis, steatosis and possibly steatohepatitis. Fat in parenteral nutrition may aggravate these abnormalities and a combination of nutritional and intestinal factors may ultimately lead to liver insufficiency especially in neonates.

Treatment of the compromised gut consists of surgical or/and medical restoration of normal bowel passage and function as well as of treatment of primary infection/inflammation. Adaptation of the nutritional regimen (immuno-nutrition) may play an adjunctive beneficial role.

References

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