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 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 absorbs short chain fatty acids derived from fermentation of soluble fibre;
- The degree of malfunction of the intestine in trauma and disease depends on the severity of the disease and of the trauma. Several anatomical and functional abnormalities (stenoses, blind loops, pouches, constipation, severe disease, radiation) lead to inflammation and interfere with the adequate absorption of nutrients. Sometimes malabsorption occurs without inflammation or loss of intestinal length as in severe motility disorders such as pseudo-obstruction or scleroderma;
- Bacterial overgrowth is an important cause of malfunction of the intestine especially in chronic intestinal pseudo-obstruction;
- 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 composition of parenteral nutrition may induce or aggravate compromised bowel-associated hypertriglyceridermia, cholestasis and steatohepatitis;
- Correction of anatomical abnormalities (stenoses, defunctionalized small bowel segments, stagnant or dilated loops) and activation of the gut by (distal) enteral nutrition improves bowel function.

1. Physiology of the Gut

   Appropriate intestinal function is the result of the interaction between humoral, neural and local factors on the underlying structure. Alterations of these complex relationships may result in intestinal failure, in which inadequate intestinal activity prevents the body’s ability to absorb nutrients effectively enough to maintain health. Knowledge of anatomical and physiological aspects of the gastrointestinal tract is crucial for understanding of the compromised gut.

1.1. Anatomy

   The length of the GI-tract depends on the age, body size, and the technique which was used for measurement (i.e. in vivo or at autopsy, normal muscle tonus or relaxed). Consequently, during operation, only a rough estimate can be given for true length and size of gastrointestinal (GI) tract or its remnant. Taking the above into consideration, individual parts of the normal GI tract measure as follows:
   a) the distance from oral orifice to the oesophagus is about 15 cm;
   b) the oesophagus, which starts 15 cm from teeth and ends within the stomach inlet (cardia) – measures approximately 25-30 cm;

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c) an average estimate of the length of the stomach varies between 25 and 50 cm, but it must be remembered that its length depends on whether it is measured along the lesser or greater curvature; 
d) the duodenum, which derives its name from the fact that in medieval times it was considered to measure 12 fingers, amounts to roughly 30 cm; it ends at the ligament of Treitz, where the jejunum begins; 
e) the small bowel, which can be divided into jejunum and ileum. The borderline between them is, however, not easy to mark, because instead of a sharp transition there is just a gradual decrease in thickness of the intestine. The jejunum is at least twice as thick and more than twice as heavy per centimeter as the ileum, which is also reflected in its function. Jejunum and ileum differ in terms of motility: ileal transit is three-times slower than jejunal one. The total length of the small intestine measured at surgery is between 3 and 6 metres. 
f) the large bowel (colon), which starts at the ileocaecal valve (Bauhin’s valve) and is approximately 100-120 cm long. The last part of the large bowel, 15 cm long, is called the rectum.

1.2 Digestion and Absorption

Digestion commences in the oral cavity with the actions of amylase, which can be found in saliva. The oesophagus does not contribute much to the process. Both oral cavity and the oesophagus are resistant to hypertonic foods due to their multi-layered squamous epithelia.

The next part of GI tract, which is the stomach, continues the digestive process thanks to its enzymes from chief cells. This is not, however, its only function – it creates a hostile environment for bacteria because it secretes hydrochloric acid which protects other parts of the GI tract from contamination and helps to digest meals. It also dilutes food components so they may become isotonic instead of hypertonic, releases predigested food gradually into the duodenum (gastric sieving) protecting the intestine from large boluses that could result in dumping. This process is rapid for liquids, but slow and regulated by particle size & nutrient type in the case of solid food. Gastric emptying is also slowed down by the presence of intestinal content in the distal part of small intestine (the ileal brake), it is, however, enhanced by small bowel resection (1, 2).
Dumping syndrome may occur in patients after gastrectomy. It may result in substantial loss of weight and fatigue, dizziness and even loss of consciousness. It is caused by the sudden and substantial release of hormones (mostly insulin) provoked by quick passage and large volumes of predigested food into the jejunum.

Most secretion and absorption takes place in the small intestine, where intestinal enzymes together with pancreatic and biliary secretions break down remaining large food particles. The digestive process occurring in the small intestine can be divided into three phases: intraluminal (mainly hydrolysis), the brush border membrane phase (= mucosal phase – further degradation of polysaccharide and peptides + absorption) and the incorporation phase (transport to portal vein and lymphatic tracts) (Fig. 1).
The proximal part of small bowel absorbs more vital nutrients that the distal part, except for bile salts and vitamin B12, which are absorbed only in the ileum. The jejunum is also the place of more intense metabolic processing of amino acids, carbohydrates and lipids. Particularly glutamine degradation and conversion to glutamate, alanine, citrulline and ammonia takes predominantly place in the jejunum.

The site of reabsorption may depend on the nature of the meal as well (3). With a low-osmotic meal, most of the fluid is absorbed in the jejunum, whereas a high-osmolarity meal is mostly absorbed in ileum.

Water and electrolytes are - in varying amounts - released into the lumen and rapidly absorbed again. Hypertonic solutions are diluted by water secretion, hypotonic solutions are made isotonic by secretion of cations (especially Na+); both types of solutions are subsequently reabsorbed.

Because of the mechanisms described above, a fluid flux across the GI tract occurs of approximately 8-10 litres in 24 hours. 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 all parts of small bowel and in the colon, which explains the fact that after resection of substantial parts of the small and large bowel water and electrolytes (Ca++, K+, Mg++, Cl−) cannot be efficiently absorbed (See also Module 12.2).

The impact of such a big fluid flux across the GI tract results in huge intestinal fluid retention in the case of mechanical obstruction, and causes potent water and electrolyte
shifts between the extravascular and intravascular compartments as well as the intra- and extracellular ones. This fluid shift results in hypotension or even hypovolaemic shock in emergency surgical patients. It is crucial that whenever possible, water and electrolyte abnormalities are corrected before surgery.

In addition to the absorption of water and electrolytes by the small bowel, the ileum plays an essential 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 of fat soluble vitamins and cations like Ca$^{2+}$ and Mg$^{2+}$ bound to fatty acids.

Vitamins are absorbed mostly proximally; the only vitamin that is predominantly absorbed in the ileum is vitamin B12, hence the loss of this part of the intestine leads to anaemia.

In the colon, the 1000-1500 ml of fluid bowel content normally coming from the ileum is largely absorbed, producing a solid stool containing 100 – 150 ml of water. The large bowel is therefore a potent part of GI tract as far as water absorption is concerned – the colon’s efficiency in water absorption reaches 90%, thanks to tight intracellular junctions. Water absorption is 44% in the jejunum and 70% in the ileum, while the equivalent figures for sodium are 13% and 72%, respectively (3). 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, and bile acids. 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 diarrhoea (6).

1.3 Motility of Gastrointestinal Tract

Intestinal motility plays an important, yet belittled role in nutrient absorption. Animal studies demonstrate an adaptive response with slowed gastric emptying and slowed transit after proximal resection of the small intestine (4). A prolongation of migrating motor complexes (MMC), an increase in MMC Phase II and reduction in MMC Phase I durations were observed. The intestinal remnant shows also post-prandial inhibition of MMC. Distal resection results only in minor changes. Moreover, studies in human show that the intestinal remnant is characterized by shorter duration MMC-cycles after major resection (when only < 100 cm of intestine was left). All of the above confirms the adaptive potential of the intestine from a motor point of view.

2. Severe Inflammatory Illness

Severe inflammation or infection influences the whole organism regardless of the location of the primary site. 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 (7, 8). In the case of the GI tract those processes impair digestive function and absorption not only of water, electrolytes, macro- and micronutrients, but also of other substances such as bile acids. The degree of impairment depends on the severity of disease.

The disturbance of absorption is the result of impairment of ATP-driven ion-transport. Not only systemic changes influence absorption; those processes may also occur because of local inflammatory sites in the course of abdominal inflammatory processes such as...
appendicitis, exacerbated Crohn’s disease or diverticulitis. Even the intact intestine in walling off an infectious site can exhibit “collateral” inflammation, which harms active water and electrolyte transport. This mechanism explains the presence of intra-luminal fluid levels encountered around the inflammatory mass on plain abdominal X-rays and the presence of diarrhoea in these patients. Not only absorption is disturbed; also digestion and motility are compromised in either generalized inflammatory states or in local inflammatory processes in the abdomen. This is the result of cytokine release. Animal studies showed that endotoxin challenge interfered with normal progression of migrating motor complexes and peristalsis (9). As a consequence of these disturbances patients with severe localized or generalized inflammatory illness may have diarrhoea or obstruction. Consequently, the feasibility of enteral nutrition varies depending on the severity of inflammatory illness. Enteral nutrition in patients with multiple organ failure (MOF) should be carefully initiated with small amounts of iso-osmolar nutrition, containing adequate amounts of sodium in patients with adequate GI passage. Very often motility disorders are caused by generalized motility disorders in the whole gastro-intestinal tract, and are not limited only to stomach or large bowel (10). Disturbances in passage can be restricted, however, to the proximal digestive tract in case of local impediments, such as necrotizing pancreatitis with a “locked-in” duodenum. Even in these situations enteral nutrition may be initiated by the use of a thin feeding tube inserted into a more distal, intact part of the intestine. Enteral diets should be administered continuously in the intestine, not in a bolus form, and should generally be isotonic. Administration of water is not recommended as the jejunum is less resistant to hypertonic or hypotonic feedings than the stomach. It may also be important to use peptide enteral diets during jejunal feeding instead of whole protein formulas to enable complete absorption. In critical illness and other hypovolaemic states the perfusion of the bowel may be impaired, and this state may be further aggravated by the infusion of enteral nutrition, leading even to intestinal necrosis (11, 12). In such patients combinations of enteral and parenteral nutritional may be useful to cover protein-energy requirements. The composition of the nutritional regimen is more critical in severe illness than in metabolically stable patients. Metabolic instability includes insulin resistance and glucose intolerance as well as hypertriglyceridaemia, therefore those patients require 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 more importantly, on the other, to support the 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 protein catabolism (more protein breakdown than synthesis) will persist, hence nutritional support is necessary for survival in chronically ill patients (see Topic 18: Nutritional Support in ICU).

3. Bacterial Overgrowth

Bacterial overgrowth represents a threat to the whole organism due to risk of evoking mucosal inflammation, impairment of gut barrier, bacterial translocation and bacteraemia/sepsis. Symptoms include diarrhoea, bloating, distension, abdominal pain, weight loss, fatigue and liver dysfunction. There are two major components of bacterial overgrowth: increase in adherence and pathogenicity of bacterial strains forming the normal gut microbiome, particularly
enterobacteriaceae (Klebsiella, E.Coli, Pseudomonas spp.); and a decrease in “protective” bacterial strains (such as Lactobacilli, Bifidobacteria spp) (13-16). Overgrowth is enabled by a reduced intestinal secretion of sIgA, which permits an increase in adherence and pathogenicity of bacterial strains as well as changes in bacterial phenotypes as demonstrated by enhancement of virulence (17, 18).

There are several conditions that predispose to bacterial overgrowth. They include:

a) protein malnutrition
b) stenosis of the intestine
c) dysmotility
d) exclusion of bowel segments
e) pouchitis.

Protein malnutrition disrupts indigenous GI tract microflora by decreasing anaerobe and lactobacilli populations, allowing overgrowth of aerobic bacteria. It impairs host defense. Fortunately, this condition does not lead to bacterial translocation.

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. The other usual reasons are post-surgical 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. Sometimes motility disorders are encountered in diabetes, some dysmotility syndromes, and in scleroderma, but also in radiation enteritis.

All of these conditions lead to a situation in which virulence factors of commensal bacteria will be stimulated, leading to bacterial overgrowth.

Exclusion enteritis is a clinical entity, detected at endoscopy in excluded colorectal segments. Excluded bowel segments show macroscopic and microscopic inflammatory signs. 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 (19). 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 (20, 21).

Pouchitis (inflammation of a pouch surgically created from the small intestine to replace an excised rectum) occurs in approximately 30% of patients with ileal pouches. Its symptoms include an increase in stool frequency, abdominal discomfort, pain and bleeding and sometimes steatorrhoea. Bacterial overgrowth, characterized by disturbances in the balance between Clostridia spp and Lactobacilli/Bifidobacteria and increased concentration of bile acids, plays an important role in the pathogenesis (22, 23, 24). In most cases pouchitis responds favorably to antibiotics like metronidazole or ciprofloxacin. Other probable causes of pouchitis include a lack of nutrients like glutamine and butyrate, and obstruction caused by pouch itself (25).

4. Gut-Liver Axis

4.1 Intestinal Inflammation and Liver Disease

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 (26, 27, 28). The impairment of the
GI tract can be so advanced that surgeons use terms such as ‘abdominal catastrophe’ to emphasize the impact of such a state on the whole organism. Bacteria and bile acids can play a prominent role in the genesis of intrahepatic cholestasis, because bacterial hydroxylation of primary bile acids yields secondary bile acids, some of which are cholestatic or directly hepatotoxic (29, 30). Bile acid metabolism is changed in the short bowel syndrome, and patients with bile acid malabsorption are more prone to develop diarrhoea and cholestasis. The exact mechanism is not fully elucidated but secondary bile acids can be cytotoxic both for the biliary tree and for the colon.

Mechanisms that prevent hepatotoxicity include intricate mechanisms, such as balanced bile acid composition, effective secretory pathways depending on hepatocyte nuclear receptors, cytokines, ileal peptides and adequate phospholipid secretion (31, 32). Several reports demonstrate beneficial effects of ursodeoxycholic acid used therapeutically in cholestasis because of its normalization of the bile acid pool (31, 32, 34). Secretory IgA (sIgA) also is of utmost importance in the mechanism of liver failure due to disturbance of the gut-liver axis, because it constitutes a major defence mechanism against bacterial invasion of the gut mucosa. The decrease of its concentration increases bacterial mucosal adherence, the proliferation of enterobacteria thus impairs mucosal defense, as precisely shown in studies in rats (28). Starvation of the gut always results in the decrease of sIgA in bile, even if the organism is fed parenterally (27).

The clinical case of a patient, presented in Fig. 2, indicates clearly that gut impairment can lead to liver dysfunction and that treatment of this condition may help the patient to recover.

This patient suffered from a bowel wall disruption and a jejunal fistula opening into the wound as a double barrelled stoma. In this patient the proximal output of the fistula was collected and re-infused into the distal part of the small bowel. He required total parenteral nutrition and developed cholestasis (increased alkaline phosphatase, gamma-GT and bilirubin) accompanied by hypertriglyceridaemia and fatty liver. However, after re-infusion of gut secretion into the distal defunctionalized part of the small bowel these values normalized (26). “Refunctionalisation” of the gut relieved the liver abnormalities.

![Image](https://via.placeholder.com/150)

**Fig. 2** Proximal jejunal fistula in the midline of the abdomen. Suction drain brown yellow. Infusion drain white.
4.2. Pathological States and the Gut-Liver Axis

4.2.1. Short Bowel Syndrome (SBS)

After a major ileal resection, there is interruption of the enterohepatic cycle of bile salts. This disturbance of the gut-liver axis may result in severe liver steatosis and cholestasis, progressing to fibrosis, cirrhosis and hepatic insufficiency. The clearest demonstration of this is in premature birth infants with necrosing enterocolitis (NEC) which has led to major resection and SBS requiring total parenteral nutrition (TPN). Those patients develop liver failure quickly, which serves to prove the importance of the gut-liver axis (33, 35, 36). Their liver condition may also be worsened by depletion of body mass, lack of glutamine and bacterial overgrowth as well as by the parenteral feeding regimen itself (37).

4.2.2. Bypass Operations for Morbid Obesity and 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 several reports in the literature have described liver transplantation being necessary for this condition (38, 39). This pathological state proves that parenteral nutrition is not a requirement for the development of liver disturbances in situations of iatrogenic shortened or bypassed bowel. The functional short bowel that is created and/or the presence of a blind loop are important and sufficiently causative factors for liver disease. Supportive evidence for this also comes from the observation that treatment with metronidazole attenuates the fatty liver component of the disease in patients (19). Similarly, removal of the blind loop has been shown to be beneficial in dogs (40).

4.2.3 Sepsis

Sepsis, particularly when recurrent, may be the cause of liver disturbances. Most septic patients demonstrate elevated liver enzymes, such as GGPT, alkaline phosphatase, and, most importantly, hyperbilirubinaemia. Signs of sepsis are, however, often blunted due to poor nutritional status, or accompanying disease (9, 11, 13, 41-45). Patients under the care of nutrition support teams are therefore at special risk, through failing to demonstrate typical signs of infection, such as fever or an increase in serum C-reactive protein (CRP). Clinical signs of uncontrolled sepsis may however include tachycardia, fatigue, encephalopathy, fluid retention and oedema, undice, and, ultimately, features of new or worsening organ failure (41-44). It is imperative therefore to identify and treat causes of sepsis. Many patients receiving nutritional support are post-operative and at high risk of intra-abdominal sepsis; in them there should be a low threshold for investigation for abdominal abscess and its percutaneous or surgical drainage. Non-abdominal sources of sepsis also need to be considered, pneumonia being the most common of them (41-44). The central venous catheter should always be considered as a possible source of infection (43, 44), but this diagnosis should not be assumed without some supportive evidence or exclusion of other possible foci. Only in septicemic shock is it appropriate to remove a central catheter solely because of the presence of infection.
4.2.4. Cholestasis and Cholestatic Liver Diseases

The presence of a normal bile acid pool and normal composition of bile acids and content of sIgA is important for the resistance of the gut and the liver against bacterial actions. The absence of normal bile and sIgA during extrahepatic cholestasis may therefore lead to a vicious circle and aggravate the situation by adding an intrahepatic component to the extrahepatic component. In clinical practice it may be advisable to administer bile enterally when bile can be collected as in the case of drained extrahepatic biliary obstruction.

Primary Sclerosing Cholangitis (PSC)
Primary Sclerosing Cholangitis (PSC) is an enigmatic disease usually accompanying Inflammatory Bowel Disease. Recently circumstantial (epidemiological) evidence has been presented that patients with PSC 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 perhaps be derived from the observation that patients with poorly controlled coeliac disease (who have similarly leaky guts but very little else in common with PSC) have an increased risk of developing liver cirrhosis. The inflammatory signs in the liver are alleviated by strict adherence to a gluten-free diet and concomitant improvement of gut morphology and function. An important question remains as to why the bile ducts are particularly affected in IBD whereas this is not the case in coeliac disease.

Primary biliary cholangitis (PBC), IBD may also coincide with primary biliary cholangitis (PBC) (previously called primary biliary cirrhosis). This also implies that IBD is not specifically or exclusively related to PSC (26). Again the evidence points to a link between the severity of the inflammatory process in the gut as 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.

4.3. Parenteral Nutrition and Liver Disease

For some decades it was thought that correctly administered long-term parenteral nutrition could itself be the reason for liver insufficiency. The condition was called parenteral nutrition associated related liver disease (PNALD), and was recognized to have a poor prognosis potentially ending in cirrhosis and end-stage liver disease. However newer data and better understanding of pathophysiology have led ESPEN and other authorities to abandon this term completely. It is now considered that chronic liver disease seen in patients with intestinal failure is a multifactorial consequence of the intestinal failure and not of a direct complication of the PN alone. This does not discount an important contribution from the PN but serves to direct attention to all factors potentially susceptible to amelioration. Severe forms of the condition now termed IF-associated liver disease (IFALD) can certainly be responsible for fibrosis, cirrhosis and death. Severe IFALD is characterized by encephalopathy, ascites, portal hypertension, GI bleeding and coagulopathy. IFALD can be attributed to (30, 32, 41-44):

a) patient-related factors: presence of SBS without ileum or SBS < 150 cm with ileum, colonic exclusion, sepsis, bacterial translocation, and especially with ultra-short bowel.
b) nutrition-related factors: energy overfeeding (> 40 kcal/kg/day), excess of glucose administration (> 7 g/kg/d), excess of intravenous lipids (> 1.0 g/kg/d), lack of essential fatty acids or choline, continuous PN regimen, multi-bottle system (instead of all-in-one admixtures), the use of LCT lipid emulsions and particularly those based purely on soya oil.

In most if not all cases, multiple additive causes will be present. Treatment usually needs to be multimodal and will include change to the PN regimen (isocaloric feeding, and a move away from pure soya LCT by using MCT/LCT, omega-3-FA, olive oil based emulsions or mixtures like SMOF or Lipoplus), reconstruction of GI tract, antibiotics, intraluminal SCFAs flushes, taurine administration, cyclic feeding and the use of ursodeoxycolic acid. The formal evidence base for these interventions remains poor at present but there is increasing support for a reduced reliance on soya-based lipid emulsions.

5. Therapeutic Measures to Improve Gut Integrity

Many studies have confirmed increased intestinal uptake of nutrients and fluids after even extensive resections due to reactive increases in mucosal surface area (adaptation). The adaptive response of enterocytes starts within hours after resection, as in the case of the sodium/glucose transporter, or the activity of digestive enzymes. In most cases these positive mechanisms are insufficient to assure proper absorption and some therapeutic measures can be helpful.

5.1. Restoration of GI tract Continuity and Supportive Treatment

The restoration of the normal passage of food and enterohepatic cycle of bile acids should be one of main goals of treatment (see 4.1). Other surgical goals include refunctionalisation of blind loops or widening of stenotic segments, which may help to overcome obstruction, bowel distension and bacterial overgrowth. Antibiotics are often necessary to delete potentially pathogenic microbiota. Supplementation with bile acids (ursodeoxyxycolic acid) helps to normalize the size and composition of the bile acid pool (34, 42-44). A strategy for maximizing intestinal adaptation should focus on: restoration of continuity, provision of optimal dietary constituents, augmentation of growth factors and at the same time suppression of inhibitory factors.

5.2. Specific Enteral and Parenteral Formulas

Enteral nutrition regimens may have beneficial effects on the gut microbiota and consequently on intestinal inflammation. While true in general terms there is interest also in modified feeds intended to address particular clinical scenarios. These modifications especially regard adaptations of the amino acid composition, the fat content, and with respect to the pre- and/or probiotic composition of the enteral nutrition.

5.2.1. Amino Acid and Fatty Acids Composition

A formula containing arginine, omega-3 fatty acids and RNA has shown favorable effect on intestinal function, especially in elective surgery patients (22, 23, 46). The multimodality character of the adapted formula has precluded identification of the specific component in the intervention responsible for the benefit. Nor was it possible to
identify the mechanism underlying the benefit, however it is possible that omega-3 fatty acids contribute by changing the composition of pro- and anti-inflammatory mediators. Meta-analyses are unambiguous that the addition of glutamine to parenteral feeding regimens (approximately 20 g in adults/day) have beneficial effects in some surgical patients and in some other patients not receiving enteral nutrition, by improving mucosal barrier function and in critically ill patients for less well explored reasons (46, 57). The non-critically ill patient population with compromised bowel has not been specifically studied for obvious ethical reasons, but enteral glutamine also shows beneficial effects in trauma and burned patients (46).

5.2.2. Pre- and Probiotics

The use of pre- and probiotics have seemed to be helpful in chronic irritable bowel syndrome (IBS) and in patients with constipation. Although a beneficial trend can be identified, the multitude of different combinations currently precludes a specific recommendation for highest benefit. However the prebiotics oligofructoses and inulin (in combination with probiotics) look promising in IBS and pouchitis (47-55). These soluble fibres 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 (54). Similar general recommendations can be given regarding probiotics. There is however a multitude of potentially beneficial strains (for example Lactobacillus spurium, Lactobacillus acidophilus, Lactobacillus plantarum 299V, Lactobacillus GG, Bifidobacterium lactis, Lactobacillus lactis, Streptococcus thermophiles), which have different and sometimes contrary effects making definitive conclusions impossible at this stage.

Promising results are available with a probiotic mixture (8 different strains) for prevention and treatment of refractory pouchitis (55). A word of caution should be expressed regarding the use of probiotics in critically ill patients. Recently probiotics given twice daily (10^10 bacteria total/day) to patients with severe pancreatitis receiving a fibre-containing enteral formula proved to cause non-occlusive small bowel necrosis in a high proportion of cases (56). At present it 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 (54, 55). At present the focus of this research is Crohn’s disease, in which a continuing imbalance between pro-inflammatory cytokines (eg TNF-alpha, IL 1) and anti-inflammatory cytokines (eg 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.

5.3 Factors Promoting Intestinal Adaptation

Generally, factors promoting intestinal adaptation may be grouped as those which are:

a) Luminal contents
   - luminal nutrients
   - luminal secretions
b) Gastrointestinal regulatory peptides
c) Systemic factors
   - growth factors
   - hormones
The role of luminal nutrients is particularly important after proximal resection, and the intestinal response (adaptation) is blunted if nutrients are administered intravenously, and not orally. The stimulation depends on the type of nutrient: glucose and other sugars act mainly on the proximal intestine, whereas fat acts more distally (jejunoileal). LCTs stimulate adaptation to greater extent than MCTs, and disaccharides are more effective than monosaccharides. It is also important to avoid deficiencies, such as of zinc or vitamin A, as those states impair adaptation (58). Some gastrointestinal regulatory peptides, such as calcitonin gene-related peptide (CGRP), cholecystokinin (CCK), glucagon-like peptide-2 (GLP-2), gastrin, gastric inhibitory polypeptide (GIP), peptide YY, neurotensin and neuropeptide Y may influence adsorption and stimulate adaptation. Of those, GLP-2 is currently the best studied (58) and is now therapeutically available (albeit at great cost) as a treatment for SBS patients (see LLL 12.2). Hormones with more global actions such as human growth hormone can be shown to have useful but with greater anxiety about their concomitant side effects, and other hormones such as somatostatin and vasoactive intestinal polypeptide (VIP) actively counteract adaptation (4).

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 fibre 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 – a frequent feature of intestinal inflammation - in the translocation of bacteria and the genesis of multiple organ dysfunction syndrome is uncertain, but there is a clear pathogenic 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 gastrointestinal continuity and optimizing function as well as the treatment of primary infection/inflammation. Adaptation of the nutritional regimen (immuno-nutrition) may play an adjunctive beneficial role.
7. References


