

Intestinal failure: Pathophysiological elements and clinical diseases

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Received: 2003-11-22 **Accepted:** 2003-12-16

Abstract

There are two main functions of gastrointestinal tract, digestion and absorption, and barrier function. The latter has an important defensive effect, which keeps the body away from the invading and damaging of bacteria and endotoxin. It maintains the systemic homeostasis. Intestinal dysfunction would happen when body suffers from diseases or harmful stimulations. The lesser dysfunction of GI tract manifests only disorder of digestion and absorption, whereas the more serious intestinal disorders would harm the intestinal protective mechanism, or intestinal barrier function, and bacterial/endotoxin translocation, of intestinal failure (IF) would ensue. This review discussed the theory of the intestinal failure, aiming at attracting recognition and valuable comments by clinicians.

Ding LA, Li JS. Intestinal failure: Pathophysiological elements and clinical diseases. *World J Gastroenterol* 2004; 10(7): 930-933
<http://www.wjgnet.com/1007-9327/10/930.asp>

INTRODUCTION

It is traditionally considered that the gut is quiescent in diseases. That is why the GI tract is not paid much attention and protected like other organs as heart, lungs and kidneys by ICU doctors. It is considered that the metabolism of the body takes place mainly in liver. Because of the advancements in research and surgical technology, issues in gastrointestinal metabolism, nourishment, anatomy, physiology and the like have been further understood. It is very important for functions of GI tract when body suffers from hunger and stress. It bears not only digesting and absorbing nutrients, but also supplying and modulating systemic immunity. Moreover, the GI tract can prevent germs and toxin from entering into the body (so-called barrier function). Capability in GI tract sometimes determines the recovery or deterioration of a disease. It is of traditional nutrition support that makes the intestinal mucous membrane in hunger and that would aggravate the intestinal dysfunction, or accelerate the occurrence of the intestinal failure. The further study and recognition of gut physiological function and pathophysiology hence, is of initial importance to gastroenterologists^[1-3].

RECOGNITION OF GI TRACT FUNCTION

There are unusual structures for GI tract: villus, microvillus,

crypt and tight junction. Small holes (about 0.4-0.7 nm in radius) bestrew the epithelial surface of the GI tract. The epithelial cells of small intestine is one of the tissues that most rapidly grow and metabolise in the body. It renews in 2-5 d for a cycle. The circular folds, villi and microvilli expand the absorptive area of small intestine to hundreds times of its primary area, reaching to 600 m²^[4-6]. Modern technology reveals that GI tract has following actions or functions except for digestion and absorption.

Gut is the primary one of four bacterial reservoirs in the body

There is a homeostasis between intestinal epithelium, total system and the flora in the bowel. Bacteria generally divide once every 20 min, but they only reproduce 4 to 5 generations within the bowel lumen. Once the balance destroyed, intestinal failure follows, bacteria translocation and morbidity would ensue. The upper GI tract and proximal jejunum are considered aseptic in general, because the number of bacteria in these sites is smaller or approximately equals to 10³^[7-11]. Table 1 lists the normal flora in the bowel^[7].

Table 1 Normal Flora in Humans' GI Tract

	Stomach	Jejunum	Ileum	Feces
Total bacterial count	0-10 ³	0-10 ⁵	10 ³ -10 ⁷	10 ¹⁰ -10 ¹²
Aerobic facultative or anaerobic bacteria				
Enterobacteria	0-10 ²	0-10 ³	10 ² -10 ⁶	10 ⁴ -10 ¹⁰
Streptococci	0-10 ³	0-10 ⁴	10 ² -10 ⁶	10 ⁵ -10 ¹⁰
Staphylococci	0-10 ²	0-10 ³	10 ² -10 ⁵	10 ⁴ -10 ⁷
Lactobacilli	0-10 ³	0-10 ⁴	10 ² -10 ⁵	10 ⁶ -10 ¹⁰
Fungi	0-10 ²	0-10 ²	10 ² -10 ³	10 ² -10 ⁶
Anaerobic bacteria	0	0	0	0
Bacteroids	Rare	0-10 ²	10 ³ -10 ⁷	10 ¹⁰ -10 ¹²
Bifidobacteria	Rare	0-10 ³	10 ³ -10 ⁵	10 ⁸ -10 ¹²
Gram-positive cocci ¹	Rare	0-10 ³	10 ² -10 ⁵	10 ⁸ -10 ¹¹
Clostridia	Rare	Rare	10 ² -10 ⁴	10 ⁶ -10 ¹¹
Eubacteria	Rare	Rare	Rare	10 ⁹ -10 ¹²

¹Includes peptostreptococcus and peptococcus.

Secretion and absorption of digestive juice

Secretions of gastrointestinal fluid during 24 h vary in different site or segments. They are: saliva, 500 mL, gastric juice, 1 000-2 000 mL, bile, 800 mL and pancreatic juice, 700 mL daily. Chyme in upper segment of jejunum (200 cm lower from duodenum-jejunal flexure) can be diluted into 5 to 8 times more than that of ingested amount. That is why stoma in proximal jejunum and the higher intestinal fistula could cause severely lose of water, electrolytes and nutrients^[1].

Immunological Functions

GI tract is the largest immune organ in the body. The mucosal immune system is made up of gut-associated lymphoid tissue (GALT), which contains 10¹⁰ cells/m and accounts for 80% of the total body immunocytes^[12].

Absorption function of different intestinal segments

Stomach and duodenum do not nearly absorb any nutrients.

The upper jejunum (a segment in 200 cm long distal from Treitz's ligament), absorbs carbohydrates, protein and most of water soluble vitamins, whereas the fat absorption needs a longer segment of jejunum. The ending segment of ileum contributes to absorption of vitB12 and re-absorption of bile-salts for circulation of intestine-liver. Right half of colon is in charge of absorption water and inorganic salts; and left half of colon, in charge of storage and excreting feces. Adaptation and compensation happens in structure and function of the rest small intestines and colons after resection of most parts of small intestine^[1].

A specific mechanism for nutrients absorption

Nutriments that all the organs and tissues needed in the body are supplied solely by arteries, but the intestinal mucous epithelia has a completely different mode of nutrient uptake. It receives 30% of nutrients from the artery and takes in the other 70% from the contents within the lumen directly. That is why total parenteral nutrition (TPN) could result in an atrophy of intestinal mucosa^[10,11].

INTESTINAL BARRIER FUNCTION

Conception of gut barrier and bacterial/endotoxin translocation

In normal situations the GI tract can only absorb the needed nutrients selectively. It is the largest reservoir of germs in the body and contains about 10^{12} of bacteria, occupying about 1/3 of dry weight of feces^[7]. Such an astronomical figures of bacteria produces a great quantity of toxin, which was not taken in by the intestine because of presence of the mucosal barrier function and hence no sickness was resulted by the toxin. Generally, the intestinal mucosa barrier is consisted of three parts: mechanical, biological and immune barriers. Any etiological factors that impair these barriers would cause bacterial/endotoxin translocation (a phenomenon that bacteria/endotoxin gets across the gut barrier and enter into blood and other aseptic tissues)^[13,14].

Mechanical Barrier

It consist of closed-lining intestinal epithelial cells^[5,6]. Many harmful factors and diseases could destroy this structure, such as intestinal obstruction, haemorrhagic and necrotic enteritis, chemotherapy, radiotherapy, using some medicines (for example, anti-inflammatory drugs of non-steroids) for a longer time and shock^[11,15].

Structure of intestinal mechanical barrier

It is constituted by intestinal epithelial cells and the tight-junction between enterocytes^[5,6]. The enterocyte apical membrane is interspersed with water-filled pores (<0.8 nm in radius), which permit the permeation of non-lipid polar molecules. The tight junction between enterocytes constitutes only a small proportion ($<5\%$) of the total surface area of the intestinal epithelium, which is about 0.95 nm in radius and permits transition of larger molecules. The dual saccharides test for measuring intestinal permeability is devised according to this structure^[5].

Immune barrier

It is composed of intra-epithelial secreting IgA, intra-mucosal lymphocytes, Payer's nodules and mesenteric lymph nodes. It is also called the GALT^[12]. Any factors that destroy the body's immunity, such as protein malnutrition, leukemia, systemic chemotherapy and HIV infection, would damage the barrier^[9,16].

Biological barrier

It is made up of normal inhabitant flora in GI tract, and hence the colonization resistance comes into being^[7,17]. It is an effect

of the flora that prevents the external or harmful bacteria from colonizing in the bowel because of the intrinsic flora holding the surface of intestinal mucosa. The colonization resistance would be destroyed by the alterations of inhabitant bacteria in the bowel. These diseases are bacterial enteritis, ileus (bacterial overbreeding), antibiotic enteritis (double infection), and so on^[1,18].

Micro-ecological equilibrium

There is a micro-ecological balance between bacteria in bowel with intestinal mucosal epithelia and the body system (the intestinal flora would colonizes for a postnatal infant in a few days). Any alterations in each of these three aspects would impair the balance and lead to sickness. Such cases are the impairment of systemic immunity (damage of immune barrier), destruction of intestinal mucosal structure (damage of mechanical barrier), and overgrowth of bacteria in the bowel (damage of biological barrier)^[1,17].

GASTROINTESTINAL TRACT IS A CENTRAL ORGAN FOR SURGICAL STRESS

Developments in different disciplines since the middle of last century have led to our current understanding and treatment of intestinal failure. This owes to the advances in 3 aspects: First, the application to both normal subjects and those with intestinal resection of new laboratory techniques, has advanced understanding of small intestinal function; Second, the scope of surgical treatments has extended to more complex operations on the intestine so that intestinal failure occurs more frequently and is often more severe; Third, clinical necessity has stimulated the application of innovative techniques to treat the condition in the short- or long-term^[1].

Clinical phenomena

(1) No matter what the cause is for critically-illed patients, infection would happen during the course of disease, and is one of the main causes of death. The mostly infected bacteria are normal intestinal flora. (2) Although isolated in aseptic wards for patients with transplantation of bone marrow, leukemia, and severe burns, they still had a high morbidity of infection. The pathogens cultured were mainly those of normal intestinal inhabitants. (3) Treatments with intravenous antibiotics and selected digestive decontamination therapy to these patients could markedly reduce the morbidity of infection. (4) Treatment with antibiotics excessively would cause a "double infection"^[1,18].

Animal experiments

(1) Enterocytes and colon cells proliferate rapidly (the enterocyte renew once in 5-7 d), and cover a broad area of intestinal inner surface. So metabolism and energy need for them are high. Windmueller *et al.*^[19] investigated the metabolism of mucosal epithelia with an isolated, vascularly perfused preparation of rat intestine. They discovered that small intestine extracted large amounts of glutamine as energy fuel when fed enterally miscellaneous nutriment quantitatively. The mucosal enterocyte converts most of the glutamine into metabolites of ammonia, alanine, citrulline. The epithelium metabolize the ketones (β -hydroxybutyrate, acetoacetate and acetone) as fuel, and colon combust short chain fatty acids. (2) It has been discovered through immunologic research that there are a great deal of intraepithelial lymphocytes, Peyer's nodules, secreted IgAs, lymphatic follicles and mesenteric lymph nodes (named as GALT- Gut associated lymphatic tissue) in gut. When stimulated by stresses, an intense immunologic responses in them would happen^[1,12]. (3) Phenomena revealed by experiments that phagocytosis of intestinal mucous epithelium and bacteria gain

access to blood stream and other tissues across the epithelia (so-called bacterial translocation) explain the existence of mucosal barrier of the gut^[18,20]. (4) Animals with intestines resected had a better resistance to trauma and strike than that of not resected when given equal parenteral nutrition. They had lived for a longer time and had a low morbidity of infection (such as Hammer-Hodges test that blocks the upper mesenteric artery temporarily so as to induce a lethal endotoxin shock in rabbits)^[21]. (5) Specific pathogen-free and gnotobiotic animals tolerate well to harmful stimulations and have lower morbidity of infection than that of ordinary animals.

Based on researches and advances we mentioned above, especially developments in medical sciences of last century, Wilmore^[17] suggested in 1988 that 'gut is a central organ after surgical stress'. The main contents of the hypothesis are as follows: The breakage of gut barrier occurs in patients after injury, multiorgan system failure, or severe burns and in persons with cancer after undergoing chemotherapy or bone marrow transplantation, which results in the entrance of bacteria and endotoxin into the blood stream and other tissues across the mucous epithelium from the gut. The cytokines produced by the reticular- endothelial system when body suffers from invasions of bacteria and endotoxin would stimulate pituitary-adrenal gland axis, and hence stress responses ensue. There are active metabolic effects for GI tract, especially when stimulated by stresses.

CONCEPTS OF INTESTINAL FAILURE

Historical retrospect

In the beginning of last century, Dr. Metchnikoff, the father of hypothesis of phagocytosis suggested that the entrance of microbes and associated toxin from the bowel into the body was an important cause of early death^[1]. In 1970's, the theory of multiple organs failure for death was put forward, underlying the facts that many critical-ill patients die of organs failure. But the concept have not given the course of evolving and transforming of a disease, whereas it just told a clinical phenomenon of a terminal patient^[22]. This is less helpful to treatments for patients by doctors. The studies in animal experiment and clinical investigation on physiology and pathophysiology of gastrointestinal tract have been increasingly reported since 1980s^[20,23-26]. The concept of multi-organs dysfunction syndrome (MODS) and systemic inflammatory response syndrome (SIRS) were raised since 1990s, and recognition in essence of inflammation, infestation and of the gut functions, and re-defining on them was made at the same time^[27-29]. All these have established a steady foundation for hypothesis of intestinal failure, which is a magnitude in gastroenterology, critical care medicine and infection-immunology *etc*^[1].

Definition of intestinal failure

The term 'intestinal failure' was first used by Irving and colleagues in the title of a paper published in 1980^[30]. The following year, a book chapter by Flamming and Remington^[1] gave the first definition as a 'reduction in functioning gut mass below the minimal amount necessary for adequate digestion and absorption of nutrients'. Now the viewpoint is further advanced. It widens the concept that 'reduced gastrointestinal absorption to the extent that macronutrient and/or fluid supplements are required', which includes the need for enteral or parenteral supplements to maintain a normal nutritional state. Malnutrition and/or dehydration would happen if supplements are not given or compensation does not work during the time^[31]. Comparative to description on functional failure of heart, lungs, brain and kidneys, it is no doubtful that the concept emphasized the equal importance of GI tract as other vital organs during the course of diseases.

CLASSIFICATION AND TREATMENTS OF INTESTINAL FAILURE^[1]

Staging of intestinal failure

Acute intestinal failure It is divided into reversible (in 6 mo) and causative surgical factors (such as percutaneous fistula, ileus), and those of internal medicine (such as chemotherapy or enteritis caused by acute radioactive injury, or infectious enteritis including HIV infection).

Chronic intestinal failure It results from following diseases: gastrointestinal resections (such as short bowel syndrome and gastrectomy), intestinal bypass operations (such as surgery for obesity treatment), and dysfunction of small intestine (such as pseudo-ileus, chronic enteritis - Crohn's and radioactive, microvilus atrophic or autoimmune enteropathy). Total or subtotal gastrectomy with a remnant of gastrointestinal disorders often needs nutrients complements and also belongs to intestinal failure.

Grading of intestinal failure

The severity of intestinal failure can be graded as follows according to the method by which macronutrients/fluid are given.

Severe intestinal failure Parenteral nutrition and/or parenteral saline are required because health cannot be sustained by exposing the small bowel mucosa to more, continuous or altered nutrients and/or electrolytes.

Moderate intestinal failure An enteral tube is used for the administration of macronutrients and/or a glucose/saline solution.

Mild intestinal failure Dietary adjustments, oral nutrients and/or a glucose/saline solution (or sodium chloride supplements) are needed.

A patient may change, due to compensatory mechanisms, from severe to mild IF with time. For example, a patient who has had a massive small intestinal resection, and in whom intestinal adaptation has occurred, may with careful dietary advice and appropriate drug therapy be able to stop parenteral nutrition (such as the intestinal rehabilitation therapy in short bowel syndrome).

COMMON DISEASES UNDERLYING IF

Acute IF

The usual conditions that cause an IF are as follows: (1) inflammatory diseases: in their attacks of Crohn's disease and ulcerous colonitis, especially in cases with surgical complications; (2) peptic ulcer; (3) pancreatitis; (4) mesenteric vascular disease; (5) malignancy; (6) external intestinal fistula; (7) cases receiving chemotherapy and transplantation of bone marrow; (8) AIDs; (9) others: such as acute ileus, gastric paralysis, inflammatory intestinal obstruction, severe intestinal infections (for example, shigellosis, cholera), external abdominal trauma (blunt or sharp and viscera rupture).

Chronic IF

(1) pseudo-intestinal obstruction; (2) radioactive enteritis; (3) post-gastrectomy; (4) short bowel syndrome; (5) post-surgery for obesity; (6) others: such as constipation resulting from various etiological factors.

The concept of IF presented above involves miscellaneous diseases and it seems confused because of that the meaning of the word 'failure' is different in Chinese from the English original word. It describes a broad functional status of an organ from dysfunction to complete loss of function in English meaning, whereas the word 'failure' denotes the function of an organ being severely injured or complete lost in Chinese. The gut has two functions: digestion and absorption, and barrier function. Therefore, we comprehend that the IF contains two implications: gastrointestinal dysfunction when there is only disorder of

digestion and absorption, whereas it would be named as IF when there is a disorder of barrier function. The former presents a less sick situation clinically and recovers easily, and the latter is complicated by critical illness or manifestations of severe enteropathy and has a high morbidity and mortality because of bacterial/endotoxin translocation. The suggested classification seems more reasonable, practical and directive.

EPILOGUE

Theory of IF is a great advancement in clinical medicine, especially in gastroenterology. It comes from developments and researches in the disciplines of critical care medicine, immunology in infection, clinical nutrition support and others. It also profits from developments in modern surgical technology and its clinical application. The IF theory has a significant guiding role to gastroenterologists. We should pay attention to the capability of GI tract in diseases and do not neglect protecting the barrier function of GI tract in clinical practice.

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Edited by Zhang JZ and Xu FM