REVIEW ARTICLE

Intestinal failure – its nature, pathophysiology and treatment

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The existence of 'intestinal failure' was proposed. This pathologic condition may occur in two distinct forms, ie short bowel syndrome marked by a gross reduction in functioning gut mass and impaired intestinal function (impairment of motility and extensive parenchymatous disorders). This has been newly recognized as a complex independent entity on account of an increasing number of patients that now survive thanks to the recent progress in nutritional management, especially total parenteral nutrition (TPN). In view of many unresolved clinical questions regarding long-term TPN and loss of gut mass, it is hoped that future research efforts will be directed towards settlement of these issues and how to surmount difficulties in bowel transplantation.

Introduction

'Intestinal failure' has come to be recognized as an established pathologic entity, as a consequence of the recent advance in total parenteral nutrition (TPN), which has made it possible to rehabilitate even patients with a total loss of intestinal function – a condition formerly believed to be incompatible with life.

This pathologic condition was defined by Miles Irving[1] as 'A reduction in functioning gut mass below that necessary for adequate digestion and absorption of food'. In other words, 'intestinal failure' is referred to when there is a sufficient loss of normally functioning intestine to make prolonged TPN an absolute necessity. This condition may roughly be divided into two types: one characterized by an absolute reduction in normally functioning gut mass and the other marked by an intestine suffering extensive lesions or functional insufficiency. It should be noted that the loss of intestinal function in either type signifies not merely a diminution of digestive and absorptive functions but also impairment of the ability of intestine as a barrier organ.

Frequency

At present, there is a move in many countries towards the concept of promoting the spread and registration system of home parenteral nutrition (HPN). It must be possible to obtain a rough estimate of the number of patients with intestinal failure in a given area from records kept at an HPN registry system. In the USA a special project named OASIS (Oley-ASPEN Information System) was set up in 1984 through collaboration of the Oley Foundation and the American Society for Parenteral and Enteral Nutrition (ASPEN) to fulfil the task of compiling data concerning home parenteral and enteral nutrition. According to an OASIS report published in 1990[2], there were 1703 HPN-treated cases registered during the year 1988 and, of a total of 1697 cases having definite diagnostic labels, the largest proportion (26.5%) was accounted for by malignant tumors, followed by Crohn's disease (16%), ischemic intestinal diseases (12.4%), disturbance of intestinal motility (9.9%) and others.

In Europe, on the other hand, Messing et al.[3] reported, in 1989, similar epidemiological data compiled from 27 European institutions up until 1986. According

Table 1. The current status of home parenteral and enteral nutrition in Asian countries.

	HPN	HEN
Australia	yes	yes (LRD)
China	yes	yes (ED, LRD)
Hong Kong	no	yes (ED, LRD)
Indonesia	no	yes (ED)
Japan	yes	yes (ED, LRD)
Korea	yes	yes (ED)
New Zealand	yes	yes (LRD)
Philippines	yes	yes (LRD)
Singapore	no	yes (ED)
Taiwan	yes	yes (ED)
Thailand	no	yes (ED, LRD)
	yes: 7, no:4	yes:11, no:0

ED: elemental diet.
LRD: low residue diet.

Table 2. The current status of home parenteral nutrition in Asian countries.

	'yes' or 'no'	Patients' number in 1992	Registry system
Australia	yes	>10	yes (previously)
China	yes	12	no
Hong Kong	no	0	no
Indonesia	no	0	no
Japan	yes	299	yes
Korea	yes	<10	no
New Zealand	yes	20	no
Philippines	yes	3	no
Singapore	no	0	no
Taiwan	yes	14	no
Thailand	no	0	no
	yes:7; no:4		yes:2; no:9

Table 3. Indication for home parenteral nutrition.

	Short bowel syndrome	Bowel dysfunctions	Malignant	Others	Total
China	9	3	–	–	12
Korea	–	–	yes (gastric cancer)	–	<10
Japan	83	62	141	13	299
New Zealand	15	5	–	–	20
Philippines	1	2	–	–	3
Taiwan	8	6	–	–	14

to them, Crohn's disease was most frequent, accounting for 30% of entire HPN cases registered, followed by ischemic intestinal diseases (22%), cancer of the digestive organs (17%), radiation enteritis (13%) and disturbance of intestinal motility (6%).

In Asian countries, including Australia and New Zealand, a survey of home nutrition by simple questionnaire was recently made by the author[4]. According to this report, 11 countries had experiences of home enteral nutrition, whereas seven of them (63.6%) had HPN experiences (Table 1).

As regards the yearly number of HPN patients, no other countries except Japan experienced over 20 patients in 1992 (Table 2). Indications of HPN in those countries are shown in Table 3.

In Japan, 'The Society for Home Parenteral Nutrition' was organized in 1985 and subsequently in 1990 the HPN registration system was set up. Hence, it was not until 1990 that yearly published reports on TPN cases were available to researchers at large[5]. According to registries for 1991, there were 299 HPN cases, of which: 143 (47.8%) were accounted for by malignancies; 55 (18.4%) by ischemic diseases of the intestine; 48 (16.0%) by inflammatory bowel disease; 24 (8.0%) by disturbance of intestinal motility; 14 (4.7%) by diarrheal and other benign digestive diseases; and 15 (5.0%) by miscellaneous disorders. Of these 299 cases, 82 (27.4%) had undergone extensive bowel resection. The relative predominance of malignant diseases, as seen in HPN registries in the USA, might reasonably be regarded as a reflection of the HPN promotion policy that has been carried out in recent years in Japan. At Osaka University Hospital, we had 37 HPN cases as of January 1993[6]. These comprised: 11 cases receiving a massive bowel resection; 13 cases of extensive intestinal dysfunction (six Crohn's disease, six infantile diarrhea and one nonspecific multiple ulceration of the small intestine); five cases of impaired intestinal motility (Chronic Idiopathic Intestinal Pseudo-obstruction – CIIPS); and eight cases of other disorders.

Individual categories of intestinal failure

Intestinal failure (chronic) can be roughly classified into two categories: massive bowel resection (short bowel syndrome); and bowel dysfunctions. The latter is further divided into disturbances of intestinal motility and extensive intestinal parenchym. The former category is of a physical reduction in functioning intestinal mass, while the latter pertains to functional impairment.

Massive bowel resection (short bowel syndrome)

Thanks to the recent progress in and standardization of techniques of TPN, it has become possible for short bowel patients to be rehabilitated and survive for a long time. Diseases of the intestine known to require massive bowel resection include: ischemic bowel disease (mainly in adults); volvulus; congenital multiple atresia of the small intestine; extensive intestinal aganglionosis; necrotizing enterocolitis; Gardner's syndrome; and extensive intestinal adhesion. The amount of functional loss resulting from massive bowel resection can be estimated from the length of intestinal remnant (jejunoileal) and also varies depending upon whether or not the ileocecal valve is removed, as pointed out by Wilmore in his previous literature survey[7]. He described that in infants with an intact ileocaecal valve, none survived with less than 15 cm of jejunum or ileum, while death occurred in all infants with ileocecal resection and remaining small intestinal segments measuring less than 40 cm. However, patients with an even shorter length of remaining intestine can successfully be weaned from parenteral nutrition if an appropriate nutritional regimen is used concomitantly and the lower limit of remaining gut length compatible with successful weaning from tube feeding is

Table 4. Factors influencing intestinal adaptation after small bowel resection.

Luminal nutrition
- oral nutrition (Wilmore, 1971[11])
- macromolecular nutrients (Buts, 1977[12], Eastwood, 1977[13])
- glucose, amino acids (Spector, 1977[14], Weser, 1981[15])
- pectin (Matsuo, 1987[16])
- zinc (Vanderhof, 1987[17], Tamada, 1992[18])

Parenteral nutrient components
- hydrolyzed casein (Vanderhof, 1983[19])
- monoacetoacetin (Kripke, 1988[20])
- short chain fatty acids (Koruda, 1988[21])
- long chain triglycerides (Morin, 1982[22])
- menhaden oil (Vanderhof, 1990[23])
- alanyl-glutamine (Tamada, 1992[24])

Hormonal factors
- gastrin (Johnson, 1975[25])
- enteroglucagon (Al-Muklar, 1982[26])
- epidermal growth factor (Saxena, 1992[27])
- insulin-like growth factor (Vanderhof, 1992[28])
- urogastrone-epidermal growth factor (Goodlad, 1985[29])

Pancreatico-biliary secretions

Mucosal blood flow

Neural effects

estimated to be 30 cm or less in children[8,9]. In adults, on the other hand, the extent of compensatory hypertrophy of remnant bowel will require lifelong parenteral nutrition. A good recovery of intestinal function can be expected from efficient use of numerous factors stimulating regeneration and hypertrophy of the remnant intestinal mucosa, in addition to prolonged nutritional management with appropriate enteral and parenteral nutritional regimens[10].

Varieties of factors, as listed in Table 4, are known to contribute to regeneration and hypertrophy of the intestinal mucosa and it is of the utmost therapeutic importance to make the best use of these factors. Among these factors, glutamine has received much attention recently, since this non-essential amino acid is taken up particularly by enterocytes in the intestinal mucosa and becomes a fuel for proliferation[30,31]. Tamada in our laboratory[24] performed massive small bowel resection in rats and gave alanyl-glutamine-enriched TPN for seven days, and noted a significant increase in villus height, crypt depth, mucosal protein and mucosal dissacharidase activity in the alanyl-glutamine-enriched group as compared with the standard TPN or conventional amino acid enriched (Isonitrogenous) groups. Recently, Wilmore et al[32] performed the first clinical trial of combined glutamine, growth hormone and dietary fiber in a short-gut patient and demonstrated its usefulness in retention of calorie, nitrogen, and potassium. A careful scrutiny of patients who are being switched to oral feeding without difficulty after long-term parenteral nutrition will often reveal complications of TPN, such as gall-stones, fatty liver, renal stones, osteoporosis and vitamin and trace element deficiencies. These are thought to be attributable to a loss of intestinal mucosa which is the main site of absorption of electrolytes, vitamins and trace elements as well as to an inappropriate composition of TPN solution used[8].

Impaired intestinal motility

In 1958, Dudley et al.[33] described a pathologic condition of intestine in which there occurred repeated episodes of ileus-like symptoms apparently in the absence of mechanical obstruction of intestine and named it intestinal pseudo-obstruction. Since then, there have reportedly been sporadic cases of a similar condition and, as the number of patients afflicted with this disorder but surviving with HPN (prolonged TPN regimen is the only salvage treatment for severe cases) increases, the existence of this pathologic condition as an independent entity has become widely recognized, although the alternative name for this disease 'Chronic Idiopathic Intestinal Pseudo-obstruction (advocated later by Maldonado[34]) is now more popular and widely accepted. Berdon et al.[35], in 1976, described a similar condition in the newborn infant marked by functional obstruction of intestine and designated it 'Megacystis Microcolon Intestinal Hypoperistalsis' (MMIHS). Some are of the opinion that these two conditions merely represent different aspects of a single entity, however, CIIPS is now classified into two varieties, one with muscular involvement (visceral myopathy) and the other with neuronal involvement (neuronal myopathy). This pathologic condition is extremely difficult to diagnose and its diagnosis can still now be made only by exclusion. According to Shuffler[36], LES (lower esophageal sphincter) pressure on esophageal manometry and dysperistalsis (synchronous contraction) of the lower esophagus are pathognomonic. Treatment is solely by prolonged parenteral nutrition at the present time, but there are a growing number of survivors, apparently as a result of setting up the long-term HPN aimed at improving the patient's quality of life. In the nutritional management of CIIPS, ample precautions should be exercised to maintain the water–electrolyte balance in view of the outpouring of secretion from the upper digestive tract. The prolonged TPN-associated development and exacerbation of hepatic failure is also a significant clinical problem. In fact, the patient died of hepatic failure in seven of our cases[37]. Autopsy findings in the liver of these patients were invariably those of liver cirrhosis. It is thought that bacterial translocation owing to atrophy of intestinal mucosa, prolonged endotoxemia and sepsis (infection) might have accelerated the onset of hepatic failure[38,39].

Extensive parenchymatous disorders of intestine

Conditions that fall under this category include Crohn's disease, nonspecific multiple intestinal ulcer and intractable infantile diarrhea. It is widely recognized that Crohn's disease is associated with a more severe protein malnutrition as compared to ulcerative colitis and it is in Crohn's disease that TPN, when performed on fasted patients, proves to be markedly effective in improving the general condition and in ameliorating intestinal lesions[40]. Since then, however, more recent studies have shown that such bowel rest can be obtained by elemental diet also, the indications for TPN are currently being limited to pre- and postoperative management and those special types of intestinal disease in which the entire small bowel is involved and, accordingly, conventional enteral nutrition is of no therapeutic benefit. The availability of TPN has made it possible for those patients to survive longer who would otherwise have died and will thereby provide a basis for etiological studies of intestinal diseases and conditions of unknown etiology.

Problems relating to long-term TPN

The aforementioned pathologic conditions, though quite distinct from each other, are all those for which long-term TPN has proven to be absolutely indicated. It should be recognized, however, that there are many problems to be solved before long-term TPN is performed safely and with success, of which the most important are: catheter-related sepsis; micronutrient abnormalities; and liver dysfunctions.

Of these major complications of TPN, catheter-related sepsis is the earliest recognizable one, the incidence of which has not been reduced to zero despite various preventive measures proposed and taken in many studies. However, the risk of severe septic complication has been greatly reduced by the use of a central venous catheter made of ingeniously chosen material, careful management of central venous line against contamination following strict protocol and immediate treatment of catheter once infected[41].

With regard to supplementation of micronutrients, specifically trace elements, zinc and/or copper deficiency was reported when long-term parenteral nutrition

became feasible. Subsequently, as the number of cases receiving TPN of years duration increased, selenium, chromium, molybdenum or manganese deficiency came to be documented, thus calling attention to the physiologic significance of these essential trace elements. Now that various trace elements preparations for intravenous use are commercially available and measurement of trace elements has become a routine procedure in most of institutions, the incidence of deficiencies in these trace elements in general is on the decrease as a natural consequence. Instead, the existence of unknown essential trace elements[42] and occult trace element deficiency have become new issues.

Parenteral nutrition-associated liver dysfunction, because of the complexity and difficulty of therapeutic access, is probably a problem of greatest concern. It has long been known that prolonged parenteral nutrition is accompanied by a transient elevation of hepatic enzymes (mainly transaminases), gallstone formation and appearance of fatty liver, which infrequently becomes serious. However, cholestasis often seen in neonates, and severe fibrosis and cirrhosis of the liver which occurs following massive bowel resection or in association with retention of intestinal contents may frequently and ultimately lead to hepatic failure and not infrequently have a fatal outcome, thus posing a significant problem[37,43]. Possible involvement of infection in the pathogenesis of these hepatic disorders has been suggested and it is postulated that gut-associated sepsis[44] or endotoxemia caused and perpetuated by increased bacterial translocation within the intestinal mucosa gives rise to cellular infiltration, bile canaliculitis and biliary stasis in the intrahepatic portal area, which in turn facilitates the development of hepatic fibrosis.

Future problems

Intestine as an organ in multiorgan failure (acute intestinal failure)

As mentioned earlier, there are two forms of intestinal failure – acute and chronic – as is the case with any other organ. Recent studies have implicated co-existing infection as an important factor in multiorgan failure (MOF). And it is the intestine that is deemed to be largely and primarily responsible for such infection[44]. The intestine, which is constantly exposed to foreign bodies and is the habitant of intestinal bacteria, so to speak, is provided with an intricate system of ingenious anti-infective defense mechanisms in the mucosa and lymph nodes to protect the body against invading and noxious agents from the outside. The intestinal mucosa is normally covered with a thick layer of mucus, wherein are contained diversities of active substances having antimicrobial action, enzymes, secretory IgA (sIgA), lymphocytes and macrophages to form a barrier against antigens. However, once an invasion or accident affecting the entire body (eg infection, trauma, burns and malnutrition) happens, the defense mechanisms become so deranged that they permit intestinal bacteria and toxins to pass through the intestinal mucosa and thereupon cause sepsis and hepatic injury (bacterial translocation). In such an emergency, cytokines, such as tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-2 and IL-6, and prostaglandins are released from macrophages and monocytes to act themselves as a factor to facilitate hepatic injury. It has also been indicated that, under such circumstances, hypersecretion of various stress hormones (eg cortisol, catecholamines and glucagon) occurs and greatly affects the metabolism of energy substrates in the body, which points to the importance of supplying the necessary amounts of energy yielding and protein sources for replenishing depleted body sources.

Intestinal transplantation

In many countries, organ transplantation has recently become a routine surgical procedure, thus transplantation programs owe much or their current proliferation to the advent of immunosuppressive agents, notably cyclosporin-A (CyA) and FK506. Encouraged by these circumstances are attempts at clinical transplantation of the small intestine, an organ whose transplant, it has been believed, is the least viable.

Transplantation of the small intestine, generally, is thought to be indicated for three groups of intestinal diseases: intestinal failure (short bowel syndrome); a group of diseases characterized by severe intestinal dysfunction (Crohn's disease, chronic idiopathic intestinal pseudo-obstruction, infantile diarrhea, etc); and special metabolic disorders (Crigler-Najjar syndrome, etc)[45].

The small intestine, being abundant in gut-associated lymphoid tissue (mesenteric lymph nodes, Peyer's patches), is far more potent in immunogenicity than any other organ and, accordingly, rejection cannot be completely prevented by any currently available immunosuppressive drugs whatsoever. This drawback has made clinical application of small bowel transplants lag far behind other fields of organ transplantation.

Since the introduction of cyclosporin-A (CyA) into clinical practice in the 1980s, overall results of organ transplantation have remarkably improved. In 1985, the first small bowel transplantation using CyA was performed by Cohen et al. of Toronto[46] and similar attempts were subsequently made in succession by groups in Chicago, Paris, Kiel, London (Canada) and Pittsburgh. At the twelfth International Conference on Transplantation in 1988, small bowel transplantation was taken up as the topic for one of the symposia and the first International Symposia on Small Bowel Transplantation was held in London, UK in October 1989. In 1989, Starzl and Todo[47] began to actively perform transplantation of the small intestine or multiple organs using not only CyA but also a new immunosuppressive agent, FK506.

In October 1991, the second International Symposium on Small Bowel Transplantation was held in London, Canada. While European (mainly French) results with CyA were not substantially improved compared with those presented in the previous reports, results of simultaneous transplantation of the intestine and liver obtained by several groups were encouragingly good. This is possibly due to the tolerance induction by liver transplants per se. In small bowel transplantation, an entire organ transplant is not always required (a minimum of 50 cm of bowel is said to be enough for fulfilling necessary digestion and absorption in adults) and it is possible to procure a transplant from a living donor as in the case of renal transplantation. Moreoever, as the recipient's life can be well maintained until transplant

implantation with the aid of parenteral nutrition, HL-A matching can be done thoroughly. Thus, clinical transplantation of the small intestine is feasible and amply justifiable in Japan where a consensus on brain death has not been reached yet. Recently there has been a rapid increase in clinical cases of small bowel transplantation, and by the end of December 1992, over 70 clinical cases were reported, in which about half of the patients survived[48]. Thus, clinical transplantation of the small intestine is no longer an experimental attempt but is already becoming a therapeutic reality. Also in Japan, recent studies have aroused growing interest in small bowel transplantation as an ultimate approach to the problem of intestinal failure and it is felt that its application to actual clinical cases will be made before long.

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腸衰竭 —— 它的性質、病理生理和療法

摘要

腸衰竭的產生已被提出。此病理情況，有兩種明顯的類型。那就是短腸綜合症（以功能腸段大量減短爲特徵）和腸功能損害（腸能動性損害和廣泛的腸實質性疾病）。由於病人數目的增加，最近已承認爲一種複雜、獨立的疾病，感謝最近營養處理，特別是全靜腺內營養（TPN）的進展，使病人得以存活下來。從許多未解決的臨床問題看來，如長期 TPN 和腸主體的喪失，希望將來研究直接解決這些問題和怎樣克服腸移植的困難。

腸管不全なる病態の存在を提起した。この病態は二種の病態即ち短腸症候群（機能しうる腸管容積の著しい減少）および腸管機能障害（腸管運動障害および腸管広汎実質障害）に大別される。これらの病態は最近の進歩著しい各種栄養法とりわけ静脈栄養法の進歩により延命しうる患者数が増加し、その存在が認識されるようになったものである。長期静脈栄養施行上の問題点、或いは腸管機能脱落に伴う合併症の発生など、今後解決されるべき問題はなお多い。腸管移植の実現への努力をも含めて患者治療成績の向上が期待される。