Intestinal permeability and systemic infections in critically ill patients: Effect of glutamine*

Daurea A. De-Souza, MD, PhD; Lewis J. Greene, PhD

Objective: **This article provides a critical review of the evidence indicating that an increase in intestinal permeability is associated with the installation of bacteremia, sepsis, and the multiple organ failure syndrome and that glutamine in pharmacologic doses reduces the acute increase of intestinal permeability and the infection frequency in critically ill patients.**

Data Source: **All studies published until December 2004 about intestinal permeability, bacterial translocation, and glutamine were located by search of PubMed and Web of Science. The reference lists of review articles and primary publications were also examined to identify references not detected in the computer search.**

Study Selection: **Clinical and experimental studies investigating the correlation between intestinal permeability, bacterial translocation, and frequency of infections, associated or not with the effect of glutamine administration.**

Data Extraction: **Information regarding patient population, experimental design, glutamine doses and routes of administration, nutritional therapy prescribed, methods used to assess intestinal permeability, metabolic variables, and the frequency of infections were obtained from the primary literature.**

Data Synthesis: **Intestinal permeability is increased in critically ill patients. The results have not always been consistent, but the studies whose results support the association between intestinal permeability and systemic infections have had better design and more appropriate controls. The administration of glutamine by the intravenous or oral route and at the doses recommended before or immediately after surgery, burns, or the administration of parenteral nutrition has a protective effect that prevents or reduces the intensity of the increase in intestinal permeability. Glutamine reduces the frequency of systemic infections and may also reduce the translocation of intestinal bacteria and toxins, but this has not been demonstrated.**

Conclusions: **Glutamine administration improves the prognosis of critically ill patients presumably by maintaining the physiologic intestinal barrier and by reducing the frequency of infections. (Crit Care Med 2005; 33:1125–1135)**

KEY WORDS: glutamine; intestinal permeability; bacterial translocation; systemic infections; multiple organ failure syndrome; critically ill patients

ASSOCIATION OF INCREASED INTESTINAL PERMEABILITY WITH SYSTEMIC INFECTIONS AND THE MULTIPLE ORGAN FAILURE SYNDROME

Several investigators have suggested that the increase in paracellular intestinal permeability demonstrated in critically ill patients is associated with an increased incidence of bacteria and toxin translocation from the intestinal lumen to the systemic circulation, causing infectious complications including sepsis and the multiple organ failure syndrome (MOFS) (1, 2). This possibility was first explored by Ziegler et al. (3), who measured the urinary excretion of an orally ingested mixture of lactulose and mannitol (4) and demonstrated that the intestinal permeability of burn patients increases with the presence of infection (lactulose/mannitol ratio = 0.113 ± 0.033 among burn patients with infection vs. 0.035 ± 0.005 among healthy persons). At the time of the study, noninfected burn patients had lactulose/mannitol ratios equal to those of healthy persons (0.036 ± 0.007). Despite its originality and importance, the study had some limitations. Few patients were studied (n = 15) and they were evaluated only 15 ± 4 days (noninfected burn patients) and 18 ± 5 days (infected burn patients) after the burn. It was not clear whether the burn injury caused the increase of the intestinal permeability, whether the increase of intestinal permeability caused systemic infections, or whether the systemic infections increased the intestinal permeability.

One of these questions was clarified by Deitch (5), who demonstrated that paracellular intestinal permeability (lactulose/mannitol ratio) of patients with burns covering >20% of their body surface, in stable hemodynamic condition and without infection, is increased within 24 hrs after the injury (0.052 ± 0.011 among burn patients vs. 0.017 ± 0.002 among healthy persons); that is, the situation of severe burn *per se* increases intestinal permeability. In addition, Le Voyer et al. (6) showed that burn patients who developed clinical infections within 2–14 days after the injury had a significantly greater increase in intestinal permeability (lactulose/mannitol ratio = 0.208 ± 0.02) than burn patients who did not develop infection (lactulose/mannitol

***See also p. 1175.**

From the Department of Internal Medicine, Faculty of Medicine, Federal University of Uberlândia (DADS), Uberlândia, MG, Brazil; Protein Chemistry Center (DADS, LJG); Regional Center for Hemotheraphy of Ribeirão Preto (DADS, LJG) and the Department of Cellular and Molecular Biology and Pathogenic Bioagents (LJG), Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.

Supported, in part, by CNPq (PRONEX), FAPESP (CEPID) and the Regional Center for Hemotheraphy of Ribeirão Preto.

Address requests for reprints to: Lewis J. Greene, PhD, Regional Center for Hemotheraphy of Ribeirão Preto, Rua Tenente Catão Roxo 2501, 14051-140, Ribeirão Preto, SP, Brazil. E-mail: ljgreene@fmrp.usp.br

DOI: 10.1097/01.CCM.0000162680.52397.97

ratio = 0.082 ± 0.02) and than control healthy subjects (lactulose/mannitol ratio = 0.017 ± 0.003).

The relationship between intestinal permeability and systemic infections was clarified by Faries et al. (7), who demonstrated that on the fourth day after admission, patients with multiple traumatic injuries present a significant correlation between increased intestinal permeability and all indexes of injury severity used (ASCOT, Trauma and Injury Severity Score, Injury Severity Score, RTS, and Acute Physiology and Chronic Health Evaluation II). Compared with patients with moderately increased intestinal permeability (lactulose/mannitol ratio of 0.030–0.100, n = 18), patients with markedly increased intestinal permeability (lactulose/mannitol ratio ≥0.100, n = 11) presented a higher frequency of the systemic inflammatory response syndrome (SIRS, 83% vs. 44%), infectious complications (58% vs. 13%), and MOFS (55% vs. 17%). Similar results were obtained by Doig et al. (8) when they compared the increase of intestinal permeability (lactulose/mannitol ratio) of 47 critically ill patients with the development of MOFS. The increase in intestinal permeability was the only variable predictive of MOFS among the 28 patients (60% of the sample) who developed this complication. In addition, the intensity of the increase of intestinal permeability was associated with the severity of MOFS, as assessed by the classification system of Marshall et al. (9). The patients who developed MOFS continued to have increased intestinal permeability, presenting a significant delay in its normalization compared with patients who did not.

In view of the results of these studies, we conclude that severe injury *per se* (5) and the presence of infection (6) are associated with increased intestinal permeability and that, the greater the intensity (7) and duration of the increase in intestinal permeability (8), the greater the severity of the clinical signs and symptoms of the patients and the risk of the onset of infectious complications, SIRS, and MOFS.

In contrast to these studies demonstrating an association between increased intestinal permeability and systemic infections, other laboratories have not demonstrated this association (10–13). The data in Table 1 provide an analysis of studies that obtained both positive and negative results. The following criteria were satisfied by most of the studies that demonstrated an association between increased intestinal permeability and systemic infections: a) a relatively large number of patients were studied; b) inclusion/exclusion criteria for the patients under study were well defined; c) the patients were better stratified regarding the severity of injury and/or the intensity of the increase in intestinal permeability; d) conditions were established to increase the accuracy of the test measuring intestinal permeability, such as better pairing of patients with controls, use of the ratio of the urinary excretion of two specific markers, and determination of reference values for the geographic region in which of the population under study resides (14); e) the urine samples were refrigerated and/or bacteriostatic agents were added during and/or immediately after the execution of the permeability test; f) two or more measurements of intestinal permeability were performed for the same patient at different times; and g) similar mannitol excretion values were obtained for the healthy controls and for the patients under study since the intestinal permeability for mannitol (transcellular) is not altered by injury and/or infection (15). On the basis of the considerations summarized in Table 1, it is clear that those studies whose results demonstrated an association between intestinal permeability and systemic infections had a better design and used better controls than those whose results did not.

BACTERIAL TRANSLOCATION

Can the translocation of bacteria and toxins from the intestinal lumen to the systemic circulation explain the association between increased intestinal permeability and systemic infections in critically ill patients? In clinical practice, critically ill patients frequently present bacteremia, sepsis, or MOFS in the absence of an identifiable focal point of infection. Goris et al. (16) demonstrated that no septic focus was detected clinically or even at autopsy in 31 patients (34% of the sample) with bacteremia who developed clinical sepsis or MOFS. This observation is consistent with the view that the intestine is a reservoir of bacteria and of bacterial products (endotoxins, exotoxins, and cell wall fragments) that may escape from the intestinal lumen to the mesenteric lymph nodes, bloodstream, and inner organs (1, 17). In critically ill patients, the intestine is believed to be not only the target but also the site responsible for the production of inflammatory mediators that may contribute to the installation of SIRS as well as bacteremia, sepsis, or MOFS (8, 18, 19). The risk of infectious complications caused by enteric bacteria is higher among patients with ischemia/reperfusion of the intestine after a cardiopulmonary bypass (20) or hemorrhagic shock (21); among patients with intestinal obstruction (22), immunosuppression (23), or malnutrition (24); and among alcoholic patients with cirrhosis (25).

Bacterial translocation has been demonstrated directly in laboratory animals on the basis of monitoring bacterial migration using tissue histology, microbial culture of internal organs, and dissemination of specifically labeled intestinal bacteria (26–28). In humans, there are a limited amount of data demonstrating intestinal bacterial translocation (for reviews, see Refs. 17, 29, 30). Recovery of viable enteric bacteria from mesenteric lymph nodes is considered by some to be one of the most sensitive direct methods to demonstrate gut barrier failure and bacterial translocation (1, 31), but others argue that is not clear whether positive nodes merely represent a normal immunogenic event or reflect some form of a morbid state (17, 18).

An increase of gut wall permeability measured by tracers (e.g., lactulose/mannitol) was considered by Redl et al. (32) to be an indirect demonstration of bacterial translocation. The adequacy of lactulose and mannitol as probes for the measurement of intestinal permeability in humans has been validated by the demonstration that 100% of these intravenously administered markers are recovered in the urine and by the fact that the distribution volumes and patterns of excretion of these markers are virtually identical and the oxidation of intravenously administered mannitol accounts for only about 1% of the dose (33). Recently some of the assumptions underlying the differential sugar permeability test have been questioned (34). For example, healthy rats submitted to fluid loading present an increased lactulose/rhamnose ratio independent of changes in intestinal permeability (35). Furthermore, the diffusion of markers across rat colonic mucosa is directional and temperature-dependent, suggesting that active processes are involved (36). These contradictory results may reflect only differences between species or tissues, and further investigation is necessary.

The methods used to demonstrate the translocation of intestinal bacteria in lab-

Table 1. Studies that do or do not demonstrate an association between high intestinal permeability and systemic infections in hospitalized patients

	An Association Was Demonstrated Between High Intestinal Permeability and Infection	No Association Was Demonstrated Between High Intestinal Permeability and Infection
No. of patients	A large number of patients was used 15 patients exposed to burns (6) 29 patients with multiple traumas (7) 47 critically ill patients (8)	A smaller number of patients was used, and/or patients with different pathologies divided into subgroups 16 patients in the ICU, with different pathologies (10) 11 patients with trauma and 8 patients with aneurysms (11) Patients with multiple injuries divided into 11 patients with and 21 patients without multiple organ failure syndrome (12) 21 patients with cancer of the esophagus, 27 patients with gastric cancer, 20 patients with pancreatic carcinoma submitted to surgery (13)
Inclusion/exclusion criteria (chronic renal failure, anuric renal failure, chronic intestinal inflammatory disease, use of anti-inflammatory agents, use of lactulose and mannitol as part of the treatment plan, among others)	A better definition of criteria of patient inclusion/exclusion (6–8)	Less well-defined criteria for patient inclusion/exclusion (10–13)
Patient stratification according to severity of injury	A good stratification was performed Mean burned body surface: 53.5 ± 5.1% (6) ASCOT, TRISS, ISS, RTS, APACHE II (7) APACHE II, TISS, APS (8)	A more simplified stratification was performed APACHE II, TISS (10) APACHE II for all patients, ISS for patients with trauma (11) ISS (12) Patients with gastric, esophageal and pancreatic cancer (13)
Patient stratification according to the intensity of the increase in intestinal permeability	Stratification was performed Increased intestinal permeability—L/M[a] between 0.030 and 0.100 highly increased intestinal permeability—L/M[a] > 0.100 (7) Upper normal L/M[a] limit: 0.030 (several hundreds of healthy persons) (8)	Stratification was not performed (10–13)
Mean age of the control group and of the patient group	Similar values 25.6 ± 1.9 yrs for the control group vs. 32.7 ± 3.6 yrs for burn patients (6) 28 ± 2 yrs for the control group vs. 33 ± 16 yrs for critically ill patients (7)	Different values Mean age of 22 yrs for the control group vs. 55 yrs for critically ill patients (10) 31 ± 9 yrs for the control group vs. 69 ± 6 yrs for patients with aneurysms (11) There was no control group (13)
Values of urinary mannitol excretion for the healthy controls and for the patients under study	Similar values 10.3% for the control group vs. 9.2% for burn patients (6)	Different values 10.4% [7.1 to 14.8] for critically ill patients vs. 31.07% [20.8 to 37.5] for the control group (10) 9.2 ± 11.6% for patients exposed to trauma and 9.6 ± 8.3% for patients with aneurysms vs. 21.9 ± 8.3% for the control group (11) No mention of a control group. Literature reference values were used (13)
Conservation of urine containing sugars (lactulose, mannitol, etc.) during and/or immediately after the test	Procedures executed Urine refrigeration and later freezing at −20°C (6) Addition of triethanolamine buffer (7) Addition of gentamicin and 10% thymol (8)	No report of the measures used for urine conservation during or immediately after the test (12)
No. of measurements of intestinal permeability	2 or more measurements (6–8)	One measurement (11)

ICU, intensive care unit; TRISS, Trauma and Injury Severity Score; ISS, Injury Severity Score.
The numbers in parentheses are reference numbers.

oratory animals usually cannot be applied to humans (32). However, the results of several clinical studies have demonstrated that bacteria isolated from patients with systemic infections are often of the same strain as bacteria predominantly present in the fecal flora (37), that Gram-negative bacteria present in the intestine often are the agents responsible for infectious complications in high-risk hospitalized patients (38), and that enteric bacteria which presumably have translocated are sometimes recovered from the mesenteric lymph nodes of high-risk patients submitted to surgery (39). In addition, the incidence of infectious complications can be reduced by the administration of antibiotics for selective decontamination of the gastrointestinal tract (40, 41), and other therapeutic measures directed at intestinal dysfunction also improve the prognosis of critically ill patients (for reviews, see Refs. 42, 43). This favorable patient response can be explained by the reduced production of proinflammatory factors after intestinal injury and by the reduction of the expression of virulence genes of the bacteria of the intestinal flora. The interactions between microbes and enterocytes can be modified by circulating stress hormones (for reviews, see Refs. 44, 45). The expression of PA-1 lectin/

Table 2. Effect of glutamine on intestinal permeability of patients with acute and chronic diseases

Effect of Glutamine vs. Type of Injury	Reference	Clinical conditions: Patients Under Study	Clinical conditions: Control Patients	Dose of Glutamine	Glutamine Administration Initiation Route Duration
"Protective" effect of glutamine in patients exposed to acute injury	Jiang et al (87)	60 patients undergoing major abdominal surgery	60 patients undergoing major abdominal surgery	0.50 g/kg/day of the alanine-glutamine dipeptide (Dipeptiven, Fresenius Kabi Bad Homberg, Germany), equivalent to 0.34 g glutamine/kg/day	1st day postsurgery Intravenous route 6 days
	Zhou et al (88)	20 patients exposed to severe burns	20 patients exposed to severe burns	0.50 g/kg/day of the alanyl-glutamine dipeptide (Ajinomoto, Tokyo, Japan) equivalent to 0.35 g L-glutamine/kg/day	1st day after burn Enteral route 11 days
	Peng et al (89)	25 patients exposed to severe burns	23 patients exposed to severe burns	0.50 g/kg/day of the glutamine "granules" (Chongqing Yao You Pharmaceutical)	Within 48 hrs after burn Oral route 14 days
	van der Hulst et al (86)	10 patients with inflammatory bowel disease and neoplastic disease	10 patients with inflammatory bowel disease and neoplastic disease	0.23 g (0.20–0.26) glutamine/kg/day Glycyl-L-glutamine	1st day of the total parenteral nutrition Intravenous route 10–14 days
"Therapeutic" effect of glutamine in patients with chronic diseases	Noyer et al (90)	16 patients with AIDS (8 patients in each subgroup)	8 patients with AIDS	4 g or 8 g of glutamine/day	Outpatients in treatment for AIDS Oral route 28 days
	Den Hond et al (91)	7 patients with Crohn's disease	7 patients with Crohn's disease	21 g of glutamine/day (ICN Biomedicals, Cleveland, OH)	Patients in treatment for Crohn's disease Oral route 4 wks

L/M ratio, lactulose/mannitol ratio.

[a]Compared with control patients; [b]compared with patients under study. The numbers within parentheses refer to references.

adhesin, a key virulence determinant of experimental *Pseudomonas aeruginosa* gut-derived sepsis, may be induced in mice submitted to surgical stress (46). Furthermore, strains of cecal *Escherichia coli* harvested from stressed mice after hepatectomy-starvation present major adherence and reduce the transepithelial electrical resistance of cultured mouse colon cells (47).

Wells and Erlandsen (31) suggested that, although the available data provide only circumstantial evidence, they are consistent with the view that the translocation of bacteria from the intestinal lumen to the systemic circulation is responsible for the development of bacteremia and sepsis in critically ill patients. More recently, however, the clinical relevance of bacterial translocation in humans has been questioned (19) and even rejected (44). In a study by Moore et al. (48), 20 critically ill patients were analyzed after major torso trauma (13 patients with blunt trauma and seven patients with penetrating trauma), some of them in a state of shock at the time of hospitalization (systolic blood pressure <90 torr in 12 patients, i.e., 60% of cases), who required emergency laparotomy. Among these patients, the presence of bacteria was rarely detected in portal vein blood cultures (eight positive cultures among 212 carried out on blood samples obtained during laparotomy and then 6, 12, 24, and 48 hrs and 5 days after

Table 2. *Continued*

Results			
Intestinal Permeability of Patients			
Patients Under Study		Control Patients	Intestinal Permeability of Healthy Control Subjects
L/M ratio = 0.058 ± 0.049 (n = 30)	Day 3 before surgery	L/M = 0.047 ± 0.029 (n = 30)	—
L/M ratio = 0.097 ± 0.063 (n = 30) Glutamine administration	Day + 7 after surgery $p = .02^a$	L/M = 0.132 ± 0.081 (n = 30) Balanced amino acid solution administration	
L/M ratio = 0.268 ± 0.202 (n = 20)	Postburn day + 1 $p = .538$	L/M ratio = 0.221 ± 0.169 (n = 20)	L/M ratio = 0.022 ± 0.0016 Healthy Chinese (n = 40)
L/M ratio = 0.025 ± 0.008[a] (n = 20) Glutamine administration for 2 days	Postburn day + 3 $p = .01^a$	L/M ratio = 0.049 ± 0.016 (n = 20) Balanced amino acid mix administration	
L/M ratio = 0.018 ± 0.003[a] (n = 20) Glutamine administration for 5 days	Postburn day + 6 $p = .034^a$	L/M ratio = 0.051 ± 0.013 (n = 20) Balanced amino acid mix administration	
L/M ratio = 0.018 ± 0.013 (n = 20) Glutamine administration for 11 days	Postburn day + 12 $p = 0.23$	L/M ratio = 0.036 ± 0.021 (n = 20) Balanced amino acid mix administration	
L/M ratio = 0.25 ± 0.06 (n = 25)	Before treatment	L/M ratio = 0.26 ± 0.09 (n = 23)	L/M ratio = 0.03 ± 0.01 Healthy university students (n = 10)
L/M ratio = 0.12 ± 0.09[a] (n = 25) Glutamine administration for 14 days	$p < .01^a$	L/M ratio = 0.20 ± 0.06 (n = 23) Placebo	
Lactulose = 1.4% (0.4–3.7) (n = 10) Mannitol = 8.5% (5.2–13.5) (n = 10)	Day 0	Lactulose = 0.7% (0.4–5.1) (n = 10) Mannitol = 15.6% (6.5–35.8) (n = 10)	Healthy volunteers (n = 12) Lactulose = 0.4% (0.2–0.6) Mannitol = 17.6% (13.3–21.3)
Lactulose = 1.0% (0.6–2.0) (n = 10) Mannitol = 7.9% (1.0–10.5) (n = 10)		Lactulose = 1.5% (0.6–5.1) (n = 10) Mannitol = 9.4% (2.0–18.1) (n = 10)	
Total parenteral nutrition + glutamine administration		Total parenteral nutrition with the same amount of nitrogen and calories, and the same volume	
	Last day		
The difference between the L/M ratio on day 0 and the last day was not significant		The difference between the L/M ratio on day 0 and the last day was significant ($p < .01$)[b]	
L/M ratio = 0.07 ± 0.02 (4 g Gln/day, n = 8) L/M ratio = 0.07 ± 0.02 (8 g Gln/day, n = 8)	Before glutamine administration	L/M ratio = 0.06 ± 0.01 (placebo, n = 8)	
L/M ratio = 0.11 ± 0.08 (4 g Gln/day, n = 8) L/M ratio = 0.07 ± 0.03 (8 g Gln/day, n = 8) After glutamine administration for 28 days	No significant	L/M ratio = 0.13 ± 0.04 (placebo, n = 8) Placebo—6 g table sugar	—
^{51}Cr EDTA = 2.32 ± 0.77% (n = 7)	Before glutamine administration	^{51}Cr EDTA = 2.29 ± 0.67% (n = 7)	Increased permeability was defined as a 6-hr cumulative excretion > 1.1% of the dose of ^{51}Cr-EDTA
^{51}Cr EDTA = 3.26 ± 2.15% (n = 7) After glutamine administration for 4 wks	No significant	^{51}Cr EDTA = 2.27 ± 1.32% (n = 7) Placebo—Glicine	

injury). Furthermore these positive cultures may have been the result of contamination since only one systemic blood culture was positive. However, during the postoperative period, six patients (30% of cases) presented MOFS.

The apparent contradiction between the relatively low number of positive cultures from the portal vein blood and the installation of MOFS demonstrated by Moore et al. (48) has been used as an argument to question the view that bacterial and/or toxin translocation is the primary or sole cause of the development of MOFS after intestinal ischemia/reperfusion (19, 44). However, damage to the physiologic intestinal barrier permits the adherence and/or internalization of intestinal bacteria by cells of the intestine (49, 50). The early translocation of bacteria and/or toxins to the intestinal wall may trigger SIRS and dysfunction of distant organs by activating the intestinal inflammatory response, even when the translocated bacteria are destroyed by the immunologic and nonimmunologic cells of the intestine. Under these conditions, the intestine could become a producer of cytokines and other proinflammatory factors and the mesenteric microcirculation the site of activation of circulating neutrophils (19). On the other hand, late bacterial translocation due to the break of the intestinal barrier induced by many factors in immunodeficient hosts and in injured patients who are terminal on ar-

rival may lead to bacteremia, sepsis, and MOFS (18).

The view that the intestinal lymphatics are the principal pathway for toxic or proinflammatory factors produced by the intestine and that subsequently reach the systemic circulation is supported by clinical and experimental data. Lymphatic mesenteric nodules are the first and frequently the only tissue to present a positive culture for enteric bacteria (19, 29), and elevated levels of endotoxin of intestinal origin have been identified in the thoracic duct before their subsequent detection in the portal circulation (51). Recently it has been shown that unidentified biologically active factors are present in the mesenteric lymph, but not the portal plasma, of rats with intestinal injury induced by hemorrhagic shock or burns (52). These substances are toxic for endothelial cells and activate neutrophils, conditions that can lead to gut-origin organ failure. The ligation of the mesenteric lymphatic duct minimizes or inhibits the installation of pulmonary injury induced by hemorrhagic shock in primates (53). In humans, the translocation of lymphatic bacteria and toxins has been rarely studied. In a study developed in intensive care patients, Lemaire et al. (54) presented evidence for endotoxin translocation beyond the mesenteric lymph nodes into the thoracic duct, but differences in endotoxin concentrations in lymph and blood were not demonstrated between patients with and without MOFS, and the quantity of endotoxin transported by the thoracic duct was low (41–63 units/L). However, the lymph cytokines and cytokine-receptor-antagonist levels were higher in the MOFS group. These results with patients add further support to the experimental studies indicating that the intestine could become a proinflammatory organ and that nonbacterial factors produced in the intestine and present in mesenteric lymph can contribute to distant organ injury.

These interpretations reconcile the results of apparently contradictory studies, identifying the role of the intestine as the principal organ responsible for the production of inflammatory mediators of SIRS and for the installation of MOFS, despite the demonstration of negative cultures of portal vein blood from patients with MOFS. Although at present there is no direct demonstration of bacterial translocation from the intestinal lumen to the systemic circulation and only limited evidence for the translocation of intestinal endotoxins to the lymphatic circulation in humans, it is probable that intestinal bacteria and toxins may trigger, maintain, and exacerbate the SIRS and MOFS in patients with dysfunction of the physiologic intestinal barrier.

INTESTINAL BARRIER

The physiologic intestinal barrier is formed primarily by the mechanical cell barrier and by intercellular junctions, by the immunologic barrier, by the normal microbial flora, and by the liver-intestine axis (55). Alterations in all of these components of the intestinal barrier have been reported to be responsible for bacterial and toxin translocation (56). The failure of the intestinal barrier is primarily characterized by impaired nutrient absorption, compromised intestinal immunologic response, and increased intestinal permeability (1, 2). An increase of intestinal permeability has been demonstrated in critically ill patients admitted to intensive care units due to diverse clinical conditions (8, 10), in patients exposed to burns (3, 5, 6), in patients submitted to cardiopulmonary bypass (20), in victims of severe polytraumatic injury (7, 11), in recipients of bone marrow transplantation (57), and in alcoholics with cirrhosis (25).

The increase of intestinal mucosa permeability is triggered by a set of changes such as oxidative stress with increased production of nitric oxide and its derivatives, release of proinflammatory cytokines, reduction of intramucosal pH, and hypoxia (58, for a review see Ref. 59). The increase in intestinal permeability is closely related to the presence of mucosal ischemia (60). In situations of increased metabolic rate secondary to sepsis and other critical illnesses, the cells of the intestinal mucosa require increased oxygen. Paradoxically, in these situations there is a reduction in oxygen availability to values below critical levels due to the reduction in oxygen release and extraction by intestinal mucosal cells (61). Intracellular oxygen concentrations that are inadequate to support normal mitochondrial respiration induce anaerobic glycolysis with adenosine triphosphate depletion and intracellular acidosis, factors that predispose an increase in the permeability of the intestinal mucosa (62). The injury to the mucosa caused by ischemia may be aggravated by reperfusion, probably by activation of the xanthine oxidase pathway causing an increased formation of reactive oxygen species such as superoxide anion (63). Free radicals derived from oxygen cause additional microcirculatory disorders by injuring endothelial cells and activating neutrophils, which in turn generate more reactive oxygen species (61). These alterations result in increased damage to the tissue microcirculation with exacerbation of the ischemic intestinal injury and of the increase in intestinal permeability (64, 65).

In clinical situations and experimental models associated with increased paracellular epithelial permeability, the intercellular tight junction is the target of injury. Tight junctions and paracellular epithelial permeability are controlled physiologically by intracellular mediators probably by modulation of the actin-based cytoskeletal ring (for reviews, see Refs. 66, 67). However, in the presence of systemic inflammation in response to infusion of lipopolysaccharide to mice, there is an increase in the activity of the induced form of nitric oxide synthase causing a generalized dysfunction of epithelial tight junctions, as has been demonstrated in the intestine (68), liver (69), and lungs (70). Similar results have been demonstrated in human colonic Caco-2 and HT29 c1.19A cell monolayers with combinations of cytokines containing interferon-γ (e.g., interferon-γ, interleukin-1β, and tumor necrosis factor-α) (71, 72). The effects of cytokines are potentiated under acidic conditions (73) and in the presence of superoxide radical anion (72) because of an increase in nitric oxide conversion to products with a greater oxidation power such as peroxynitrite and peroxynitrous acid (74, 75). These potent oxidants damage cellular DNA and promote the peroxidation of lipid membranes, the oxidation of several essential molecules such as thiols and ascorbate, the inactivation of mitochondrial aconitase, and the down-regulation of the expression of several key tight junction proteins of the ileum and colon (68, 76, 77). Changes in the cytoskeleton of enterocytes, associated with increased adherence and paracellular transmigration of *Proteus mirabilis*, *E. coli*, and *Enterococcus gallinarum* (49, 50), have been demonstrated after exposure of monolayers of Caco-2 intestinal cells to the toxins of *Clostridium difficile* (49), to ethanol (76), and to cytochalasin (78). Furthermore, in rats exposed to burns it has been shown that the reduction of peroxynitrite levels by the inhibition of the induced form of nitric oxide synthase by S-methylisothiourea reduces the translocation of intestinal bacteria to mesenteric lymph nodes

(four of ten vs. 11 of 11), to the liver (two of ten vs. ten of 11), and to the spleen (zero of ten vs. six of 11) (79).

The clinical implication of the demonstration that in the presence of intramucosal acidosis the toxic subproducts of nitric oxide and the cytokines increase the intestinal permeability is that goal-directed therapy using gastric tonometry, together with the administration of vasoactive drugs and antioxidants, may preserve intestinal permeability (74). Inotropic agents that improve splanchnic perfusion by adjusting blood flow and oxygen supply to metabolic needs (e.g., dobutamine) and the avoidance of agents that redistribute blood away from the intestinal mucosa may maintain paracellular intestinal permeability and mucosal integrity in patients with injury (for reviews, see Refs. 60, 80). Furthermore, it has been demonstrated in monolayers of Caco-2 intestinal cells that agents that scavenge peroxynitrite or diminish the formation of peroxynitrite from nitric oxide and superoxide radical attenuate the deleterious effects of both peroxynitrite-generating systems and ethanol (76, 81). Antioxidants such as N-acetylcysteine, reduced glutathione, L-cysteine, and glutamine also limit the production of peroxynitrite and peroxynitrous acid, reducing the production of superoxide radicals and the increase in intestinal permeability (74, 76). In laboratory animals exposed to intestinal ischemia/reperfusion it has been shown that intravenous glutamine infusion partially maintains the levels of intestinal glutathione and reduces cellular membrane lipidic peroxidation (82).

EFFECT OF GLUTAMINE ON INTESTINAL PERMEABILITY

Glutamine and Intestinal Permeability. The results obtained evaluating the effects of glutamine on intestinal permeability have been variable and depend primarily on the duration of administration and the dose (83, 84, for a recent review see Ref. 85). An important aspect of the experimental design is when glutamine administration is started in relation to the occurrence of the injury. Some investigators have demonstrated that glutamine administered before (86) or immediately after (87–89) the occurrence of the injury prevents the increase in intestinal permeability. A different protocol is used by investigators who want to determine whether an established increase in intestinal permeability is reduced or eliminated by glutamine administration (90, 91). These experimental protocols provide different information, and therefore we propose that the results of studies that evaluate the relationship between glutamine and intestinal permeability be analyzed in terms of the "protective" effect of glutamine that prevents and/or minimizes an acute increase in intestinal permeability and of the "therapeutic" effect of glutamine on a chronically established increase in intestinal permeability (Table 2).

Clinical and animal studies have demonstrated that the administration of glutamine before or immediately after surgery, burns, or the administration of parenteral nutrition has a protective effect, preventing and/or reducing the intensity of the increase in intestinal permeability (Table 2). Jiang et al. (87), in a prospective, double-blind, multiple-center study conducted on 120 patients submitted to major elective abdominal surgery, demonstrated that the addition of 0.50 g/kg/day of the alanine-glutamine dipeptide (equivalent to 0.34 g glutamine/kg/day) to the parenteral nutrition solution for 6 days minimized the intensity of the increase of intestinal permeability during the postoperative period. In this study, the lactulose/mannitol ratio was 0.058 ± 0.049 vs. 0.047 ± 0.029 before surgery and 0.097 ± 0.063 vs. 0.132 ± 0.081 ($p = .02$) on the seventh postoperative day in the patients of the glutamine and control groups, respectively. The patients who received glutamine presented a better cumulative nitrogen balance and were hospitalized for a shorter period of time (12.5 days, i.e., 4 days less than the control group), and no patient developed infection in the surgical incision (three patients in the control group presented infectious complications). Similar results were obtained by Zhou et al. (88), who demonstrated that the increase in intestinal permeability of 20 patients exposed to severe burns, as demonstrated by the lactulose/mannitol method on the first day after injury, was reduced (third day), normalized (sixth day), and maintained normal (twelfth day) by the administration of an enteral diet supplemented with glutamine dipeptide at the dose of 0.5 g/kg/day (equivalent to 0.34 g L-glutamine/kg/day) for 11 days. The patients in the glutamine group also presented significantly better wound healing (86 ± 2% complete vs. 72 ± 3% complete on day 30, $p = .041$) and a reduction of the duration of hospitalization (67 ± 4 days vs. 73 ± 6 days, $p = .026$). Peng et al. (89) confirmed and extended these results by reporting that the accentuated increase in intestinal permeability of 25 patients exposed to severe burns was reduced by the oral administration of 0.5 g/kg/day glutamine "granules" (Chongqing Yao You Pharmaceuticals). In this study, the lactulose/mannitol ratio was 0.25 ± 0.06 vs. 0.26 ± 0.09 before treatment and 0.12 ± 0.09 vs. 0.20 ± 0.06 ($p < .01$) after glutamine treatment for 14 days in the patients of the glutamine and control groups, respectively (lactulose/mannitol ratio = 0.03 ± 0.01 for control healthy subjects). The patients treated with glutamine also presented the largest reduction of plasma diamine oxidase activity (1.36 ± 0.48 vs. 2.05 ± 0.82 IU/mL, $p < .01$), of serum endotoxin levels (0.13 ± 0.05 vs. 0.21 ± 0.07 EU/mL, $p < .01$), and of length of hospital stay (46.59 ± 12.98 vs. 55.68 ± 17.36 days, $p < .05$).

In addition to these results, van der Hulst et al. (86) demonstrated that the administration of total parenteral nutrition with the addition of the dipeptide glycyl-L-glutamine (0.23 g glutamine/kg/day for patients receiving 1.56 g protein/kg/day) prevented exacerbation of the increase in intestinal permeability (lactulose/mannitol) in patients with chronic intestinal inflammatory disease or with intestinal neoplasias. All patients who received total parenteral nutrition without the addition of glutamine presented exacerbation of the increase in intestinal permeability.

In contrast to its positive "protective" effect in acute situations of high permeability, administration of pharmacologic doses of glutamine (≥20 g/day, see Refs. 92, 93) has essentially no effect on the chronic increase in intestinal permeability (Table 2). Noyer et al. (90) assessed the effect of low doses of orally administered glutamine (4 g/day, 0.062 g/kg/day or 8 g/day, 0.124 g/kg/day, for 28 days) on the chronic increase in intestinal permeability (lactulose/mannitol) of patients with AIDS. In this study, the patients who had received a placebo (n = 8) or 4 g of glutamine/day (n = 8) presented an increase in intestinal permeability. Among the patients who received 8 g of glutamine/day (n = 8), intestinal permeability remained high but with no further increase. Similar results were obtained by Den Hond et al. (91), who, after administering 7 g of glutamine by the oral

route, three times a day for 4 wks to seven patients with Crohn's disease with high intestinal permeability (^{51}Cr-EDTA), failed to demonstrate a significant reduction in the increased intestinal permeability, in the index of inflammatory activity of the disease, or the increase in plasma glutamine levels. These results can be explained by the fact that low doses of glutamine (90) were administered by the oral route to patients who presumably present a reduction of intestinal absorptive capacity (90, 91). However, it is also possible that the mechanisms responsible for the increase of intestinal permeability associated with chronic disease are different from those associated with acute injury and are not responsive or are less responsive to glutamine treatment.

Most of the successful applications of the administration of pharmacologic doses of glutamine to critically ill patients (83–85) have used the intravenous route because it permits a more effective postoperative recovery of serum glutamine levels in patients submitted to surgery (94), and it is particularly indicated for patients with reduced intestinal absorptive capacity. The question of the route of administration and the dose of glutamine should be evaluated cautiously because the oral administration of larger amounts of glutamine in an attempt to obtain a "therapeutic" effect may be ineffective or even harmful if the decision is made to maintain the total amount of nitrogen administered per day while reducing other protein sources that provide essential amino acids (95) or alternatively to increase the total amount of nitrogen administered per day to unreasonable levels (96). This problem is also present when large amounts of glutamine are administered intravenously in the form of a dipeptide, which contains glutamine plus the nonessential amino acids alanine or glycine. One hundred milliliters of the commercial product Dipeptiven (Fresenius Kabi, Bad Homberg, Germany) contains 20 g of N (2)-L-alanyl-L-glutamine, which corresponds to 8.20 g of L-alanine and 13.46 g of L-glutamine. Consider a critically ill patient weighing 70 kg who should receive 1.5 g of protein/kg/day, that is, 105 g of protein/day (16.8 g of nitrogen). If we administer 30 g of glutamine/day (5.8 g of nitrogen) we will also administer 18.3 g of alanine (2.9 g of nitrogen). This implies that other proteins corresponding to only 8.1 g of nitrogen (i.e., 50.6 g of other protein sources that supply essential amino acids) will need to be administered. This final amount of protein obtained from other sources (<1.0 g of protein/kg) is less than that currently recommended for critically ill patients (1.5 g/kg/day, Ref. 97).

The apparent superiority of intravenous administration of glutamine (85) must be reevaluated because it recently has been shown that the enteral administration of the alanyl-glutamine dipeptide (88) or glutamine "granules" (89) is effective in reducing the increase of intestinal permeability in burn patients presumably with intact intestinal absorptive capacity. Although the question of enteral vs. parenteral administration requires more investigation, it is possible that the ineffectiveness of enteral diets enriched with glutamine on the reduction of intestinal permeability of critically ill patients (98, 99) is related to the usual difficulties of delivering enteral diets, with subsequent reduction in the dose of glutamine administered, the delay in initiating the administration of enteral diet (e.g., by the presence of adynamic ileum) (100), and the effect of other pharmacologic nutrients such as arginine and ω-3 fatty acids in the immune-enhancing diets. Recently it has been demonstrated that arginine increases nitric oxide production and intestinal permeability in critically ill patients (59, 75). These considerations about the route of glutamine administration are not just academic. The dipeptide and amino acids administered intravenously are at least 100 times more expensive than enteral or oral glutamine administration.

Results obtained in clinical studies suggest that intravenous administration of glutamine before (86) or immediately after the installation of a situation of injury (87), in doses of about 0.34 g of glutamine/kg/day, corresponding to 0.50 g of the dipeptide alanine-glutamine/kg/day, has a "protective" effect by preventing or reducing the intensity of the increase in intestinal permeability. Positive effects on the reduction of the increase of intestinal permeability have also been demonstrated by the enteral administration of pharmacologic doses of glutamine in the form of dipeptide (88) or "granules" (89) to patients with acute injury. On the basis of these considerations we recommend the administration of glutamine as a pharmacologic supplement adjunct to primary therapy for patients exposed to situations of acute and severe injury, in doses of about 0.34 g/kg/day. Furthermore, this glutamine should not be calculated as part of the patient's nutritional protein intake. At present it is not possible to conclude if glutamine has a "therapeutic" effect on a chronically established increased intestinal permeability. In the few studies in which this question was considered, the patients received an insufficient dose of glutamine (90) by the oral route (90, 91) even though they may have had reduced intestinal absorptive capacity.

Glutamine, Bacterial Translocation, and Systemic Infections. The effect of glutamine to preserve or recover intestinal barrier function, thus reducing translocation and the systemic dissemination of intestinal bacteria, has been demonstrated in laboratory animals submitted to different types of injury, such as burns (28), methotrexate (101), or radiation (102). The administration of enteral diets enriched with glutamine maintains the intestinal barrier (102); reduces the extent of bacterial translocation to mesenteric lymph nodes and improves the ability to kill translocated *E. coli* bacteria (28); reduces the dissemination of bacteria to the liver, spleen, blood, and lung; and reduces mortality rate (28, 101).

No study has been conducted thus far on humans using methods such as mesenteric lymph node culture demonstrating the effects of glutamine supplementation on the translocation of intestinal bacteria (for reviews, see Refs. 17, 30). Although there is no consensus in the literature (103), it has been demonstrated in several clinical studies that glutamine administration reduces the number of infections in critically ill patients with SIRS (98) and in patients with multiple trauma (104), reduces the frequency of *P. aeruginosa* infections (105) and of Gram-negative bacteremia in patients exposed to severe burns (106), and reduces the frequency of *Candida* infections and the mortality caused by them, with improved survival during a period of 6 months after admission to the intensive care unit (84). Although these results may be related to an improvement of the immunologic response of glutamine-supplemented patients (107, for a review, see Ref. 108), it is also possible, although not confirmed, that glutamine reduces the translocation of intestinal bacteria in humans. Consistent with this interpretation is the fact that intravenous administration of the dipeptide L-alanyl-L-glutamine (0.3 g/kg/day) to critically ill patients prevents the

Glutamine administration improves the prognosis of critically ill patients presumably by maintaining the physiologic intestinal barrier and by reducing the frequency of infections.

atrophy of the mucosa, with maintenance of the intestinal absorptive capacity (D-xylose test) (109).

CONCLUSIONS

Should glutamine be routinely administered to patients exposed to severe acute injury? The causal relation between increased intestinal permeability, SIRS, bacteremia, sepsis, and MOFS has not been definitively established in humans. However, in view of available clinical evidence (6–8) and of the potential importance of this association for the prognosis of critically ill patients, it is clear that the adoption of the therapeutic conducts, for example, glutamine administration for the prevention and/or treatment of the intestinal dysfunction and reduction of systemic infection of these patients, would be prudent. Positive effects in relation to reversing and/or preventing the increase in intestinal permeability have been demonstrated with glutamine administration before (86) or immediately after the injury (87–89), in pharmacologic doses of about 0.34 g of glutamine/kg/day, by the intravenous route (86, 87) or with enteral administration of glutamine in the form of dipeptide (88) or "granules" (89). These conclusions are consistent with those of recently published studies (83–85) which report that more evident and reproducible benefits concerning the reduction of the frequency of infections, the time of hospital stay, and the mortality rate of critically ill patients are obtained with the administration of larger doses of glutamine (>0.2 g/kg/day) by the parenteral route (alanine-glutamine dipeptide) for a longer period of time (≥9 days).

More definitive conclusions with respect to the effect of glutamine on intestinal permeability and on systemic infections in critically ill patients could be obtained by clinical studies that examine the relationship between bacteria and intestinal toxins and the triggering of SIRS and MOFS in patients with acute intestinal barrier dysfunction. In addition, it is important to identify the molecular mechanisms of action of glutamine and its metabolites in maintaining the physiologic intestinal barrier and to identify situations in which just glutamine can be effective when administered by oral or enteral route because of the high cost of the glutamine dipeptide.

REFERENCES

1. Swank GM, Deitch EA: Role of the gut in multiple organ failure: Bacterial translocation and permeability changes. *World J Surg* 1996; 20:411–417
2. Rombeau JL, Takala J: Summary of round table conference: Gut dysfunction in critical illness. *Intensive Care Med* 1997; 23: 476–479
3. Ziegler TR, Smith RJ, O'Dwyer ST, et al: Increased intestinal permeability associated with infection in burn patients. *Arch Surg* 1988; 123:1313–1319
4. Bjarnason I, Macpherson A, Hollander D: Intestinal permeability: An overview. *Gastroenterology* 1995; 108:1566–1581
5. Deitch EA: Intestinal permeability is increased in burn patients shortly after injury. *Surgery* 1990; 107:411–416
6. Le Voyer T, Cioffi WG, Pratt L, et al: Alterations in intestinal permeability after thermal injury. *Arch Surg* 1992; 127:26–30
7. Faries PL, Simon RJ, Martella AT, et al: Intestinal permeability correlates with severity of injury in trauma patients. *J Trauma* 1998; 44:1031–1036
8. Doig CJ, Sutherland LR, Sandham JD, et al: Increased intestinal permeability is associated with the development of multiple organ dysfunction syndrome in critically ill ICU patients. *Am J Respir Crit Care Med* 1998; 158:444–451
9. Marshall JC, Cook DJ, Christou NV, et al: Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995; 23:1638–1652
10. Harris CE, Griffiths RD, Freestone N, et al: Intestinal permeability in the critically ill. *Intensive Care Med* 1992; 18:38–41
11. Roumen RMH, Hendriks T, Wevers RA, et al: Intestinal permeability after severe trauma and hemorrhagic shock is increased without relation to septic complications. *Arch Surg* 1993; 128:453–457
12. Pape HC, Dwenger A, Regel G, et al: Increased gut permeability after multiple trauma. *Br J Surg* 1994; 81:850–852
13. Kanwar S, Windsor ACJW, Welsh F, et al: Lack of correlation between failure of gut barrier function and septic complications after major upper gastrointestinal surgery. *Ann Surg* 2000; 231:88–95
14. Menzies IS, Zuckerman MJ, Nukajam WS, et al: Geography of intestinal permeability and absorption. *Gut* 1999; 44:483–489
15. Shippee RL, Johnson AA, Cioffi WG, et al: Simultaneous determination of lactulose and mannitol in urine of burn patients by gas-liquid chromatography. *Clin Chem* 1992; 38:343–345
16. Goris JA, Boekhorst TPA, Nuytinck JKS, et al: Multiple organ failure. Generalized autodestructive inflammation? *Ann Surg* 1985; 120:1109–1115
17. Lipman TO: Bacterial translocation and enteral nutrition in humans: An outsider looks in. *J Parenter Enteral Nutr* 1995; 19: 156–165
18. Moore FA: The role of the gastrointestinal tract in postinjury multiple organ failure. *Am J Surg* 1999; 178:449–453
19. Deitch EA: Bacterial translocation or lymphatic drainage of toxic products from the gut: What is important in human beings? *Surgery* 2002; 131:241–244
20. Riddington DW, Venkatesh B, Boivin CM, et al: Intestinal permeability, gastric intramucosal pH, and systemic endotoxemia in patients undergoing cardiopulmonary bypass. *JAMA* 1996; 275:1007–1012
21. Rush BF, Sori AJ, Murphy TF, et al: Endotoxemia and bacteremia during hemorrhagic shock. *Ann Surg* 1988; 207:549–554
22. Deitch EA: Simple intestinal obstruction causes bacterial translocation in man. *Arch Surg* 1989; 124:699–701
23. Cicalese L, Sileri P, Green M, et al: Bacterial translocation in clinical intestinal transplantation. *Transplantation Proc* 2000; 32: 1210
24. Welsh FKS, Farmery SM, MacLennan K, et al: Gut barrier function in malnourished patients. *Gut* 1998; 42:396–401
25. Keshavarzian A, Holmes EW, Patel M, et al: Leaky gut in alcoholic cirrhosis: A possible mechanism for alcohol-induced liver damage. *Am J Gastroenterol* 1999; 94:200–207
26. Deitch EA, Morrison J, Berg R, et al: Effect of hemorrhagic shock on bacterial translocation, intestinal morphology, and intestinal permeability in conventional and antibiotic-decontaminated rats. *Crit Care Med* 1990; 18:529–536
27. Jones WG, Minei JP, Barber AE, et al: Bacterial translocation and intestinal atrophy after thermal injury and burn wound sepsis. *Ann Surg* 1990; 211:399–405
28. Gianotti L, Alexander JW, Gennari R, et al: Oral glutamine decreases bacterial translocation and improves survival in experimental gut-origin sepsis. *J Parenter Enteral Nutr* 1995; 19:69–74
29. Lemaire LCJM, Van Lanschot JJB, Stoutenbeek CP, et al: Bacterial translocation in multiple organ failure: Cause or epiphenomenon still unproven. *Br J Surg* 1997; 84:1340–1350

30. Lichtman SM: Bacterial translocation in humans. *J Pediatr Gastroenterol Nutr* 2001; 33:1–10
31. Wells CL, Erlandsen SL: Bacterial translocation: Intestinal epithelial permeability. *In*: Gut Dysfunction in Critical Illness. Rombeau JL, Takala J (Eds). Berlin, Springer-Verlag, 1996, pp 131–149
32. Redl H, Bahrami S, Schlag G: Is bacterial translocation clinically relevant? *In*: Gut Dysfunction in Critical Illness. Rombeau JL, Takala J (Eds). Berlin, Springer-Verlag, 1996, pp 150–163
33. Elia M, Behrens R, Northrop C, et al: Evaluation of mannitol, lactulose and ^{51}Cr-labelled ethylenediaminetetra-acetate as markers of intestinal permeability in man. *Clin Sci* 1987; 73:197–204
34. Fink MP: Intestinal epithelial hyperpermeability: Update on the pathogenesis of gut mucosal barrier dysfunction in critical illness. *Curr Opin Crit Care* 2003; 9:143–151
35. Hallemeesch MM, Lamers WH, Soeters PB, et al: Increased lactulose/rhamnose ratio during fluid load is caused by increased urinary lactulose excretion. *Am J Physiol Gastrointest Liver Physiol* 2000; 278: G83–G88
36. Tomita M, Menconi MJ, Delude RL, et al: Polarized transport of hydrophilic compounds across rat colonic mucosa from serosa to mucosa is temperature dependent. *Gastroenterology* 2000; 118:535–543
37. Wells CL, Juni BA, Cameron SB, et al: Stool carriage, clinical isolation, and mortality during an outbreak of vancomycin-resistant enterococci in hospitalized medical and/or surgical patients. *Clin Infect Dis* 1995; 21: 45–50
38. Vincent J, Bihari DJ, Suter PM, et al: The prevalence of nosocomial infection in intensive care units in Europe. Results of the European prevalence of infection in intensive care (EPIC) study. *JAMA* 1995; 274: 639–644
39. Sedman PC, Macfie J, Sagar P, et al: The prevalence of gut translocation in humans. *Gastroenterology* 1994; 107:643–649
40. Selective decontamination of the digestive tract trialists' collaborative group: Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract. *Br Med J* 1993; 307:525–532
41. D'Amico R, Pifferi S, Leonetti C, et al: Effectiveness of antibiotic prophylaxis in critically ill adult patients: Systematic review of randomised controlled trials. *BMJ* 1998; 316:1275–1285
42. Ziegler TR, Evans ME, Fernández-Estívariz C, et al: Trophic and cytoprotective nutrition for intestinal adaptation, mucosal repair, and barrier function. *Annu Rev Nutr* 2003; 23:229–261
43. Wiest R, Rath HC: Bacterial translocation in the gut. *Best Pract Res Clin Gastroenterol* 2003; 17:397–425
44. Alverdy JC, Laughlin RS, Licheng W: Influence of the critically ill state on host-pathogen interactions within the intestine: Gut-derived sepsis redefined. *Crit Care Med* 2003; 31:598–607
45. Lyte M: Microbial endocrinology and infectious disease in the 21st century. *Trends in Microbiology* 2004; 12:14–20
46. Wu L, Holbrook C, Zaborina O, et al: *Pseudomonas aeruginosa* expresses a lethal virulence determinant, the PA-I lectin/adhesin, in the intestinal tract of a stressed host. *Ann Surg* 2003; 238:754–764
47. Rocha F, Laughlin R, Musch MW, et al: Surgical stress shifts the intestinal *Escherichia coli* population to that of a more adherent phenotype: Role in barrier regulation. *Surgery* 2001; 130:65–73
48. Moore FA, Moore EE, Poggetti R, et al: Gut bacterial translocation via the portal vein: A clinical perspective with major torso trauma. *J Trauma* 1991; 31:629–638
49. Feltis BA, Kim AS, Kinneberg KM, et al: *Clostridium difficile* toxins may augment bacterial penetration of intestinal epithelium. *Arch Surg* 1999; 134:1235–1242
50. Feltis BA, Garni RM, Wells, CL: Clostridium difficile toxins and enterococcal translocation *in vivo* and *in vitro*. *J Surg Res* 2001; 97:97–102
51. Olofsson P, Nylander G, Olsson P: Endotoxin: Routes of transport in experimental peritonitis. *Am J Surg* 1986; 151:443–446
52. Deitch EA: Role of the gut lymphatic system in multiple organ failure. *Curr Opin Crit Care* 2001; 7:92–98
53. Deitch EA, Forsythe R, Anjaria D, et al: The role of lymph factors in lung injury, bone marrow suppression, and endothelial cell dysfunction in a primate model of trauma-hemorrhagic shock. *Shock* 2004; 22: 221–228
54. Lemaire LCJM, van Lanschot JJB, Stoutenbeek CP, et al: Thoracic duct in patients with multiple organ failure: No major route of bacterial translocation. *Ann Surg* 1999; 229:128–136
55. Farhadi A, Banan A, Fields J, et al: Intestinal barrier: An interface between health and disease. *J Gastroenterol Hepatol* 2003; 18: 479–497
56. Marshall JC: Clinical markers of gastrointestinal dysfunction. *In*: Gut Dysfunction in Critical Illness. Rombeau JL, Takala J (Eds). Berlin, Springer-Verlag, 1996, pp 114–128
57. Johansson JE, Ekman T: Gastro-intestinal toxicity related to bone marrow transplantation: Disruption of the intestinal barrier precedes clinical findings. *Bone Marrow Transplant* 1997; 19:921–925
58. Ziegler TR: Molecular mechanisms of intestinal injury, repair, and growth. *In*: Gut Dysfunction in Critical Illness. Rombeau JL Takala J (Eds). Berlin, Springer-Verlag, 1996, pp 25–52
59. Alican I, Kubes P: A critical role for nitric oxide in intestinal barrier function and dysfunction. *Am J Physiol* 1996; 270: G225–G237
60. Pastores SM, Katz DP, Kvetan V: Splanchnic ischemia and gut mucosal injury in sepsis and the multiple organ dysfunction syndrome. *Am J Gastroenterol* 1996; 91: 1697–1710
61. Haglund U: Pathophysiology of gut dysfunction in shock and sepsis. *In*: Gut Dysfunction in Critical Illness. Rombeau JL, Takala J (Eds). Berlin, Springer-Verlag, 1996, pp 3–11
62. Fink MP: Intestinal mucosal hyperpermeability in critical illness. *In*: Gut Dysfunction in Critical Illness. Rombeau JL, Takala J (Eds). Berlin, Springer-Verlag, 1996, pp 12–24
63. Parks DA, Granger DN: Ischemia-induced vascular changes: Role of xanthine oxidase and hydroxyl radicals. *Am J Physiol* 1983; 245:G285–G289
64. Ar'Rajab A, Dawidson I, Fabia R: Reperfusion injury. *New Horiz* 1996; 4:224–234
65. Kong SE, Blennerhassett LR, Heel KA, et al: Ischaemia-reperfusion injury to the intestine. *Aust N Z J Surg* 1998; 68:554–561
66. Madara JL: Regulation of the movement of solutes across tight junctions. *Annu Rev Physiol* 1998; 60:143–159
67. Turner JR, Rill BK, Carlson SL, et al: Physiological regulation of epithelial tight junctions is associated with myosin light-chain phosphorylation. *Am J Physiol* 1997; 273: C1378–C1385
68. Han X, Fink MP, Yang R, et al: Increased iNOS activity is essential for intestinal epithelial tight junction dysfunction in endotoxemic mice. *Shock* 2004; 21:261–270
69. Han X, Fink MP, Uchiyama T, et al: Increased iNOS activity is essential for hepatic epithelial tight junction dysfunction in endotoxemic mice. *Am J Physiol Gastrointest Liver Physiol* 2004; 286:G126–G136
70. Han X, Fink MP, Uchiyama T, et al: Increased iNOS activity is essential for pulmonary epithelial tight junction dysfunction in endotoxemic mice. *Am J Physiol Lung Cell Mol Physiol* 2004; 286:L259–L267
71. Rodriguez P, Heyman M, Candalh C, et al: Tumour necrosis factor-α induces morphological and functional alterations of intestinal HT29 c1.19A cell monolayers. *Cytokine* 1995; 7:441–448
72. Chavez AM, Menconi MJ, Hodin RA, et al: Cytokine-induced intestinal epithelial hyperpermeability: Role of nitric oxide. *Crit Care Med* 1999; 27:2246–2251
73. Unno N, Hodin RA, Fink MP: Acidic conditions exacerbate interferon-γ-induced intestinal epithelial hyperpermeability: Role of peroxynitrous acid. *Crit Care Med* 1999; 27:1429–1436
74. Marik PE, Iglesias J: Intestinal mucosal permeability: Mechanisms and implications for treatment. *Crit Care Med* 1999; 27: 1650–1651
75. Fink MP: Modulating the L-arginine-nitric oxide pathway in the septic shock: Choosing the proper point of attack. *Crit Care Med* 1999; 27:2019–2022
76. Banan A, Fields JZ, Decker H, et al: Nitric

oxide and its metabolites mediate ethanol-induced microtubule disruption and intestinal barrier dysfunction. *J Pharmacol Exp Ther* 2000; 294:997–1008
77. Castro L, Rodriguez M, Radi R: Aconitase is readily inactivated by peroxynitrite, but not by its precursor, nitric oxide. *J Biol Chem* 1994; 269:29409–29415
78. Wells CL, van de Westerlo EMA, Jechorek RP, et al: Cytochalasin-induced actin disruption of polarized enterocytes can augment internalization of bacteria. *Infect Immun* 1998; 66:2410–2419
79. Chen LW, Hsu CM, Wang JS, et al: Specific inhibition of *i*NOS decreases the intestinal mucosal peroxynitrite level and improves the barrier function after thermal injury. *Burns* 1998; 24:699–705
80. Silva E, DeBacker D, Creteur J, et al: Effects of vasoactive drugs on gastric intramucosal pH. *Crit Care Med* 1998; 26:1749–1758
81. Banan A, Choudhary S, Zhang Y, et al: Ethanol-induced barrier dysfunction and its prevention by growth factors in human intestinal monolayers: Evidence for oxidative and cytoskeletal mechanisms. *J Pharmacol Exp Ther* 1999; 291:1075–1085
82. Harward TRS, Coe D, Souba WW, et al: Glutamine preserves gut glutathione levels during intestinal ischemia/reperfusion. *J Surg Res* 1994; 56:351–355
83. Goeters C, Wenn A, Mertes N, et al: Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med* 2002; 30:2032–2037
84. Griffiths RD, Allen KD, Andrews FJ, et al: Infection, multiple organ failure, and survival in the intensive care unit: Influence of glutamine-supplemented parenteral nutrition on acquired infection. *Nutrition* 2002; 18:546–552
85. Novak F, Heyland DK, Avenell A, et al: Glutamine supplementation in serious illness: A systematic review of the evidence. *Crit Care Med* 2002; 30:2022–2029
86. van der Hulst RRWJ, van Kreel BK, von Meyenfeldt MF, et al: Glutamine and the preservation of gut integrity. *Lancet* 1993; 341:1363–1365
87. Jiang ZM, Cao JD, Zhu XG, et al: The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: A randomized, double-blind, controlled study of 120 patients. *J Parenter Enteral Nutr* 1999; 23:S62–S66
88. Zhou Y, Jiang Z, Sun Y: The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: A randomized, double-blind, controlled clinical trial. *J Parenter Enteral Nutr* 2003; 27:241–245
89. Peng X, Yan H, You Z, et al: Effects of enteral supplementation with glutamine granules on intestinal mucosal barrier function in severe burned patients. *Burns* 2004; 30:135–139
90. Noyer CM, Simon D, Borczuk A, et al: A double-blind placebo-controlled pilot study of glutamine therapy for abnormal intestinal permeability in patients with AIDS. *Am J Gastroenterol* 1998; 93:972–975
91. Den Hond E, Hiele M, Peeters M, et al: Effect of long-term oral glutamine supplements on small intestinal permeability in patients with Crohn's disease. *J Parenter Enteral Nutr* 1999; 23:7–11
92. De-Souza DA, Greene LJ: Pharmacological nutrition after burn injury. *J Nutr* 1998; 128:797–803
93. Kelly D, Wischmeyer PE: Role of L-glutamine in critical illness: New insights. *Curr Opin Clin Nutr Metab Care* 2003; 6:217–223
94. Fish J, Sporay G, Beyer K, et al: A prospective randomized study of glutamine-enriched parenteral compared with enteral feeding in postoperative patients. *Am J Clin Nutr* 1997; 65:977–983
95. Harper AE, Benevenga NJ, Wohlhueter RM: Effects of ingestion of disproportionate amounts of amino acids. *Physiol Rev* 1970; 50:428–558
96. Garlick PJ: Assessment of the safety of glutamine and other amino acids. *J Nutr* 2001; 131:2556S–2561S
97. Wolfe RR: Relation of metabolic studies to clinical nutrition—The example of burn injury. *Am J Clin Nutr* 1996; 64:800–808
98. Conejero R, Bonet A, Grau T, et al: Effect of a glutamine-enriched enteral diet on intestinal permeability and infectious morbidity at 28 days in critically ill patients with systemic inflammatory response syndrome: A randomized, single-blind, prospective, multicenter study. *Nutrition* 2002; 18:716–721
99. Velasco N, Hernandez G, Wainstein C, et al: Influence of polymeric enteral nutrition supplemented with different doses of glutamine on gut permeability in critically ill patients. *Nutrition* 2001; 17:907–911
100. De Jonghe B, Appere-De-Vechi C, Fournier M, et al: A prospective survey of nutritional support practices in intensive care unit patients: What is prescribed? What is delivered? *Crit Care Med* 2001; 29:8–12
101. Fox AD, Kripke SA, Paula JD, et al: Effect of a glutamine-supplemented enteral diet on methotrexate-induced enterocolitis. *J Parenter Enteral Nutr* 1988; 12:325–331
102. Chun H, Sasaki M, Fujiyama Y, et al: Effect of enteral glutamine on intestinal permeability and bacterial translocation after abdominal radiation injury in rats. *J Gastroenterol* 1997; 32:189–195
103. Hall JC, Dobb G, Hall J, et al: A prospective randomized trial of enteral glutamine in critical illness. *Intensive Care Med* 2003; 29:1710–1716
104. Houdijk AP, Rijnsburger ER, Jansen J, et al: Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* 1998; 352:772–776
105. Garrel D, Patenaude J, Nedelec B, et al: Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: A prospective, controlled, randomized clinical trial. *Crit Care Med* 2003; 31:2444–2449
106. Wischmeyer PE, Lynch J, Liedel J, et al: Glutamine administration reduces Gram-negative bacteremia in severely burned patients: A prospective, randomized, double-blind trial versus isonitrogenous control. *Crit Care Med* 2001; 29:2075–2080
107. Newsholme P: Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? *J Nutr* 2001; 131:2515S–2522S
108. Newsholme P, Lima MMR, Procopio J, et al: Glutamine and glutamate as vital metabolites. *Braz J Med Biol Res* 2003; 36:153–163
109. Tremel H, Kienle B, Weilemann LS, et al: Glutamine dipeptide-supplemented parenteral nutrition maintains intestinal function in the critically ill. *Gastroenterology* 1994; 107:1595–1601