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Gut failure in critical care: old school versus new school

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Abstract

The concept of bacterial translocation and gut-origin sepsis as causes of systemic infectious complications and multiple organ deficiency syndrome in surgical and critically ill patients has been a recurring issue over the last decades attracting the scientific interest. Although gastrointestinal dysfunction seemingly arises frequently in intensive care unit patients, it is usually underdiagnosed or underestimated, because the pathophysiology involved is incompletely understood and its exact clinical relevance still remains controversial with an unknown yet probably adverse impact on the patients' outcome. The purpose of this review is to define gut-origin sepsis and related terms, to describe the mechanisms leading to gut-derived complications, and to illustrate the therapeutic options to prevent or limit these untoward processes.

Keywords Gut failure, bacterial translocation, selective gut decontamination, immunonutrition

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Introduction

The gut is considered to play a significant role in the processes of systemic inflammation, sepsis and multiple organ dysfunction syndrome (MODS) following hemorrhagic shock, trauma, burns, pancreatitis, major abdominal operations, and in critically ill patients in general [1-5]. The concept of gut as a great player in critical illness dates back to the 1940s, when live enteric bacteria were found in the peritoneal washings of dogs after hemorrhagic shock [6]. In 1954, Fine *et al* [7] proved *in vivo* that intestinal bacteria crossed the intact gut wall after hemorrhage, chemical injury of the peritoneal surface and trauma. Later, Polk [8] and Fry [9] reported that approximately 50% of the patients in the intensive care unit (ICU) who were septic had no obvious infection but an occult infection in the abdomen, while Berg and Garlington [10] finally termed the phenomenon of bacterial passage through the intestinal wall as bacterial translocation (BT).

Piton [11] defined gut failure as an acute reduction in the enterocyte mass and/or acute enterocyte dysfunction either associated or not with a loss of the gut barrier function. BT is defined as the process whereby bacteria or other antigenic macromolecules (such as lipopolysaccharide and peptidoglycan), which normally reside within the gastrointestinal (GI) lumen, spread through the intestinal mucosa barrier into normally sterile tissues, where they may either cause infection or activate the immune system leading to organ damage and failure [3,4,12,13] (Table 1). The diagnosis of BT requires the culture of intestinal bacteria in the mesenteric lymph nodes sampled at the beginning of a laparotomy [2-4,13-16].

Deitch introduced the term "gut-derived sepsis", which corresponds to the process during which gut-derived pro-inflammatory microbial and non-microbial factors induce or enhance a systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), or MODS. The diagnosis of gut-derived sepsis is based on measurements of gut barrier function (permeability) in relation with the clinical response of the patient [14].

Gut failure in ICU patients is often suspected by the lack of normal bowel sounds, regurgitation, vomiting, high gastric drainage volumes (>500 mL/day), diarrhea, abdominal distension or GI bleeding [17]. Because clinical evaluation of the intestinal function is difficult, radiological signs are non specific, subtle or absent and there is lack of universally accepted criteria for gut failure in ICU patients, gut dysfunction often goes unrecognized, leading to poor outcomes [15,17]. Reintam *et al* proposed a 5-grade GI failure scoring system for ICU patients, based on the presence of feeding intolerance and/or intra-abdominal hypertension (IAH), which correlated with ICU mortality (Table 2), although feeding intolerance is a rather subjective parameter and IAH is generally nonspecific to gut failure [17]. Plasma citrulline levels have further been proposed as a novel quantitative biomarker of significantly reduced enterocyte mass and function indicative

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Table 1 Bacteria translocation criteria [12,15]

Gut-origin bacteria or endotoxins found in the mesenteric lymph nodes or portal venous blood
Bacterial DNA or proteins found in the mesenteric lymph nodes, portal venous blood, or systemic circulation
The presence of intestinal bacteria in tissues that should be sterile
The development of infectious complications with organisms that probably originated from the gut
Increased permeability of the gut to large molecules
Increased levels of circulating and tissue cytokines and inflammatory mediators

Table 2 Gastrointestinal failure score [2]

Points	Clinical symptoms
0	Normal GI function
1	Enteral feeding <50% of calculated needs, or no feeding 3 days after abdominal surgery
2	Food intolerance or IAH
3	Food intolerance and IAH
4	ACS

GI, gastrointestinal; IAH, intra-abdominal hypertension; ACS, abdominal compartment syndrome

of gut insufficiency [11,18], while others have proposed the detection of intestinal bacterial DNA in blood or other fluids [19,20] or even the use of scintigraphy to monitor migration routes of labeled bacteria [21], although these modes have not gained broad acceptance. Furthermore, D-lactate, glutathione S-transferase (GST) and intestinal fatty acid binding protein (i-FABP) have been proposed as novel biomarkers of intestinal ischemia [22,23]. As D-lactate is produced by bacteria such as *Escherichia coli*, while animals produce only L-lactate, the quantification of D-lactate could serve as a marker of BT following mucosal injury of any cause [22]. GST is a nonspecific oxidative stress marker released from various tissues during ischemia, with limited and uncertain clinical utility [22]. I-FABPs are small proteins, bound within the cytoplasm of mature enterocytes located at the villus lip, and are released upon enterocyte death. Villi are the most vulnerable part of intestinal mucosa to ischemia, so i-FABP might be a promising biomarker for the diagnosis of a range of ischemic and inflammatory conditions [22-26], but further investigation in larger populations and critically patients with MODS using more standardized approaches is necessary.

Etiopathogenesis

The mucosa of the small intestine is a 300 m^2 epithelial surface in contact with the outside world and consists of a continuously renewed epithelial layer [27,28]. Its function is not limited to digestion and nutrient absorption only, but it consists of forms that are part of intestinal immunity specialized in sensing, processing and orchestrating immune responses against toxins, microorganisms and other non-self material originating from the lumen [15] (Fig. 1). Inflammation and sepsis produce global alterations in the mucus layer (thinning, reduced luminal coverage, poor adherence) and damages gut integrity by increasing epithelial apoptosis and permeability and suppressing cell proliferation eventually leading to loss of barrier function [5,15] (Fig. 1). Traumatic brain injury is also associated with progressive damage of the intestinal mucosa and impairment of barrier function, starting within 3 h and lasting for more than 7 days. The histopathological alterations include epithelial cell apoptosis, loss of tight junctions between enterocytes, mucosal atrophy, focal ulceration, dilatation of chyle duct, vascular dilatation, congestion and edema of villi and lamina propria, eventually leading to severe endotoxinemia [29].

The mucosal immune system prevents pathogens from penetrating the epithelium, recognizes foreign antigens from a variety of pathogens and mounts effective immune responses against luminal pathogens, if they are successful in crossing the mucosal barrier [27]. Critical illness has a profound effect on the mucosal immune cells. Sepsis enhances apoptosis in intraepithelial lymphocytes, lamina propria lymphocytes and Peyer's patches [30].

The distal human intestine is home to a complex microflora, including almost up to 10^{14} microorganisms, pertaining to approximately 500-1000 different species (mainly *Bacteroides*, *Enterobacteriaceae* and *Enterococcus* spp) [27]. Their distribution changes along the GI tract, with anaerobes almost absent in the stomach but prevailing in the distal colon [4,31,32]. This gut microflora is indispensable for the development of the GI mucosal immune system, the maintenance of gut homeostasis and for providing essential nutrients. It acts as a barrier against the colonization of opportunistic and pathogenic microorganisms with a delicate balance operating among host factors, environmental factors and microbial interactions [33]. Modifying factors related to critical illness such as gut hypoperfusion, circulating stress hormones, immunosuppression, hyponutrition, antibiotics, vasoconstrictors, proton pump inhibitors [3,16], and morphine [28,34,35] could convert normal microbiota, leading to opportunistic pathogen overgrowth [36,37].

GI motility, normally controlled by a complex mechanism consisting of the myenteric and submucosal plexi, the autonomic nervous system, hormones, neurotransmitters, and tissue pacemakers, is frequently affected in critically ill patients that may result in failure of enteral nutrition and an adverse outcome [38]. Delayed gastric emptying, noted in around 50% of mechanically ventilated ICU patients, leads to intolerance to nasogastric delivery of food, bacterial overgrowth in the upper GI tract, gastric colonization and an elevated risk for pulmonary aspiration and ICU-acquired infection [38]. Abnormal small bowel motility also causes abdominal distention with a risk of respiratory insufficiency, or osmotic diarrhea leading to hypovolemia, incomplete absorption and negative nitrogen balance. Furthermore, digestion and absorption may additionally be impaired by the small intestinal motor dysfunction and the damaged

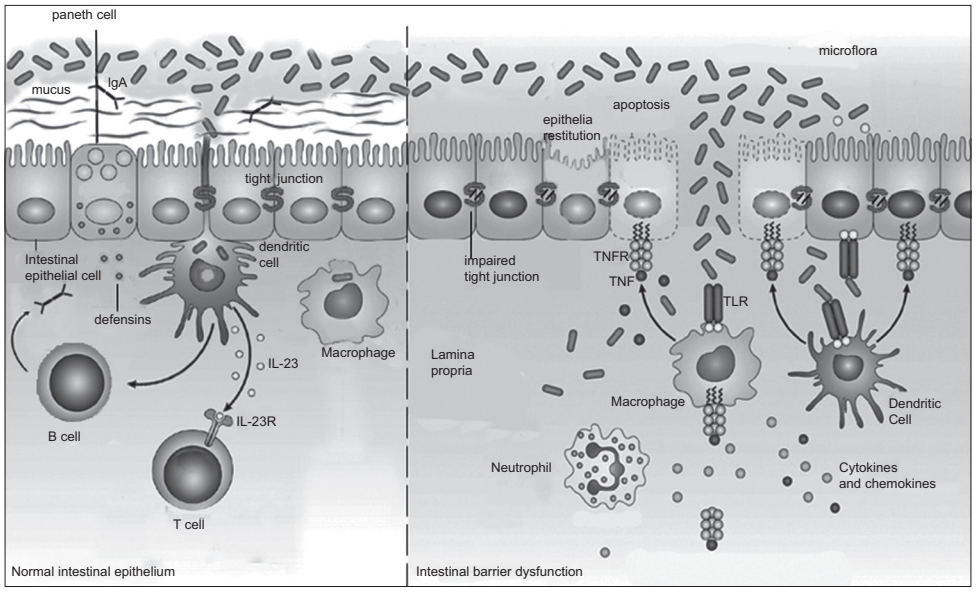

Figure 1 Events occurring as the normal intestinal barrier becomes impaired in sepsis, ischemia and other harmful conditions: enterocytes go on to apoptosis, tight junctions are breached and microbes penetrate the intestinal wall. The latter are further taken up by phagocytes, innate immune receptors are activated, chemokines and proinflammatory cytokines are released, innate and adaptive immune cells are attracted to the site and the immune response is further propagated

TLR, toll-like receptor; IL, interleukin; TNFR, tumor necrosis factor receptor; TNF, tumor necrosis factor

mucosal structure [38]. Particularly, in head-injured patients with increased intracranial pressure gastroparesis occurs very often, while in sepsis the corticotropin-releasing factor and inotropes delay gastric emptying, inhibit GI motility, and cause intestinal ischemia [38]. Those changes in GI motility in trauma and septic patients further severely depress nutrient and drug absorption from the gut [38].

The old school

The nature of the relationship between gut, sepsis, SIRS, and MODS remains to be elucidated. The gut was first described as the "motor" of multiple organ failure (MOF) by Meakins and Marshall in 1985 during a panel discussion of the Surgical Infection Society [39]. BT certainly plays a role, but appears not to be the sole acting factor. Mechanisms involved in BT include loss of intestinal barrier function, failure of the host immune system and modification of gut microflora [40,41] (Fig. 2). Several authors have demonstrated the significance of BT and gut-origin sepsis in large abdominal operations [42-44], intestinal obstruction [45], necrotic pancreatitis [46,47] liver cirrhosis [48,49], organ transplantation [50], and abdominal aorta aneurism repair [51] by finding gut-derived microbes in the mesenteric lymph nodes. Although it is usually assumed that the colon, with the much heavier bacterial load, is the most likely site of BT [3], according to Fritz *et al* BT mainly occurs in the small bowel [52]. Besides, the small intestine mucosa has been shown to be more susceptible to ischemic-reperfusion injury, while the colon is more resistant to hypoperfusion, which provides a possible explanation why patients with small intestinal ischemia tend

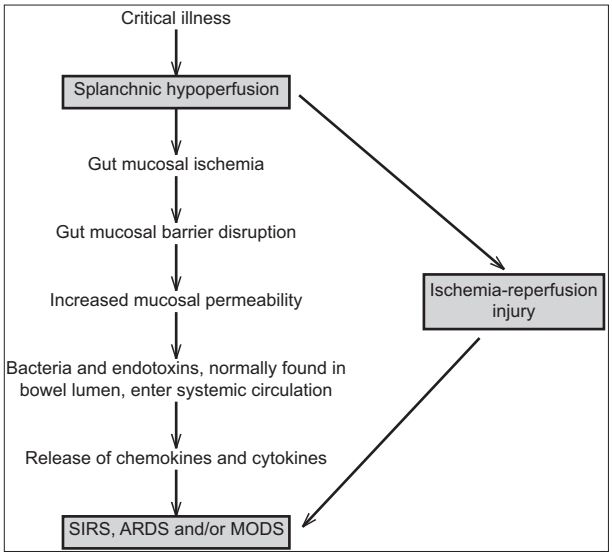

Figure 2 Overview of the "old school" approach of the pathophysiology of the gut-derived sepsis. Gut hypoperfusion and ischemia-reperfusion injury are key events for the breach of the mucosal integrity, allowing the entry of bacteria and their products in the circulation and the initiation of the sepsis cascade

SIRS, systemic inflammatory response syndrome; ARDS, acute respiratory distress syndrome; MODS, multiple organ deficiency syndrome

to have worse outcomes rather than colonic ischemia [53]. The "leaky gut" hypothesis postulates that intestinal bacteria, endotoxin or other substances cross the disrupted mucosal barrier and elicit a regional immune reaction at the gut level, which has the potential to spread and produce harmful effects on extra-intestinal organs [27].

However, not all bacteria or endotoxin passing through the intestinal barrier may cause septic complications to the host. It is possible that BT is a phenomenon that occurs normally to allow the alimentary tract to be exposed to antigens, so that the local immune response can be modified or even checked, a process known as "oral tolerance" [3]. In critically ill patients, in whom some degree of immune deficiency is usual, this physiologic process may result in septic complications [54,55].

In 2002 Deitch proposed the "three hit model" theory. According to this, an initial insult causes visceral hypoperfusion (first hit) and the gut responds by producing and releasing proinflammatory factors. Hemodynamic resuscitation leads to reperfusion, resulting in ischemia-reperfusion injury to the intestine (second hit), loss of gut barrier function and an augmented gut inflammatory response, without the need for translocation of bacteria or toxins. Once bacteria and endotoxin cross the mucosal barrier, they further enhance the immune response with the release of chemokines, cytokines and other inflammatory mediators, which affect the immune system both locally and systemically (third hit), leading to SIRS and MODS [1,3,15] (Fig. 3).

The "gut-lymph" theory, proposed by Deitch in 2006, postulates that macrophages and other immune cells in the intestinal submucosa or the mesenteric lymph nodes trap the majority of translocating bacteria. However, surviving bacteria or cell wall fragments and protein components of the dead bacteria together with cytokines and chemokines produced in the gut, travel along the mesenteric lymphatics to the cisterna chyli and finally via the thoracic duct empty into the systemic circulation at the left subclavian vein. These moieties then reach the pulmonary circulation activating the alveolar macrophages and contributing to acute lung injury or ARDS and MODS [3,15]. Several experimental models with endotoxinemia [56,57] trauma-hemorrhagic shock [58-60] or burn injury [61,62] support this theory. Concerning ICU patients, the gut-lymph pathway appears to be a basic pathogenetic mechanism of gut-origin sepsis (Fig. 4).

Clark and Coopersmith in 2007 suggested the "intestinal crosstalk" theory which assumes a three-way partnership among the intestinal epithelium, the immune tissue and the endogenous microflora of the gut. In this partnership, each element modifies the others via crosstalk, within a state where all components of the gut interact, concluding that the intestine is a complex organ which can even crosstalk with extra-intestinal tissues. In critically ill patients, loss of the balance between these highly interrelated systems results in the development of systemic manifestations of disease, whose repercussions extend far beyond the intestine [5,15,27].

The new school

Recently, it has been recognized that, apart from the intestinal ischemia-reperfusion injury, gut luminal contents, including the mucus gel layer, pancreatic proteases and gut flora, as well as the luminal response to splanchnic ischemia play also an important role in modulating gut injury [63]. For example, luminal pancreatic proteases appear to be crucial for the development of gut-derived sepsis following hemorrhagic shock [64,65], while bile-derived tumor necrosis factor-αseems to act on the luminal side of the mucosa in the endotoxin-induced gut injury model, causing intestinal damage [66].

Other studies suggest that lipid-rich enteral nutrition can minimize gut injury by activating the cholecystokinin (CCK1) receptor in the gut, through stimulation of the cholinergic anti-inflammatory pathway [67]. Particularly, while CCK-2 is mainly expressed in the central nervous system and is related to anxiety and the perception of pain, CCK-1 is expressed in the bowel, inducing exocrine pancreatic secretion, gallbladder

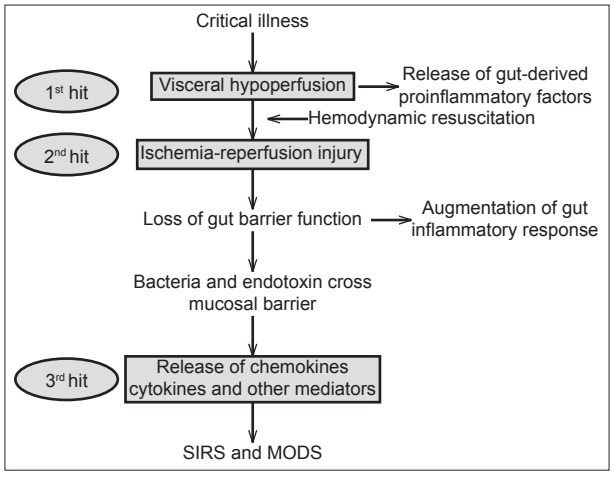

Figure 3 The three-hit hypothesis. In this model a major role is attributed to the gut immune system and its response to circulatory insults

SIRS, systemic inflammatory response syndrome; MODS, multiple organ deficiency syndrome

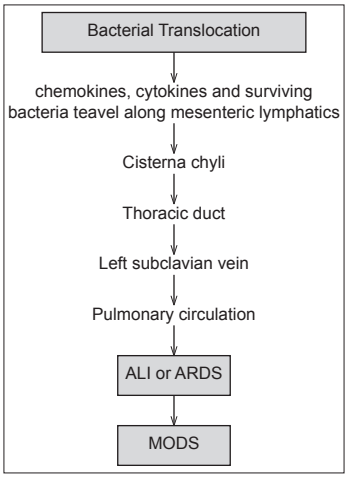

Figure 4 Overview of the "gut-lymph" theory, according to which the principal gateway of intestinal bacteria and their products is the gut lymph vessels and their downstream lymphatics up to the left subclavian vein and the pulmonary circulation, where the processes of ALI and ARDS are initiated

ALI, acute lung injury; ARDS, acute respiratory distress syndrome

contraction, gastric acid secretion, intestinal motility and the sense of satiety [63]. Ingestion of large portions of fat stimulates CCK release, which binds to CCK-1 and CCK-2 receptors located on the vagal nerve. Activation of the latter in turn stimulates vagal afferents releasing parasympathetic neurotransmitters, such as acetylcholine, which binds to nicotinic α7 receptors on macrophages and other cytokine-producing cells in peripheral organs, thereby inhibiting pro-inflammatory cytokines, such as TNF-α and interleukin (IL)-6 and ultimately suppressing cytokine-mediated inflammation and damage in the setting of endotoxinemia, severe sepsis and hemorrhagic shock [68] (Fig. 5). This protective effect of dietary fat on intestinal permeability is abolished by vagotomy and treatment with CCK and nicotinic receptor antagonists [69].

Furthermore, hepatobiliary factors, such as the bile, are involved in processes on the luminal side of the gut. In particular, biliary molecules, such as the epidermal growth factor and immunoglobulins have an important role in protecting the gut, while TNF-α seems to mediate tissue damage [66]. Indeed, in sepsis the gut appears to be a major source of norepinephrine, which upregulates proinflammatory cytokine release, such as TNF-α, IL-1β and IL-6, by Kupffer cells and suppresses hepatocellular function primarily at an early stage of sepsis. The hepatocellular function suppression occurs independent of liver hypoperfusion, known to cause hepatic dysfunction at late stages of sepsis [70]. In fact, under normal conditions the gut produces almost 50% of the total body norepinephrine, whose levels in the portal circulation are 74% higher than the systemic circulation. Kupffer cells, on the other hand, constitute 80-90% of the macrophage population that release proinflammatory cytokines [70]. In early stage of sepsis portal levels of norepinephrine rise even higher, which seems to upregulate proinflammatory cytokines, attenuate tissue responsiveness to norepinephrine, and cause organ dysfunction [70].

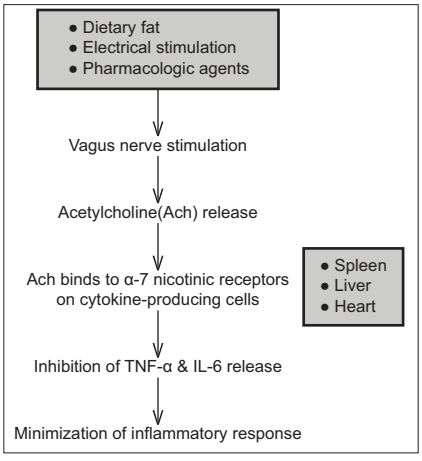

Figure 5 The cholinergic anti-inflamatory pathway. Dietary fat and other factors stimulate the vagal nerve for Ach release. The latter binds to receptors on cells of the monocyte/macrophage lineage within the liver and other organs inhibiting the release of pro-inflammatory mediators and thus minimizing the systemic inflammatory response
Ach, acetylcholine; TNF, tumor necrosis factor; IL, interleukin

Recent studies re-appraise the role of intestinal microflora in critical illness and gut-origin sepsis [71]. BT remains a central driving force for SIRS, but observations have concluded that microbial virulence is modified as well. Notably, a hierarchical system of virulence gene expression in bacteria has recently been described, known as quorum sensing (QS). According to this, bacterial virulence genes are expressed only after a critical bacterial density is reached, that is an amount necessary to overcome the host. Bacteria show a resource-saving behavior, meaning they do not release QS molecules of virulence gene activation, when nutrient supply is abundant and no threat to their survival is perceived, until they reach late phases of growth. Ischemia, hypoxia and intestinal epithelium injury induce the release of molecules that activate QS circuitry in the opportunistic pathogens, which interact with mucosal epithelium and trigger the expression of a particular proinflammatory mediator in a susceptible host [71]. *Pseudomonas aeruginosa,* for example, is a common gut colonizing and opportunistic pathogen, which has a membrane biosensor that can be activated by interferon (IFN)-γ, causing the release of the QS molecule and triggering the virulence gene expression, resulting in elevation of tight junctional permeability and gut-derived sepsis independent of BT [71]. In parallel, probiotic flora also secretes QS molecules, which are taken up by epithelial cells and act in a cytoprotective way [72]. New techniques in investigating microbial communities within gut using a genome-wide approach will offer the possibility to examine closely gut-derived sepsis [71].

Prevention and therapy

Most therapies aim at preventing gut injury and maintaining stable gut flora in order to limit the risk of gut barrier failure and BT (Table 3) [14].

Early resuscitation in order to optimize visceral blood flow: Persistent gut hypoperfusion has been suggested as an important inciting event in the pathogenesis of MOF [72,73]. The intestinal mucosa is highly sensitive to ischemia-reperfusion injury [58], since even short periods of ischemia can induce substantial tissue damage characterized by epithelial apoptosis, disruption of barrier integrity, increased mucosal permeability, release of proinflammatory substances and ultimately BT, septic complications and MODS [74,75]. It must be highlighted that in 1970 Chiu *et al*, while studying the intestinal mucosal histopathology in an experimental model of ischemia, suggested what became a widely used grading scale of small bowel mucosal damage associated with shock (Table 4) [76].

In early stage, gut ischemia causes ileus, so that the proximal gut becomes the reservoir for pathogens and toxins which contribute to late sepsis and MOF. Late infections cause further worsening of intestinal dysfunction and, therefore, the intestine plays the role of both the instigator and the victim of MOF [58]. Furthermore, the abdominal perfusion pressure, defined as the mean arterial pressure minus intra abdominal pressure, is a determinant of the small bowel blood flow. Intra-abdominal hypertension higher

Table 3 Examples of studies employing different interventions in various settings and main outcomes

Authors	Study type	Material	Results/outcomes
Early resuscitation			
De Backer, *et al* [79]	Prospective, randomized, open-label	20 patients with septic shock	Dopamine and norepinephrine have similar hemodynamic effects, epinephrine can impair splanchnic circulation in severe sepsis
Sautner, *et al* [80]	*In vivo* animal study	Porcine endotoxin shock model	Norepinephrine or dopexamine administration in endotoxin shock causes no additional impairment of intestinal integrity. Epinephrine therapy causes reduction of mucosal pH and early mucosal damage
IAP Monitoring			
Sukhotnik, *et al* [78]	*In vivo* animal study	42 male Sprague-Dawley rats	Elevated IAP from 15 to 25 mmHg results in mucosal injury of the gut, causing mucosal hypoplasia, and increases BT.
Kaussen, *et al* [79]	*In vivo* animal study	18 porcine model	A higher level of ischemic damage and more BT were observed in IAP of 30 mmHg compared to animals subjected to an IAP of 15 mmHg or controls
TPN			
MacFie J, *et al* [16]	Randomized trial	927 surgical patients	No evidence that TPN causes morphological and functional changes relating to BT and sepsis in human intestine
EN			
Lewis SJ, *et al* [84]	Systematic review and meta-analysis	1173 gastrointestinal surgical patients	Early EN is associated with reduced mortality
Heyland D, *et al* [86]	Prospective cohort study	99 ICU patients	50% of patients could tolerate the regimen
Yi F, *et al* [88]	Review and meta-analysis	381 patients with severe acute pancreatitis	Total EN support is associated with lower mortality, fewer infectious complications, decreased organ failure and surgical intervention rate compared to parenteral nutritional support
Wu XM, *et al* [89]	Randomized trial	107 patients with severe acute pancreatitis	EN related to less pancreatic necrotic infection, MOF and mortality rate
SDD			
Leone M, *et al* [91]	Case control study	360 multiple trauma patients	A relative overgrowth of gram-positive cocci was observed. Methicillin resistance of *Staphylococcus epidermidis* increased
Stoutenbeek CP, *et al* [96]	Case control study	122 multiple trauma patients	Total infection rate decreased
Stoutenbeek CP, *et al* [99]	Multicenter randomized controlled trial	401 trauma patients	SDD significantly reduces infection in multiple trauma, although no difference in MOF and mortality was found
Melsen WG, *et al* [104]	Cluster-randomized multicenter trial	2762 surgical and 3165 non-surgical ICU patients	Similar effects of SDD in reducing mortality in surgical and non-surgical ICU patients; SOD reduced mortality only in non-surgical patients
Oostdijk EA, *et al* [108]	Open clustered group-randomized cross-over study	13 ICU	SOD and SDD raise ceftazidime resistance prevalence rates in the respiratory tract and cause a substantial rebound effect of ceftazidime resistance in the intestinal tract after SDD discontinuation
de Smet AM, *et al* [110]	Open-label, clustered group-randomized, crossover study	5927 ICU patients from 13 different ICU	SDD and SOD have low levels of antibiotic resistance
Houben AJ, *et al* [112]	Multicenter case study	17 ICU	Continuous use of SOD/SDD associated with declining trends for resistance to cefotaxime/ceftriaxone and ciprofloxacin. Introduction of SOD/SDD associated with reductions in resistance rates for all antimicrobial agents included
Probiotics/prebiotics			
Kotzampassi K, *et al* [121]	Randomized controlled trial	65 critically ill trauma patients	Synbiotic-treated patients exhibited significantly lower rates of infections, SIRS, severe sepsis and mortality. Days in the ICU and days under mechanical ventilation significantly reduced versus placebo

Contd...

Table 3 Contd...

Authors	Study type	Material	Results/outcomes
Spindler-Vesel A, *et al* [122]	Randomized study	130 multiple trauma patients	Patients supplemented with synbiotics had lower intestinal permeability and fewer infections
Giamarellos-Bourboulis E.J, *et al* [123]	Randomized clinical trial	72 multiple trauma patients	Synbiotics significantly decrease the risk for sepsis by bloodstream infections and the occurrence of VAP by *A. baumannii*
Oláh A, *et al* [125]	Prospective, randomized, double blind study	62 patients with severe acute pancreatitis	Early nasojejunal feeding with synbiotics may prevent organ dysfunctions in the late phase of pancreatitis. Pancreatic necrosis infection may be associated with early phase organ failure
Besselink MG, *et al* [126]	Multicenter, randomized, double-blind, placebo-controlled trial	296 patients with severe acute pancreatitis	Probiotic prophylaxis associated with more than two-fold increase in mortality
Besselink MG, *et al* [127]	Randomized, placebo-controlled multicenter trial	641 patients with severe acute pancreatitis	Prophylaxis with probiotics reduced BT, but was associated with increased BT and enterocyte damage in subjects with organ failure
Glutamine			
Li Y, *et al* [132]	*In vivo* animal study	Wistar-to-Wistar rat Liver Transplant model	GLN-early EN is a potent protectant against intestinal mucosal barrier injury after liver transplant
Aldemir M, *et al* [133]	*In vivo* animal study	50 rats	GLN reduces the incidence of BT and preserves intestinal mucosal integrity
Fan J, *et al* [135]	*In vivo* animal study	34 mice burn-model	GLN-supplemented EN superior to conventional EN with respect to improvement of intestinal immunity
Arginine			
Quirino IE, *et al* [142]	*In vivo* animal study	Intestinal obstruction model in rats	Arginine decreased BT despite intestinal obstruction
Viana ML, *et al* [143]	*In vivo* animal study	Intestinal obstruction model in mice	Arginine supplementation reduced intestinal permeability and BT to physiologic levels
Immunonutrition			
Berger MM, *et al* [153]	Prospective randomized controlled trial	28 cardiac surgery patients	Perioperative fish oil may be beneficial in elective cardiac surgery with cardiopulmonary bypass
Senkal M, *et al* [152]	Prospectively randomized clinical trial	40 patients with major gastrointestinal surgery	Preoperative administration of oral ω-3 polyunsaturated fatty acid-enriched diet could have an impact
Sorensen LS, *et al* [154]	Randomized, double-blind, prospective, placebo-controlled, single-center intervention trial	Patients going into elective colorectal cancer surgery	Eicosapentaenoic acid rapidly incorporated into colonic mucosa and colonic muscular layer in patients given ω-3 fatty-acids daily before surgery

BT, bacterial translocation; EN, enteral nutrition; GLN, glutamine; IAP, intra-abdominal pressure; ICU, intensive care unit; MOF, multiple organ failure; SDD, selective digestive decontamination; SIRS, systemic inflammatory response syndrome; SOD, selective oral decontamination; TPN, total parenteral nutrition; VAP, ventilator association pneumonia

than 15 mmHg causes abdominal ischemia and consequently early ischemic changes in the small and large bowel leading to BT [77,78]. The burden of histomorphological damage of the intestine increases dramatically with elevated intra-abdominal pressure levels, associated with significantly higher BT, endotoxin exposure, bacteremia and procalcitonin elevation, all suggestive of gut barrier dysfunction [78]. Monitoring of abdominal perfusion pressure should be performed among patients at risk of intra-abdominal hypertension.

Adequate blood flow to the gut in critically ill patients can be achieved by maintaining intravascular volume and adequate cardiac output. Inotropic agents, such as dopexamine, dobutamine and dopamine which have vasodilatory properties, may raise visceral blood flow and limit ischemia-reperfusion injury [3,15]. The role of catecholamine type is still debated. Dopamine and norepinephrine have similar hemodynamic effects, while epinephrine can impair splanchnic circulation in severe sepsis [79] causing early mucosal damage [80]. On the other hand, aggressive fluid resuscitation and hypervolemia may also harm the intestinal mucosal barrier due to mucosal edema.

Enteral versus total parenteral nutrition (TPN): There is an old prejudice that TPN is associated with intestinal mucosa

Table 4 Grading of mucosal damage [76]

Grade	Histological changes
0	Normal mucosal villi
1	Development of subepithelial Gruenhagen's space, usually at the apex of the villus; often with capillary congestion
2	Extension of the subepithelial space with moderate lifting of epithelial layer from the lamina propria
3	Massive epithelial lifting down the sides of villi. A few tips may be denuded
4	Denuded villi with lamina propria and dilated capillaries exposed Increased cellularity of lamina propria may be noted
5	Digestion and disintegration of lamina propria; hemorrhage and ulceration

atrophy promoting increased BT and leading to sepsis, while administration of nutrition via the GI tract prevents this cause of sepsis and improves morbidity and mortality [81]. However, there is no evidence that TPN actually causes such morphological or functional changes in human intestine [16]. In fact, TPN is usually reserved for patients with impaired intestinal function, who cannot tolerate or absorb nutrients through the enteral route or are not permitted enteral feeding for other medical reasons [16]. Consequently, the actual contribution of TPN to BT in circumstances of underlying intestinal disorders is difficult to assess as TPN-related BT is impossible to separate from the pre-existing gut failure. Notably, TPN has no significant effect on rates of infections and mortality in critically ill patients, provided that glycemic control is adequate and overfeeding is avoided [82].

On the other hand, studies in surgical and non-surgical critically ill patients have reported that early enteral feeding correlates with lower mortality rates, less risk for infectious and pancreatic complications [83-85] and better nutritional outcome [86]. Moreover, studies in patients with severe trauma, burns or acute pancreatitis [87,88] have demonstrated that total enteral nutrition suppresses significantly the acute inflammatory response phase, as well as the incidence of infectious complications resulting in lower rates of organ failure, surgical interventions and mortality compared to TPN. The potential mechanism for this divergence is that feeding through the intestinal tract helps maintain the intestinal barrier function thus preventing bacterial and toxin translocation through the intestinal mucosa [85,88-90].

Selective digestive decontamination (SDD): SDD is a therapeutic modality which consists of a combination of oral nonabsorbable antibiotics (in paste or gel form) plus a brief course of systemic antibiotics to suppress the populations of pathogenic Gram-negative bacteria in favor of commensal anaerobic bacteria, in order to control secondary oropharyngeal and intestinal carriage [91-95]. Stoutenbeek [96] first introduced SDD as a measure to prevent infections in trauma patients admitted to the ICU. Although SDD covers both normal and abnormal flora, it rather targets Gram-negative bacteria than low-level pathogens, which rarely cause infections in ICU patients [95,97].

The efficacy of SDD relies on the ability of antimicrobials to clear oropharyngeal and gut carriage of both normal and abnormal potentially pathogenic bacteria in overgrowth concentrations rather than to selectively remove aerobic bacteria leaving the anaerobic intestinal flora intact [98]. Fritz *et al* showed that decontamination of the small intestine, but not of the colon alone, decreases bacterial overgrowth in the small intestine and BT [52].

Some recent single-center prospective trials and meta-analyses have shown that SDD reduces the rate of infection, but were not powered enough to detect a benefit in terms of mortality [99,100], although others have reported improvement in patient outcomes [100-105]. SDD appears more efficacious in reducing the duration of mechanical ventilation, ICU stay, hospital stay, and mortality among trauma and surgical critically ill patients, while there seems to be no such benefit for medical patients [94,106]. Undoubtedly, however, respiratory and intestinal tract decolonization decreases the occurrence of ICU-acquired Gram-negative bacteremia [107].

On the other hand, long-term use of decontamination regimens may enhance selection and emergence of resistant species [15]. Oostdijk *et al* [108] showed that selective oropharyngeal decontamination (SOD) and SDD raise the prevalence of rectal and respiratory tract colonization with ceftazidime-resistant bacteria during and after the intervention, with a rebound effect of ceftazidime resistance in the intestinal tract after SDD discontinuation. Most of ceftazidime-resistant *Enterobacteriaceae* are likely to have extended-spectrum β-lactamase genes. These pathogens are gradually overriding in most populations, up to the point to surpass more traditional multidrug-resistant pathogens, such as *Acinetobacter* and *Pseudomonas* [108]. According to Trouillet *et al* [109] intensive use of systemic antibiotics associated with the full SDD is sufficient to raise the risk of subsequent infection with *Pseudomonas aeruginosa*, suggesting that antibiotic overuse modifies the normal flora and may be a critical step in predisposition. In contrast, de Smet *et al* showed that broad use of SDD and SOD in ICU patients effectively decreases Gram-negative respiratory tract colonization, with low levels of antibiotic resistance [110]. Recently, a systematic review detected no association between SDD or SOD and the development of antimicrobial resistance in pathogens of ICU patients, challenging the assumption of a long-term SDD-related harm [111]. Moreover, Houben *et al*, in a study involving 38 ICUs in the Netherlands for 4 years, found that SOD/SDD was associated with a statistically significant reduction in rates of resistance to all antimicrobial agents [112].

Despite the evidence that SDD confers benefits in terms of morbidity and mortality, with the resistance being controlled and costs lower than 10 € per day [95,113-115], it is not common practice in the ICUs yet.

Probiotics and prebiotics: Probiotics are alive microbial (bacteria or yeast) feed supplements, which affect beneficially the host by improving its microbial balance and contain no virulence properties or antibiotic resistance cassettes [116,117]. Prebiotics are indigestible agents, mostly plant

Table 5 Probiotics mechanisms of action [119]

Promotion of the integrity of the guts defense barrier by:	Normalization of intestinal permeability Control of intestinal inflammatory responses Balancing the release of cytokines
Maintain normal microecology of gastrointestinal flora by:	Nutrient competition Alteration of local pH Stimulation of epithelial mucus production Modification of pathogen-derived toxins

fibers, that promote the growth or activity of useful bacteria, thus further benefiting the host [118]. The mechanisms whereby probiotics create an unfavorable environment for pathogens are listed in Table 5 [3,119].

A recent meta-analysis concluded that the perioperative administration of probiotics to patients undergoing major elective abdominal procedures, reduces the post-operative infection rate by more than 50%, and the length of stay, although it does not improve mortality [120]. Similar results were obtained in trauma patients [121-124].

On the other hand, a couple of studies showed that treatment of patients with severe acute pancreatitis with probiotics resulted in increased incidence of infectious complications and higher mortality, associated with early intestinal barrier dysfunction [125-127]. The timing of administration of these agents seems to be important: electively before major operations appears to be beneficial, perhaps because the gut barrier function is still intact and the intestinal flora has not been disturbed yet, while high dosages of such agents in patients with established gut injury may result in translocation of these low-virulence bacteria and ultimately increased systemic inflammation [128]. The use of probiotics in critically ill patients is controversial and still remains to be elucidated which group of patients may benefit the most from their use [116].

Immune-enhancing diets: The best studied immune-enhancing nutrients are glutamine, arginine, fish oil (ω-3 fatty acids), γ-linoleic acid and nucleotides [13,129-131]. The concept behind these diets was that supplying enterocyte-specific nutrients and immunomodulating factors enterally would limit gut injury.

Glutamine is an abundant amino acid, important for the metabolic processes of rapidly proliferating cells, such as small intestine enterocytes [132]. It is an essential dietary component for intestinal mucosal integrity contributing to reduction in the rate of endotoxinemia and BT. Although it possesses no anti-endotoxin properties [132,133], it exerts direct effects on the immune system, such as enchancing the production of immunoglobulin A and increasing B and T lymphocyte counts [134-136].

Several studies in animals have reported that early enteral nutrition with glutamine minimizes dose-dependently the damage to the intestinal mucosa, BT and endotoxinemia following surgical trauma or ischemia-reperfusion injury compared with the non-pretreated group [41,132,137-139]. In humans, glutamine has been associated with stimulation of the immune system [136], maintaining the normal intestinal barrier and reducing BT and sepsis [140].

Arginine is a semi-essential amino acid with multiple favorable metabolic and immunologic effects, particularly under stress conditions [141]. It promotes nitrogen retention and has a role in maintaining the mucosal barrier integrity and reducing intestinal permeability [85]. Arginine promotes the release of anabolic hormones, enhances immune function and improves wound healing [130].

In vivo studies in intestinal obstruction have shown reduction in BT when enteral nutrition was supplemented with arginine [142,143]. Notably, the combination of enteral glutamine and arginine seems to be more effective with respect to the protection of the intestinal mucosa in cases of endotoxinemia [144-147].

Plasma levels of arginine during sepsis vary depending on the stage at which they are measured. Deficiency is most likely in the early stages of sepsis and increases gradually as the latter progresses, particularly in the setting of MODS [148]. Therefore, the benefit of arginine supplementation during sepsis may depend on the time point at which it is administered and it may even be harmful in severely ill septic patients [149], while in trauma patients, it appears to have a limited role [150].

Fish oil-derived ω-3 fatty acids attenuate the production of inflammatory prostaglandins and prostacyclins and reduce the cytotoxicity of inflammatory cells by displacing the arachidonic acid of the cell membrane of immune cells. Fish oil-derived fatty acids, eicosapentanoic and docohexanoic acids, are the precursors of resolvins, which reduce cellular inflammation by inhibiting the gathering of inflammatory cells and mediators to the site of inflammation [151]. Although in several perioperative randomized trials ω-3 fatty acids have been shown to modulate proinflammatory and anti-inflammatory mediators in the gut and other tissues [152-154] the clinical benefit of these diets in patients undergoing elective surgery is uncertain. Marik and Zaloga [131] proposed that the effect of immunonutrition depends on the formula composition and the optimal timing. An immunomodulating enteral diet enriched in both arginine and fish oil should be considered in all high-risk patients undergoing major elective surgery and, although the optimal timing cannot be determined, it is suggested to be initiated preoperatively when feasible. Other researchers expand the indications of immunonutrition also to critically ill patients, in whom it seems to reduce the infectious complication rates, without, however, changes in mortality [155-157].

Concluding remarks

Undoubtedly, the intestine plays an important role in the development of sepsis syndrome and MOF. BT seems to occur clinically and to be responsible for the increased prevalence of infectious complications in critically ill patients. The exact pathophysiological mechanisms linking the GI tract to the development of these severe complications remain to be elucidated, although it appears that BT alone does not sufficiently explain the development of MODS in ICU patients. Gut hypoperfusion may be the missing link, whereby visceral ischemia transcends a hemodynamic situation onto

an immune-inflammatory event, through the release of biologically active factors into the mesenteric lymph vessels. Once changes in the gut immune function have taken place, the process is further carried forward through the interplay between the gut-associated immune tissue and the rest of the body. At the bedside, the identification of easily applicable biomarkers for early diagnosis and evaluation of gut failure is an important task, since prevention and therapeutic intervention at the early stages are currently the only strategies that may improve the outcomes of at-risk patients before the emergence of SIRS and MOF.

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