# Gut dysfunction in the critically ill – mechanisms and clinical implications

**L T Hill**, RD (SA), PhD

*Division of Human Nutrition, Department of Human Biology, University of Cape Town, South Africa (currently: Division of Critical Care and Department of Surgery, University of Cape Town)*

***Corresponding author:*** *L T Hill (lauren.hill@uct.ac.za)*

Gastrointestinal dysfunction is a common problem in the critically ill patient, and is commonly observed in the intensive care unit (ICU). It is recognised that a functional gastrointestinal tract is an important factor in the clinical outcome of patients in the ICU. The difficulty in clinical practice has been the lack of an objective or unified definition or understanding of what gastrointestinal dysfunction in the critically ill means. Additionally, gut problems in ICU may often be fairly occult and challenging to classify by degree. Critical illness-associated gut dysfunction is implicated in aetiological processes that drive critical illness, and is further linked to negative nutritional and infectious consequences and poor clinical outcomes. There is currently no complete, unified pathophysiological model of the phenomenon, and cross-disciplinary research opportunities therefore exist both to clarify the mechanisms and to develop treatments.

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Gastrointestinal dysfunction is a common problem in the critically ill patient. Delayed gastric emptying, abnormal motility patterns, and impaired intestinal barrier integrity are commonly observed in the intensive care unit (ICU). It has been recognised for some time that a functional gastrointestinal tract (GIT) is an important factor in clinical outcome of patients in the ICU. The development of symptoms suggestive of gut dysfunction is associated with enteral feeding failure, complications and morbidities, which may all affect survival.[1,2] A functional gut in the critically ill patient is of considerable importance and clinical relevance.

The difficulty in clinical practice has been the absence of an objective or unified definition or understanding of what gastrointestinal dysfunction in the critically ill means; it is commonly recognised by experience and clinically evaluated in a relatively intuitive manner. Additionally, gut problems in ICU may often be fairly occult and challenging to classify by degree. While organ failure can be considered a categorical state of non-functionality, organ dysfunction suggests impaired function somewhere along a continuum of functional disturbances. However, even subtle alterations in bowel function in the critically ill may have consequences of prognostic importance.

## Common gastrointestinal disturbances in ICU

Critical illness may alter gut motility and transit, or may affect non-motor function such as mucosal barrier integrity; absorptive capacity for fluids, electrolytes and nutrients; immunological activity; endocrine function and gut regulatory mechanisms. The organ system referred to as the gut comprises four broad components: the intestinal epithelium and the mucosal immune system, which are innervated by the enteric nervous system, and the commensal microflora of the gut lumen. Functional failure can occur at any level of gut physiology, and the impact can be confined to a particular region or the entire organ. The majority of critically ill patients will have at least one gastrointestinal symptom during their ICU stay.[3-5] Table 1 summarises the prevalence of symptoms observed to occur in the critically ill.

**Table 1. Prevalence of gastrointestinal symptoms in critically ill patients**

| GI symptom | Montejo 1999[4] | Montejo 2002[5] | Reintam 2009[3] |
|---|---|---|---|
| Absent/abnormal bowel sounds | Not reported | Not reported | 41% |
| Abdominal distension | 13% | 9% | 11% |
| Vomiting | 12% | 6% | 38% |
| Diarrhoea | 15% | 14% | 14% |
| Constipation | 16% | 5% | Not reported |
| High gastric residual volume | 39% | 25% | 23% |
| GI bleed | Not reported | Not reported | 7% |
| Enteral feed stoppage owing to GI symptoms | 15% | Not reported | 63% |
| Any GI symptom | Not reported | 61% | 59% |

Many of the commonly occurring problems (e.g. vomiting, gastric retention, absent/abnormal bowel sounds, diarrhoea, distension, ileus) are interpreted to be disorders of gastrointestinal motility. Indeed, motility throughout the GIT is profoundly abnormal during severe illness; gastro-oesophageal sphincter tone is extremely poor and gastro-oesophageal reflux combined with poor oesophageal peristaltic clearing of refluxed contents occurs frequently.[6]

Reportedly, at least half of patients on mechanical ventilation are affected by retarded stomach emptying, with the highest occurrence of disturbed gastric emptying in patients with multitrauma, neuro-trauma, burns and sepsis.[6] Derangements in gastric motile activity include overall disturbed motility in the various stomach regions together with poorly synchronised and unco-ordinated motor function between the fundus and antropyloric areas of the stomach.[7] This presents as higher than desirable gastric residual volumes of gastric secretions in the fasted patient and of enteral feed in the fed patient, and possibly also with vomiting in patients with large retained volumes in the stomach; this may be worsened by abnormal pyloric responses to feeds and persistent duodenal contractile motor waves that propagate in the wrong direction, provoking reflux from the duodenum in a retrograde fashion into the stomach.[7]

Motor function of the small intestine has not been researched much in the critically ill owing to technical difficulties. However, one study has investigated the gastric antrum, duodenum and proximal jejunum of patients undergoing elective repair of infra-renal aortic aneurysm.[8] The results indicated that motor activity in the small bowel is not inhibited in the same way as in the stomach, but that the small intestinal response manifests as active but grossly abnormal motility. However, limited evidence suggests that small bowel transit time does not seem to be shorter in critical illness than in healthy persons.[9]

Symptoms that are interpreted to be colonic in origin (i.e. changes in stool frequency, form and consistency) are common in the ICU. Constipation is seen with equal frequency to other common gastrointestinal symptoms,[3] and is understood to be related to the well-known postoperative slowing of colonic transit seen in a wide variety of patients. Conversely, diarrhoea is very widespread in the ICU, being experienced by up to 50% of patients during an ICU stay.[3-5]

Gastrointestinal bleeding, presenting as haematemesis, coffee grounds vomitus, blood-stained nasogastric drainage, melaena stool or clinically important gastrointestinal bleeds causing discernible drops in blood pressure or haemoglobin, reportedly occur with varying severity in up to half of all ICU patients; while almost every patient will have clinically silent endoscopic evidence of erosive mucosal damage.[10] Barring the presence of another explanation, bleeding in the intestinal tract in critically ill patients is indicative of mucosal stress injury.

In fact, GIT bleeding is only one manifestation of loss of mucosal integrity in severely stressed patients. Villous ischaemia-reperfusion injury in haemodynamic instability and hypotension leads to epithelial morphological disruption, apoptotic and necrotic cell loss, blunted villous height, and shedding of enterocytes into the gut lumen.[11] This compromises the complex process involved in normal gut barrier function, leading to increased intestinal permeability. So-called 'flat bowel syndrome' may occur whereby water, electrolytes and nutrients are malabsorbed, leading to feeding intolerance. Other barrier functional abnormalities include alterations in the secretions of ions and regulatory molecules, amino acid metabolism, intestinal mucus qualities and a breakdown in the protective immunological mechanisms governing the interaction of the gut mucosa with intra-luminal bacteria crucial for appropriate immune-inflammatory responses.[12]

Distortions in the intestinal bacterial populations with overgrowth of pathogenic bacteria have been shown to occur in patients with severe systemic inflammatory response syndrome (SIRS).[13] This pathological state in itself negatively affects gut barrier integrity, and probably also gut motility, since normal intestinal flora stimulate the initiation and propagation of migrating motor complex activity.[14] Conversely, abnormal gut motor activity is associated with small bowel bacterial overgrowth, which can result in diarrhoea and feed fermentation with abdominal distension.

# Mechanisms of gastrointestinal dysfunction

## Dysmotility

The precise mechanisms of altered gut function in the critically ill are as yet unclear, although much has been discovered about the neuro-endocrine and inflammatory pathways, molecules and mediators involved in gastrointestinal physiology and pathophysiology. Numerous factors, clinical processes and interventions could account for the disrupted gastrointestinal function seen in the critically ill.

Dysmotility in the upper gut is known to be affected by commonly employed clinical management approaches. The widespread use of opioids may be foremost among these.[15] Other factors such as the use of non-opioid sedatives, catecholamines for inotropic support, intra-abdominal hypertension, raised intracranial pressure, derangements of glucose and electrolyte levels, positive pressure ventilation, duration of surgical procedures, blood loss and surgery involving manipulation of intestines by the surgeon's hands, are well known and are virtually inevitable causes of gastric motor stasis in the postoperative period.[16,17]

Motor function in the proximal gut is under central and enteric neuro-endocrine controls that allow the highly co-ordinated smooth muscle peristaltic action typical of a healthy gut. In critical illness, overactive sympathetic activity, and catecholamine administration, may play a part in gut dysmotility.[18] This is supported by the increase in gut motility seen when epidural opioid analgesia incorporates local anaesthetic, presumably because of the sympathetic blockade achieved.[15] Conversely, vagal inhibition may impede gastric emptying since normal vagal input is necessary for the feeding-induced abolition of fasting state motility patterns. The abnormal and persistent antropyloroduodenal motor responses to feeding in the critically ill that retard gastric emptying suggest an absence of intact vagal activity.[7] Poor gut contractility and slow intestinal transit times in ICU patients also involve inhibitory neurotransmitters such as nitric oxide and vasoactive intestinal peptide, as well as tachykinins such as substance P and the neurokinin family.[19] Therefore, accelerated small bowel transit is probably not a major reason for diarrhoea in the ICU. A variety of iatrogenic and clinical factors combine to induce this disorder. Among the more relevant factors are hypo-albuminaemia associated with severe illness, and the extensive use of antibiotics. Antibiotics may have direct drug effects on smooth muscle, but also alter bowel flora populations and therefore disturb normal propulsive motor activity.[14]

A number of hormones regulate gastrointestinal motor function, but there is no research on how important the contribution of each

might be in critical illness-associated dysmotility. What is known is that excessive concentrations of cholecystokinin (CCK) and peptide YY occur in critical illness, and that high levels are correlated with feed intolerance and slow gastric emptying.[20] The role of motilin in motor function of ICU patients may be of particular importance because of the regular use of the motilin agonist erythromycin as a prokinetic agent in ICU. ICU patients appear to have an abnormally high plasma motilin response to feeding, which may be an explanation for poor gastric relaxation and volume expulsion.[21] Lastly, the profound corticotrophin-releasing factor response in severely stressed patients has been found to correlate with poor gastric emptying in our ICU (unpublished reports) as shown in other stable patient groups.[18]

Perhaps the most obvious influence on gastrointestinal dysmotility is that of the inflammatory cytokines common to the normal stress response present in all critically ill patients. Information continues to emerge indicating that the nature of the inflammatory response determines the changes in neuromuscular function that occur in different experimental stress models. Inflammation and associated oxidative stress within the muscularis layers of the gut may impede contractility, and alter smooth muscle ion channels,[22] but inhibition of contractile function also occurs via cytokine-mediated modulation of spinal afferent neurons, at least in animal sepsis models. Inflammatory cytokine responses are also inextricably linked to impaired gut barrier function.

## Barrier dysfunction

ICU patients have been shown to already have indications of gut barrier loss even on admission to ICU. It has been repeatedly demonstrated that increased pro-inflammatory cytokines, such as interleukin-6 and tumour necrosis factor-alpha, are absolutely fundamental to the loss of barrier integrity even when the insult is not directed at the gut.[23] This is because cytokines appear to induce a marked reduction in intestinal levels of membrane-associated proteins (such as occludin and zona occludens protein-1), which are crucial regulators of intestinal tight junctions, as has been shown in shock models.[24]

Shock may additionally result in intestinal hyper-permeability via an ischaemia reperfusion mechanism. Loss of intestinal barrier function is associated with severe morphological changes to the small intestine – including opening of tight junctions and epithelial cell necrosis and apoptosis – that seem to be correlated with the severity and timing of the reperfusion injury.[25] This type of tissue injury may be at least partially dependent on aspects of fluid resuscitation. Volume resuscitation with crystalloid solutions appears to result in a worse gut barrier defect, more bowel oedema, and more pronounced gut histological damage than resuscitation with colloids[26] while resuscitation fluid volume is a proxy marker for degree of shock.

Shock-associated disruption of the mucosal mucus layer and changes in mucus qualities have also been directly linked to enhanced intestinal permeability.[12] Mucus is now understood to be an important vehicle for mucin-associated regeneration and renewal of the mucosa and maintenance of barrier integrity, rather than simply a passive protective lubricant for epithelial surfaces.[27] Normal commensal flora also play a vital role in epithelial integrity by influencing mucus production in a manner that inhibits interaction of pathogenic flora with the epithelial surface, stabilises tissue inflammatory processes, protects tight junction barrier assemblies to maintain tight seals between adjacent cells, and inhibits cell loss.[28]

During critical illness with SIRS, the normal and appropriate balance of intestinal flora is not maintained, typified by a reduction in overall obligate commensals with a concomitant increase in potentially pathogenic bacterial species[13] that leads to a reduction in stool content of organic acids, such as butyrate, which are key fuels for mucosal cells as well as for stimulus of mucin production.[28] In this way, disruption of bowel microbiota during critical illness contributes to worse gut barrier functional integrity. It has been demonstrated that supplementation of critically ill trauma patients with probiotic bacteria reduces the inflammatory cytokine response and attenuates the increase in intestinal permeability observed in such patients,[29] while animal work has shown that probiotics can prevent the inflammation-induced epithelial barrier defect associated with loss of tight junction proteins.[30] There have been safety concerns around probiotics in clinical use, however, since one study reported increased mortality in patients with severe acute pancreatitis treated with probiotics.[31]

Numerous other clinical conditions have been shown to contribute to epithelial barrier defects and leakiness. Conditions such as sepsis, severe acute pancreatitis, jaundice and inflammatory bowel disease are associated with a generalised hyper-permeability of the small and large intestines.[32] Manipulation of the bowels during surgical procedures has been shown to induce oxidative stress, alterations to the mucosal membrane structure and function, and increase intestinal permeability.

Critically ill patients probably develop intestinal barrier dysfunction with enhanced permeability as well as disordered gastrointestinal motility via different mechanisms, and most likely via the cumulative effect of various mechanisms combined. Whatever the mechanism, gut pathophysiology of various kinds seems to be not only an effect of, but also a contributor to, critical illness.

# Clinical implications of gastrointestinal dysfunction

Bowel dysfunction is associated with increased morbidity and poor clinical outcomes, including increased mortality. In broad terms, there are two main inter-related clinical effects of gut dysfunction in ICU, the first being on nutrition and the second on infection risk.

## Nutritional consequences

Impaired gut function significantly compromises delivery of enteral nutrition. Feed intolerance related to gastric stasis is perhaps the most common reason for failure of enteral feeding in ICUs, and occurs with a reported 35% prevalence when defined as a gastric residual volume ≥250 ml.[5] Using gastric residual volume measurement in this way, however, is very controversial since it is not governed by a standard technique or volume cut-offs, and its clinical relevance is based on numerous assumptions only tenuously supported by evidence. Consequently, obsessive tuning of nutritional support to the gastric residual signal may unduly hinder enteral feeding, while not actually serving as a proxy for poor gastric emptying.[33]

Nevertheless, gastric residual volume, as possibly the single most widely used crude indicator of retained gastric contents, does correlate with low energy intake. Most ICU studies report an intake of only 40 - 60% of nutritional requirements, at least partly because of gastrointestinal dysfunction.[34] Retarded gastric emptying is associated with a reduced nutrient absorption rate. It has been shown in burns patients, however, that initiation of enteral feed as part of acute resuscitation measures within 6 hours of injury helps to prevent delayed gastric emptying.[35]

Small bowel factors play a role in diminished absorption as well, because nutrient delivery directly into the small intestine is also associated with lower absorption in the critically ill.[36] Normal small bowel motility is required for good nutrient absorption, and persistent fasting state motor patterns typical of sick patients may, at least theoretically, result in diarrhoea by increasing the unabsorbed nutrient load entering the colon. Diarrhoea with nutrient malabsorption can also be a result of small intestinal bacterial overgrowth associated with altered bowel flora populations, and poor mucosal repair. Diarrhoea that impedes enteral feeding may lead to a perpetuating feed-associated gastrointestinal symptom cycle, because enteral nutrients are necessary for intact mucosal function and vice versa. Nutrition deficits in critically ill patients are associated with worse clinical outcomes, including increased risk of infectious complications which at least in part are linked to gastrointestinal dysfunction.

## Infectious consequences

Proposed infectious consequences of disordered gut function include aspiration with an associated predisposition to ventilator-associated pneumonia, and gut-derived nosocomial sepsis.

Aspiration of feed in the critically ill patient is certainly one of the most anxiety-provoking morbidities associated with enteral nutrition support. Since it is associated with poor respiratory function and nosocomial pneumonia, it is also the point where goals for provision of adequate nutrition and goals for prevention of septic complications of ICU stay intersect. While the sensitivity and specificity are fairly poor, a thread of association between high gastric residual volumes and tracheobronchial aspiration of stomach contents has been shown.[37] Aspiration may or may not be a preceding event in nosocomial pneumonia, but it is assumed that pneumonia can result from gastric stasis and reflux of even a low volume of contents of a non-motile, bacterially colonised stomach into the airway.

While gastric residual volumes alone are not associated with pneumonia risk, feed intolerance defined as a combination of high retained gastric volumes together with vomiting is significantly associated with ICU-acquired pneumonia, as well as longer ICU stays and increased mortality. Ironically, inappropriately low gastric residual volume cut-offs to define enteral feeding protocols have been shown to result in unnecessary enteral feed stoppages, a phenomenon that was correlated with an increased incidence of infection and nosocomial pneumonia compared with patients who received significantly higher enteral formula volumes.[37]

Another theoretical concern is that poorly synchronised gastrointestinal motor activity in very ill patients may impair the elimination of intestinal contents and place critically ill patients at risk of prolonged exposure to antigenic and microbiological agents, which remain in contact with the compromised intestinal barrier. The clinical significance of increased gut permeability in sepsis risk is not entirely known. Original bacterial translocation theories, never demonstrated convincingly in humans, have been all but refuted. However, recent *in vivo* evidence indicates that infectious complications and mortality were significantly increased in critically ill patients with SIRS who had abnormally low obligate commensal floral counts within the intestine.[38] These data suggest that gut flora-epithelium crosstalk may be involved in new concepts of gut-derived sepsis, which are supported by several randomised, controlled studies in surgical and trauma patients that have shown reduced infectious complications with probiotic and synbiotic supplementation.[39] Most similar studies in ICU patients have been negative, although Morrow *et al*.[40] demonstrated a reduction in ventilator-associated pneumonia with probiotic prophylaxis. The currently understood mechanisms involved include the abilities of lethal pathogenic bacteria found in excess in the unbalanced gut floral environments of the critically ill to transfer their gene products into intestinal epithelial cells adjacent to the immune system, to produce and exist with biofilms resistant to antibiotic penetration, and the initiation of pathogen quorum sensing by molecular mediators in shocked and reperfusion-injured gut tissue.[41]

# Towards better definitions and diagnosis of gastrointestinal dysfunction in ICU patients

One of the difficulties in investigating gastrointestinal dysfunction in ICU patients is the lack of consistent definitions for the various aspects that are incorporated in the concept of gut dysfunction, making comparison of research from different centres problematic. Clarification is needed. In 2012, a Working Group on Abdominal Problems of the European Society of Intensive Care Medicine convened to compile an evidence- and expert opinion-based, but as yet unvalidated, list of definitions and a grading system for gastrointestinal dysfunction in the critically ill.[42] The Expert Panel Report definition and terminology list describes four grades of Acute Gastrointestinal Injury (defined as 'malfunctioning of the GIT in critically ill patients due to their acute illness') and provides definitions for a large number of gastrointestinal symptoms. The intention is that the terminology be applicable in both clinical and research applications, and possibly validated as part of organ failure scoring in the future.

The report does, however, not address gut barrier or immunological functions, or those under neuroendocrine control – possibly the most challenging aspects to pin to objectively evaluable definitions. Measurement of circulating mediators such as intestinal fatty acid binding protein (I-FABP) and citrulline may fill this gap, as they are validated indicators of enterocyte mass, villous atrophy and permeability.[43]

Although a useful start in creating consensus on symptom definition, the weakness of the report of the Working Group on Abdominal Problems is that it is not based on a unifying model of the pathophysiology of gut dysfunction in the critically ill. Researchers from the University of Washington[44] have proposed a theory that attempts to bring together the various apparently disparate and ever-changing models of critical illness-associated gut dysfunction by proposing a complex paradigm wherein the derangements of the different elements of the gastrointestinal organ interact with each other. Their paradigm attempts to incorporate all of the numerous valid ways of understanding the interrelationship between gut dysfunction and critical illness.

# Conclusion

Gut function in ICU patients is of clinical interest for a number of reasons. Dysfunction of the gut occurs so commonly in severely ill patients that it affects daily management of the critically ill. Data indicate that the disordered gastrointestinal function seen in the critically ill incorporates profound abnormalities in gut motor function, loss of barrier integrity and distortions in commensal flora populations. Mechanisms implicated in these

functional derangements include inflammatory, myoelectrical and neuroendocrine processes as well as numerous clinical conditions and treatment approaches. Critical illness-associated gut dysfunction is implicated in aetiological processes that drive critical illness, and is further linked to negative nutritional and infectious consequences and poor clinical outcomes. There is currently no complete, unified pathophysiological model of the phenomenon, but cross-disciplinary research opportunities exist both to clarify the mechanisms and also to develop treatments.

**References**


1. Gramlich L, Kichian K, Pinilla J, et al. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition 2004;20(10): 843-848. [http://dx.doi.org/10.1016/j.nut.2004.06.003]
2. Hill LT, Hill B, Miller M, Michell WL. The effect of intra-abdominal hypertension on gastrointestinal function. South African Journal of Critical Care 2011;27(1):12-19.
3. Reintam A, Parm P, Kitus R, et al. Gastrointestinal symptoms in intensive care patients. Acta Anaesthesiol Scand 2009;53:318-324. [http://dx.doi.org/10.1111/j.1399-6576.2008.01860.x]
4. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: A multicenter study: The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Crit Care Med 1999;27:1447-1453. [http://dx.doi.org/10.1097/00003246-199908000-00006]
5. Montejo JC, Grau T, Acosta J, et al. for the Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Multicenter, prospective, randomized, single-blind study comparing the efficacy and gastrointestinal complications of early jejunal feeding with early gastric feeding in critically ill patients. Crit Care Med 2002; 30(4):796-800. [http://dx.doi.org/10.1097/00003246-200204000-00013]
6. Nguyen NQ, Ng MP, Chapman M, et al. The impact of admission diagnosis on gastric emptying in critically ill patients. Critical Care 2007;11(1):R16. [http://dx.doi.org/10.1186/cc5685]
7. Nguyen NQ, Fraser RJ, Bryant LK, et al. Diminished functional association between proximal and distal gastric motility in critically ill patients. Intensive Care Med 2008;34(7):1246-1255. [http://dx.doi.org/10.1007/s00134-008-1036-5]
8. Tournadre J-P, Barclay M, Fraser R, et al. Small intestinal motor patterns in critically ill patients after major abdominal surgery. Am J Gastroenterol 2001;96:2418-2426. [http://dx. doi.org/10.1111/j.1572-0241.2001.03951.x]
9. Rauch S, Krueger K, Turan A, et al. Determining small intestinal transit time and pathomorphology in critically ill patients using video capsule technology. Intensive Care Med 2009;35:1054-1059. [http://dx.doi.org/10.1007/s00134-009-1415-6]
10. Duerkson DR. Stress-related mucosal disease in critically ill patients. Best Prac Res Clin Gastroenterol 2003;17:327-344. [http://dx.doi.org.ezproxy.uct.ac.za/10.1016/S1521-6918(03)00028-3]
11. Derikx JP, Matthijsen RA, de Bruine AP, et al. A new model to study intestinal ischemia-reperfusion damage in Man. J Surg Res 2011;166(2):222-226. [http://dx.doi.org/10.1016/j.jss.2009.09.046]
12. Rupani B, Caputo FJ, Watkins AC, et al. Relationship between disruption of the unstirred mucus layer and intestinal restitution in loss of gut barrier function after trauma hemorrhagic shock. Surgery 2007;141(4):481-489. [http://dx.doi.org.ezproxy.uct.ac.za/10.1016/j.surg.2006.10.008]
13. Shimizu K, Ogura H, Goto M, et al. Altered gut flora and environment in patients with severe SIRS. J Trauma 2006;60:126-133. [http://dx.doi.org/10.1097/01.ta.0000197374.99755.fe]
14. Husebye E, Hellstrom PM, Midtvedt T. Intestinal microflora stimulates myoelectric activity of rat small intestine by promoting cyclic initiation and aboral propagation of migrating myoelectric complex. Dig Dis Sci 1994;39:946-956.
15. Liu SS, Wong CL. Effect of postoperative analgesia on major postoperative complications: A systematic update of the evidence. Anesth Analg 2007;104(3):689-702. [http://dx.doi.org/10.1213/01.ane.0000255040.71600.41]
16. Mutlu GM, Mutlu EA, Factor P. Prevention and treatment of gastrointestinal complications in patients on mechanical ventilation. Am J Respir Med 2003;2(5):395-411. [http://dx.doi.org/10.1007/BF03256667]
17. Kariv Y, Wang W, Senagore AJ, et al. Multivariate analysis of factors associated with hospital readmission after intestinal surgery. Am J Surg 2006;191:364-371. [http://dx.doi.org.10.1016/j.amjsurg.2005.10.038]
18. Fukudo H, Tsuchida D, Koda K, et al. Inhibition of sympathetic pathways restores post-operative ileus in the upper and lower gastrointestinal tract. J Gastroenterol Hepatol 2007; 2:1293-1299. [http://dx.doi.org/10.1111/j.1440-1746.2007.04915.x]
19. Holzer P, Holzer-Petsche U. Tachykinins in the gut. Part 1. Expression, release and motor function. Pharmacol Ther 1997;73:173-217.
20. Nguyen N, Chapman M, Fraser R, et al. Feed intolerance in critical illness is associated with increased basal and nutrient-stimulated plasma cholecystokinin concentrations. Crit Care Med 2007;35(1):82-88. [http://dx.doi.org/10.1097/01.CCM.0000250317.10791.6C]
21. Nguyen NF, Bryant R, Burgstad L, et al. Abnormalities in plasma motilin response to small intestinal nutrient stimulation in critically ill patients. Gastroenterology 2010;138:S405. Abstract.
22. Akbarli H, Hawkins EG, Ross GR, Kang M. Ion channel remodelling in gastrointestinal inflammation. Neurogastroenterol Motil 2010;22(10):1045-1055. [http://dx.doi.org/10.1111/j.1365-2982.2010.01560.x]
23. Spindler-Vesel A, Wraber B, Vovk I, Kompan L. Intestinal permeability and cytokine inflammatory response in multiply injured patients. J Interferon Cytokine Res 2006;26(10): 771-776. [http://dx.doi.org/10.1089/jir.2006.26.771]
24. Han X, Fink MP, Delude RL. Proinflammatory cytokines cause NO-dependent and independent changes in expression and localisation of tight junction proteins in intestinal epithelial cells. Shock 2002;19:229-237.
25. Higuchi A, Wu R, Zhou M, et al. Gut hyper permeability after ischemia and reperfusion: attenuation with adrenomedullin and its binding protein treatment. Int J Clin Exp Pathol 2008;1:409-418.
26. Vega D, Badami CD, Caputo FJ, et al. The influence of the type of resuscitation fluid on gut injury and distant organ injury in a rat model of trauma/hemorrhagic shock. J Trauma 2008;65(2): 409-414 (discussion 414-415). [http://dx.doi.org/10.1097/TA.0b013e3181719708]
27. Cario E, Gerken G, Podolsky DK. Toll-like receptor 2 controls mucosal inflammation by regulating epithelial barrier function. Gastroenterology 2007;132(4):1359-1374. [http://dx.doi.org/10.1053/j.gastro.2007.02.056]
28. Peng LY, Li Z, Green RS, et al. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP activated protein kinase in Caco-2 cell monolayers. J Nutr 2009;139:1619-1625. [http://dx.doi.org/10.3945/jn.109.104638]
29. Giamarellos-Bourboulis EJ, Bengmark S, Kanellakopoulou K, Kotzampassi K. Pro- and synbiotics to control inflammation and infection in patients with multiple injuries. J Trauma 2009;67:815-821. [http://dx.doi.org/10.1097/TA.0b013e31819d979e]
30. Mennigen R, Nolte K, Rijcken E, et al. Probiotic mixture VSL#3 protects the epithelial barrier by maintaining tight junction protein expression and preventing apoptosis in a murine model of colitis. Am J Physiol Gastrointest Liver Physiol 2009;296(5):G1140-1149. [http://dx.doi.org/10.1152/ajpgi.90534.2008]
31. Besselink MGH, van Santvoort HC, Buskens E, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: A randomised, double-blind, placebo-controlled trial. Ned Tijdschr Geneeskd 2008;152(12):685-696.
32. Matejovic M, Krouzecky A, Rohyta R, et al. Effects of intestinal surgery on pulmonary, glomerular, and intestinal permeability, and it relation to the hemodynamics and oxidative stress. Surg Today 2004;34(1):24-31. [http://dx.doi.org/10.1007/s00595-003-2642-z]
33. Poulard F, Dimet J, Martin-Lefevre L, et al. Impact of not measuring residual gastric volume in mechanically ventilated patients receiving early enteral feeding: A prospective before-after study. J Parenter Enteral Nutr 2010;34(2):125-130. [http://dx.doi.org/10.1177/0148607109344745]
34. Heyland DK, Cahill NE, Dhaliwal R, et al. Impact of enteral feeding protocols on enteral nutrition delivery: Results of a multicenter observational study. J Parenter Enteral Nutr 2010;34(6):675-684. [http://dx.doi.org/10.1177/0148607110364843]
35. Rodriguez NA, Jeschke MG, Williams FN, Kamolz L-P, Herndon DN. Nutrition in Burns: Galveston Contributions. J Parenter Enteral Nutr 2011;36:704. [http://dx.doi.org/10.1177/0148607111417446]
36. Deane AM, Summers MJ, Zaknic, et al. Glucose absorption and small intestinal transit in critical illness. Crit Care Med 2011;39(6):1282-1288. [http://dx.doi.org/10.1097/CCM.0b013e31820ee21f]
37. Metheny NA, Schallom L, Oliver DA, et al. Gastric residual volume and aspiration in critically ill patients receiving gastric feedings. Am J Crit Care 2008;17(6):512-519 (quiz 520).
38. Shimizu K, Ogura H, Hamasaki T, et al. Altered gut flora are associated with septic complications and death in critically ill patients with systemic inflammatory response syndrome. Dig Dis Sci 2011;56:1171-1177. [http://dx.doi.org/10.1007/s10620-010-1418-8]
39. Shimizu K, Ogura H, Asahara T, et al. Probiotic/synbiotic therapy for treating critically ill patients from a gut microbiota perspective. Dig Dis Sci 2013;58(1):23-32. [Epub ahead of print 19 Aug 2012] [http://dx.doi.org/10.1007/s10620-012-2334-x]
40. Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: A blinded, randomized, controlled trial. Am J Respir Crit Care Med 2010;182:1058-1064. [http://dx.doi.org/10.1164/rccm.200912-1853OC]
41. Alverdy JC, Change EB. The re-emerging role of intestinal microflora in critical illness and inflammation: Why the gut hypothesis of sepsis syndrome will not go away. J Leukoc Biol 2008;83(3):461-466. [http://dx.doi.org/10.1189/jlb.0607372]
42. Blaser AR, Malbrain MLNG, Fruhwald S, et al. Gastrointestinal function in intensive care patients: Terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med 2012;38:384-394. [http://dx.doi.org/10.1007/s00134-011-2459-y]
43. Piton G, Manzon C, Cypriant B, et al. Acute intestinal failure in critically ill patients: Is plasma citrulline the right marker? Intensive Care Med 2011;37:911-917. [http://dx.doi.org/10.1007/s00134-011-2172-x]
44. Clark JA, Coopersmith CM. Intestinal crosstalk – a new paradigm for understanding the gut as the "motor" of critical illness. Shock 2007;28(4):384-393. [http://dx.doi.org/10.1097/shk.0b013e31805569df]