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Intestinal failure in obstructive jaundice

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TO THE EDITOR

We read with great interest the article by Ding LA and Li JS[1], which aimed to review the current knowledge on the physiology of normal intestinal barrier function and highlight the role of intestinal failure after various injurious insults in the development of septic complications or multiple organ failure with subsequent rapid clinical deterioration or even death. Nowadays it is accepted that the gastrointestinal tract is not only a passive organ of nutrient absorption, but it additionally displays important endocrine, immunologic, metabolic and barrier functions. Therefore, the authors very precisely and in accordance with the description of the functional failure of heart, lungs, brain and kidneys, use the term "intestinal failure", instead of gastrointestinal dysfunction, when there is a disorder of the complex barrier function, emphasizing concurrently on the equal importance of gastrointestinal tract as other vital organs during the course of diseases. In the mentioned article, the authors aiming at attracting recognition and valuable comments by clinicians refer to numerous common diseases, which may be complicated by intestinal failure. We would like to comment on the absence of reference on obstructive jaundice, a common clinical entity, which is often complicated by septic events and renal failure, associated with the presence of systemic endotoxemia because of intestinal barrier failure.

It has been well documented that obstructive jaundice impairs intestinal barrier function leading to bacterial and endotoxin translocation, not only in experimental animals but in clinical setting as well. Bacterial translocation was found in patients with obstructive jaundice by multiple sampling during laparotomy, demonstrating growth of translocating bacteria of primarily enteric origin despite common use of preoperative antibiotics[2]. An increase in intestinal permeability has also been found in jaundiced patients as demonstrated by the lactulose/mannitol permeability test, measurements of endotoxin concentrations in portal and systemic circulation and determination of anti-endotoxin core antibodies[3,4].

Obstructive jaundice affects globally the three levels of gut barrier as described by the authors, namely, the immune barrier, composed of secretory IgA, intra-mucosal lymphocytes, Payer's nodules, mesenteric lymph nodes and the reticuloendothelial system, the biological barrier, which is made up of normal intestinal flora -responsible for colonization resistance-, and the mechanical barrier, consisted of the closed-lining intestinal epithelial cells: (1) Obstructive jaundice depresses Kupffer cell clearance capacity[5] and natural killer cell activity[6], reduces T cells in intestinal intraepithelium[7], alters intestinal mucosal immunity[3] and deprives the gut from biliary secretory IgA and from other specific and nonspecific antibodies contained in bile that inhibit adhesion of enteric bacteria on the intestinal wall. (2) Bile salts exert bacteriostatic properties, therefore, their absence from the intestinal lumen results in quantitative and qualitative disruption of the indigenous microflora[8], which is also promoted by disturbances of the interdigestive motility[9]. (3) Absence of intraluminal bile deprives the gut from their trophic effect resulting in intestinal atrophy. We have recently demonstrated that an imbalance of cell proliferation and death in intestinal crypts, with increased apoptosis and decreased mitotic activity, underlie intestinal mucosal atrophy[10]. We have also shown that obstructive jaundice disrupts the integrity of the mechanical barrier by inducing regional loss of the key tight junction-associated protein occludin expression in the intestinal epithelium[11]. Therefore, the opened paracellular route may significantly contribute to the escape of endotoxin from the gut lumen into portal circulation.

The above cellular alterations of the mechanical barrier are associated with significant disturbances of intestinal oxidative status, with increased lipid peroxidation, protein oxidation and oxidation of non-protein and protein thiols[12]. These biochemical changes are indicative of high oxidative stress in the intestine after biliary obstruction and represent another significant parameter of intestinal injury leading to barrier failure. Investigation of the oxidant/antioxidant equilibrium is an area of great pathophysiological and therapeutic

interest given that reactive oxygen species and redox balance are involved in the regulation of almost all cellular processes, including proliferation, differentiation, stress responses and cell death[13]. In obstructive jaundice, the presence of increased intestinal oxidative stress may be related to intestinal atrophy, since reactive oxygen species may promote cell growth arrest, via a mitogen-activated protein kinases dependent pathway that alters the status of growth regulatory proteins, and apoptotic cell death, via a cytochrome c-mediated activation of the caspase family[13]. In addition, given that oxidative stress disrupts the tight junction structural complex by modulating the assembly, localization, expression and function of their molecular components[14], this factor may underlie altered intestinal occludin expression in obstructive jaundice. Besides, oxidative stress plays a pathogenic role in diverse diseases complicated by intestinal failure, such as in inflammatory bowel disease[15] and in intestinal ischemia-reperfusion[16]. Consequently, we think that the "biochemical barrier", consisted by non-enzymatic (glutathione, cysteine and other non-protein and protein thiols, vitamins C and E, bilirubin, ubiquinol) and enzymatic (superoxide dismutases, catalase and glutathione peroxidase) antioxidant defenses, which regulate the intracellular redox state, represents an additional crucial level of normal intestinal barrier function.

Research into the potential mechanisms implicated in intestinal failure in diverse pathologic conditions has a principal aim: to suggest potential therapeutic strategies for clinicians. Clinical studies in obstructive jaundice, based on the enterotrophic, bacteriostatic and endotoxin neutralizing properties of bile and bile salts, have shown that internal biliary drainage[17] or bile replacement during external biliary drainage[18] and oral bile salts[19] enhance intestinal barrier function and reduce postoperative complications. In addition, lactulose administration prevents postoperative complications and renal failure[19], probably through inactivation of gut derived endotoxin and the endotoxin-induced systemic inflammatory response. Novel cellular and biochemical alterations described, such as tight junctions disruption and oxidative stress, provide new therapeutic targets and strategies, while research into a globally acting factor affecting most of obstructive jaundice-induced intestinal alterations is an attracting field. In such an attempt, our group has recently shown that gut regulatory peptides bombesin and neurotensin exert a wide spectrum of modulating actions on intestinal barrier in experimental obstructive jaundice[10,11].

In conclusion, obstructive jaundice is a common clinical entity complicated by intestinal failure and endotoxemia, leading to high postoperative morbidity and mortality rates. Current advances in the pathophysiology of intestinal failure in obstructive jaundice have shown that the breakage of gut barrier is multi-factorial, involving disruption of the immunologic, biological, mechanical and biochemical barrier. Clinicians should take advantage of this knowledge and do not neglect protecting the intestinal barrier function, by applying the well demonstrated clinical strategies, which are continuously enriched by a valuable basic research pool.

REFERENCES

1 **Ding LA,** Li JS. Intestinal failure: pathophysiological elements and clinical diseases. *World J Gastroenterol* 2004; **10** : 930-933
2 **Kuzu MA,** Kale IT, Col C, Tekeli A, Tanik A, Koksoy C. Obstructive jaundice promotes bacterial translocation in humans. *Hepatogastroenterology* 1999; **46**: 2159-2164
3 **Welsh FK,** Ramsden CW, MacLennan K, Sheridan MB, Barclay GR, Guillou PJ, Reynolds JV. Increased intestinal permeability and altered mucosal immunity in cholestatic jaundice. *Ann Surg* 1998; **227**: 205-212
4 **Bailey ME.** Endotoxin, bile salts and renal function in obstructive jaundice. *Br J Surg* 1976; **63**: 774-778
5 **Kennedy JA,** Clements WD, Kirk SJ, McCaigue MD, Campbell GR, Erwin PJ, Halliday MI, Rowlands BJ. Characterization of the Kupffer cell response to exogenous endotoxin in a rodent model of obstructive jaundice. *Br J Surg* 1999; **86**: 628-633
6 **Lane DR,** Joshi P, Grogan JB, Nie CH, Scott-Conner CE. Suppression of natural killer cell activity in biliary obstruction. *Am Surg* 1996; **62**: 259-262
7 **Ueno K,** Ajiki T, Watanabe H, Abo T, Takeyama Y, Onoyama H, Kuroda Y. Changes in extrathymic T cells in the liver and intestinal intraepithelium in mice with obstructive jaundice. *World J Surg* 2004; **28**: 277-282
8 **Deitch EA,** Sittig K, Li M, Berg R, Specian RD. Obstructive jaundice promotes bacterial translocation from the gut. *Am J Surg* 1990; **159**: 79-84
9 **Nieuwenhuijs VB,** van Dijk JE, Gooszen HG, Akkermans LM. Obstructive jaundice, bacterial translocation and interdigestive small-bowel motility in rats. *Digestion* 2000; **62**: 255-261
10 **Assimakopoulos SF,** Scopa CD, Zervoudakis G, Mylonas PG, Georgiou C, Nikolopoulou V, Vagianos CE. Bombesin and neurotensin reduce endotoxemia, intestinal oxidative stress, and apoptosis in experimental obstructive jaundice. *Ann Surg* 2005; **241**: 159-167
11 **Assimakopoulos SF,** Scopa CD, Charonis A, Spiliopoulou I, Georgiou C, Nikolopoulou V, Vagianos CE. Experimental obstructive jaundice disrupts intestinal mucosal barrier by altering occludin expression: beneficial effect of bombesin and neurotensin. *J Am Coll Surg* 2004; **198**: 748-757
12 **Assimakopoulos SF,** Vagianos CE, Patsoukis N, Georgiou C, Nikolopoulou V, Scopa CD. Evidence for intestinal oxidative stress in obstructive jaundice-induced gut barrier dysfunction in rats. *Acta Physiol Scand* 2004; **180**: 177-185
13 **Kamata H,** Hirata H. Redox regulation of cellular signalling. *Cell Signal* 1999; **11**: 1-14
14 **Rao RK,** Basuroy S, Rao VU, Karnaky Jr KJ, Gupta A. Tyrosine phosphorylation and dissociation of occludin-ZO-1 and E-cadherin-beta-catenin complexes from the cytoskeleton by oxidative stress. *Biochem J* 2002; **368**: 471-481
15 **Kruidenier L,** Verspaget HW. Review article: oxidative stress as a pathogenic factor in inflammatory bowel disease-radicals or ridiculous? *Aliment Pharmacol Ther* 2002; **16**: 1997-2015
16 **Ferrer JV,** Ariceta J, Guerrero D, Balen E, Herrera J, Lera JM. Prevention by somatostatine and N-acetylcisteine of multiorgan failure mediated by oxidative stress after intestinal ischemia. *Transplant Proc* 1999; **31**: 2570-2571
17 **Parks RW,** Clements WD, Smye MG, Pope C, Rowlands BJ, Diamond T. Intestinal barrier dysfunction in clinical and experimental obstructive jaundice and its reversal by internal biliary drainage. *Br J Surg* 1996; **83**: 1345-1349
18 **Kamiya S,** Nagino M, Kanazawa H, Komatsu S, Mayumi T, Takagi K, Asahara T, Nomoto K, Tanaka R, Nimura Y. The value of bile replacement during external biliary drainage: an analysis of intestinal permeability, integrity, and microflora. *Ann Surg* 2004; **239**: 510-517
19 **Pain JA,** Cahill CJ, Gilbert JM, Johnson CD, Trapnell JE, Bailey ME. Prevention of postoperative renal dysfunction in patients with obstructive jaundice: a multicentre study of bile salts and lactulose. *Br J Surg* 1991; **78**: 467-469

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