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REVIEW

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Acute intestinal failure in critically ill patients: is plasma citrulline the right marker?

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Abstract *Introduction:* Small bowel functions are more complex than colon functions, and short bowel conditions are associated with increased mortality. Gastrointestinal dysfunction in critically ill patients is common, probably underestimated, and associated with a poor prognosis. However, a validated definition of acute intestinal failure is lacking, in absence of a marker to measure it. Consequently, small bowel dysfunction is not clearly integrated into the overall approach used to treat ICU patients. *Materials and Methods:* Review of the literature on gastrointestinal dysfunction in critically ill patients, and proposition of a definition of acute intestinal failure. *Conclusion:* On the one hand, small bowel ischemia is related to acute reduction of enterocyte mass and loss of gut barrier function by epithelial lifting of villi. On the other hand, systemic inflammatory response syndrome (SIRS) and sepsis could be linked to an acute dysfunction of enterocytes without enterocyte reduction. Citrulline is an amino acid mainly synthesized by small bowel enterocytes. Various contexts of chronic and acute reduction of enterocyte mass have been correlated with low plasma citrulline concentration. Critically ill patients with shock have an acute reduction of enterocyte mass and reduced gut citrulline synthesis, leading to a low plasma citrulline concentration. Acute intestinal failure could be defined as an acute reduction of enterocyte mass and/or acute dysfunction of enterocytes, associated or not with loss of gut barrier function. The influence of SIRS and acute renal failure on plasma citrulline concentration and the value of this concentration as an indicator of acute intestinal failure in critically ill patients must be further evaluated.

Keywords Acute intestinal failure · Small bowel · Multiple organ failure · Plasma citrulline

Abbreviations

ICU	Intensive care unit
SIRS	Systemic inflammatory response syndrome
CRP	C-reactive protein
IAH	Intra-abdominal hypertension
AIDS	Acute intestinal distress syndrome
GIF	Gastrointestinal failure

Introduction

The absence of colon following surgical resection generally does not impact survival. In contrast, patients with short bowel conditions have a worse prognosis, and when they cannot benefit from small bowel transplantation, they require lifelong parenteral nutrition [1–3]. The colon is mainly involved in gut barrier function against luminal flora, but also in water and electrolyte absorption in order to maintain the water balance, short-chain fatty acid absorption from bacterial fermentation, and feces transport. The small bowel is engaged in numerous functions: water, electrolyte, and nutriment absorption; secretion of various regulatory peptides; arginine metabolism via citrulline synthesis; barrier against intestinal flora and progression of aliments; and lymphocyte education within the gut-associated lymphoid tissue. Small bowel mucosa is organized in villi allowing its overall surface to reach 200 m^2. The villus structure comprises a chorion, with central arteriole capillaries and venule, and is covered by an epithelium mainly made up of enterocytes. Enterocytes originate from the crypts and progress toward the villus tip in 3–5 days depending on the villus length. Finally, mature enterocytes are lost by apoptosis and shedding into the lumen [4, 5].

Prevalence of gastrointestinal dysfunction in critically ill patients

Gastrointestinal dysfunction is common in critically ill patients. Indeed, Reintam et al. [6] found that 59% of critically ill patients have at least one gastrointestinal symptom during their stay in the intensive care unit (ICU). In most cases, gastrointestinal dysfunction is suspected because of feeding intolerance, ileus, diarrhea, digestive bleeding, or intestinal ischemia. However, evaluating the small bowel is difficult for two reasons: it is a deep organ, far from the mouth, anus, and abdominal wall, and critically ill patients are frequently not able to inform clinicians about a digestive complaint. This explains why its dysfunction may sometimes be occult or misdiagnosed, and the fact that it is not clearly integrated into the overall approach used to treat ICU patients. However, even occult small bowel dysfunction may have clinical consequences on patient prognosis.

Prognosis of gastrointestinal dysfunction

Gastrointestinal dysfunction in critically ill patients is associated with a worse prognosis. Reintam et al. [6] found that absent or abnormal bowel sounds and gastrointestinal bleeding in critically ill patients were associated with significantly higher mortality. In addition, the prevalence of gastrointestinal symptoms on the first day in ICU was predictive of patient mortality. Early diarrhea following cardiac arrest is generally considered to be a clinical sign of poor prognosis because it globally reflects the degree of ischemia [7].

History of gastrointestinal dysfunction

The gut hypothesis of multiple organ failure was first put forward more than 20 years ago [8, 9]. According to this hypothesis, the multisystemic disorders defining this syndrome could be the late consequences of a previous small bowel ischemia. Indeed, shock is responsible for non-occlusive arterial ischemia leading to organ failure. At the onset of shock, before the occurrence of arterial hypotension, gut perfusion is precociously sacrificed by vasoconstriction of splanchnic circulation [9]. The countercurrent between arteriole and venule bloodflow within the villus induces a higher sensitivity of villus tips to ischemia [10, 11]. In contrast, the absence of villi in colon mucosa could explain its stronger resistance to ischemia [12, 13]. The effect of shock on the small bowel was described in the 1970s in animal models [14, 15] and in humans [16]. The Chiu scale for grading intestinal ischemia–reperfusion has been largely used by researchers [15]. Six grades of morphological changes in the mucosa can be established, taking into account the degree of epithelial lifting and damage of lamina propria, ranging from normal mucosa (grade 0) to denuded villi with disintegrated lamina propria (grade V). Villi denudation induces the loss of barrier function and directly exposes the chorion to the content of gut lumen, explaining bacterial translocation and systemic inflammatory response syndrome (SIRS). In a model of hemorrhagic shock in rats, Chang et al. [12] observed that small bowel ischemia induces an early reduction of villi height in jejunum and ileum, causing decreased mucosal thickness. The first human model of small bowel ischemia was proposed by Derikx et al. in 2009 [17]. They showed that exposing human jejunum to 30 min of ischemia brings about an early destruction of villus tips, with enterocyte shedding into the lumen. Such epithelial destruction is associated with a rise of plasma intestinal fatty acid binding protein (I-FABP) concentration, a protein expressed in the cytosol of enterocytes, a validated marker of enterocyte necrosis [18]. The link between small bowel hypoperfusion, loss of gut barrier, bacterial translocation, and organ failure has been widely studied during severe acute pancreatitis. Rahman et al. [19] showed that severe episodes of acute pancreatitis are associated with significantly higher I-FABP levels than during mild acute pancreatitis. In this context, I-FABP levels are correlated with small bowel permeability and bacterial translocation. A recent study

evaluating gut barrier dysfunction in patients admitted to the ICU with severe acute pancreatitis emphasized the role of gut ischemia in bacterial translocation [20]. In this study, acute reduction of enterocyte mass proven by elevated plasma I-FABP concentration was associated with bacteremia, infected necrosis, and organ failure. In addition, it has been shown that critically ill patients admitted to the ICU with septic shock develop acute reduction of enterocyte mass with high I-FABP levels [21]. Human models of small bowel ischemia concur with animal studies: small bowel ischemia is responsible for acute reduction of enterocyte mass by epithelial lifting starting at the villus tip, then extending to the entire villus; such epithelial lifting causes chorion denudation and therefore loss of gut barrier function. Structural and functional small bowel alterations associated with ischemia have several consequences: firstly, increased small bowel permeability leading to bacterial translocation; secondly, local immune activation leading to SIRS; and finally, enterocyte mass reduction leading to malabsorption, feeding intolerance, and decreased gut citrulline synthesis. Because they are reversible after early reperfusion [22], the effects of ischemia on the small bowel may be compared to a "functional short bowel syndrome" or, more precisely, to a "flat bowel syndrome."

A definition of acute intestinal failure is lacking

Whereas chronic intestinal failure is defined as a non-functioning small bowel, i.e., either short bowel syndrome after extensive removal of the small bowel, or impossibility to use the enteral way because of diffuse small bowel disease [23, 24], a validated definition of acute intestinal failure among patients with normal small bowel length and structure is lacking. In addition, most organ failure scores established to evaluate the prognosis of critically ill patients limit the evaluation of digestive function to plasma bilirubin level [25–27]. Consequently, studies of gastrointestinal dysfunction in critically ill patients cannot be compared because of a wide variety of definitions. Firstly, the field of digestive failure should be clarified. Among various types of acute digestive failure we should better differentiate hepatic, pancreatic, gastric, small bowel, and colon failures, and also intra-abdominal hypertension. As is the case for chronic intestinal failure, the term of acute intestinal failure should be used only for acute small bowel failure. Secondly, a validated marker of acute small bowel failure should be identified. Ideally, a marker of organ function should reflect the functional cellular mass; its interpretation should be made in light of a pathophysiological model, it should be easy for clinicians to perform, minimally invasive for patients, with a low cost, and results should be rapidly available and sufficiently accurate to allow clinicians to make a decision. Two definitions of acute intestinal failure were recently developed. Malbrain et al. [28] proposed the term acute intestinal distress syndrome (AIDS) based upon the occurrence of intra-abdominal hypertension (IAH) in critically ill patients, defined by a sustained increase in intra-abdominal pressure equal to or above 12 mmHg measured in the bladder [29]. Indeed, IAH decreases abdominal perfusion pressure, defined by the difference between mean arterial pressure and intra-abdominal pressure, and may lead to small bowel ischemia. Measurement of intra-abdominal pressure in critically ill patients is now largely used in ICU and is recommended in patients with IAH risk factors. However, the consequences of IAH concern both intra- and extra-abdominal organs and is therefore not specific to small bowel dysfunction. Reintam et al. [30] created a gastrointestinal failure (GIF) score in critically ill patients, based upon the occurrence of feeding intolerance and IAH, ranging from level 0 (normal gastrointestinal function) to level 4 (abdominal compartment syndrome). They showed that GIF score was correlated with ICU mortality and improved the prognostic value of the sequential organ failure assessment (SOFA) score. However, despite a welcome contribution to assessing gastrointestinal dysfunction, it was noted that feeding intolerance was a subjective measurement, and that IAH was not specific to gastrointestinal dysfunction [31]. Indeed, although the GIF score appeared to be a new prognostic tool to evaluate critically ill patients, it was not based on a pathophysiological model of gastrointestinal dysfunction.

Interest and limits of using plasma citrulline concentration to determine small bowel function

Citrulline under physiological conditions

Citrulline is an amino acid mainly synthesized from glutamine by small bowel enterocytes (Fig. 1) [32]. Plasma citrulline concentration (normal 20–40 μmol/L) is mainly determined by the balance between gut citrulline synthesis and kidney citrulline degradation. Citrulline is considered to be a masked form of arginine, because it is not taken up by the liver but it is transformed by the kidney into arginine.

Citrulline in chronic intestinal failure

Crenn et al. [33] showed that plasma citrulline concentration is a simple and reliable biomarker of enterocyte mass in patients with chronic small bowel pathologies. In patients with short bowel syndrome, plasma citrulline concentration is correlated with remnant small bowel length [34]. In patients with normal small bowel length, and villous atrophy associated small bowel disease, it correlates with the

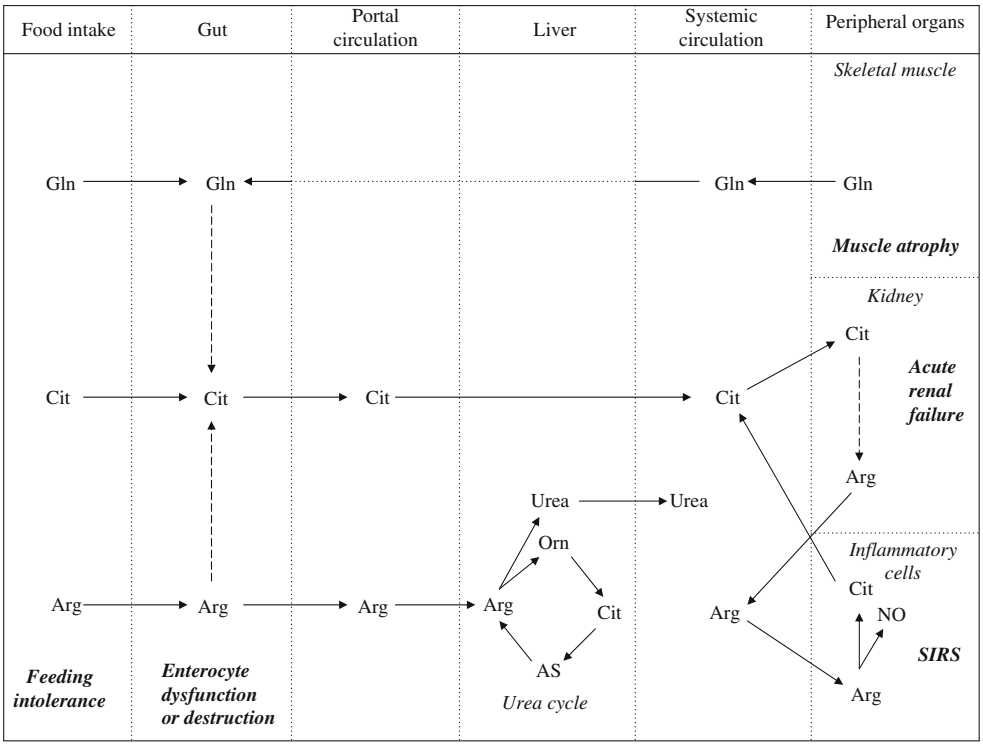

Fig. 1 Schematic representation of interorgan metabolism of amino acids, integrating particular conditions of critically ill patients. *Gln* glutamine, *Arg* arginine, *Cit* citrulline, *Orn* ornithine, *AS* argininosuccinate, *NO* nitric oxide, *SIRS* systemic inflammatory response syndrome. Particular conditions influencing interorgan metabolism of amino acids in critically ill patients appear in *italic boldface* type

severity and extent of villous atrophy [35]. Plasma citrulline concentration is consistent with small bowel absorption capacity [34, 36]. Because the kidney is the major site of citrulline removal, chronic renal failure is associated with high plasma citrulline concentrations [37]; however, hepatocellular function does not significantly influence plasma citrulline concentration [38].

Citrulline in acute intestinal dysfunction

The interest in using plasma citrulline concentration in assessing acute reduction of enterocyte mass has already been evaluated in two contexts: first, low plasma citrulline concentration is a marker of small bowel toxicity following both radiotherapy and chemotherapy [39, 40]; second, it is an early indicator of acute rejection following small bowel transplantation [41]. The link between low plasma citrulline concentration and loss of gut barrier function was suggested by Herbers et al. [42] who showed that after high-dose chemotherapy low plasma citrulline concentration is linked to bacteremia. In addition, low plasma citrulline concentration has been clearly correlated with clinical and biological evidence of mucosal barrier injury after chemotherapy in pediatric patients [43]. Because small bowel ischemia is often related to an acute reduction of enterocyte mass, it could be a third context of interest for using plasma citrulline concentration. A recent study evaluating gut dysfunction in patients with acute pancreatitis adds further evidence for using plasma citrulline as a marker of acute intestinal failure [44]. In this context, plasma citrulline concentration was lower in severe acute pancreatitis than in mild acute pancreatitis, and it was negatively correlated with serum level of I-FABP. On the contrary, serum level of I-FABP was positively correlated with a clinical score of gut dysfunction, the acute physiology and chronic health evaluation II (APACHE II) score, C-reactive protein (CRP) concentration, and length of ICU stay. This study confirms that in patients at risk of small bowel dysfunction because of SIRS and hypovolemia, clinical gut dysfunction is associated with biological evidence of enterocyte necrosis evaluated by increased I-FABP concentration; and finally, acute reduction of enterocyte mass is evidenced by lower plasma citrulline concentration. In addition to the ischemic reduction of enterocyte mass, another hypothesis is the existence of enterocyte dysfunction associated with SIRS, without enterocyte necrosis, that could reduce citrulline synthesis. Hietbrink et al. [45] showed that during experimental human endotoxemia, SIRS increases intestinal permeability, but does not affect I-FABP levels. This suggests that SIRS may induce small bowel modifications leading to increased paracellular permeability without direct enterocyte damage, and therefore, no enterocyte reduction but a possible enterocyte dysfunction. Because gut citrulline synthesis takes place in the mitochondria, it is possible that mitochondrial dysfunction associated with sepsis decreases gut citrulline synthesis. The prognostic value of low plasma citrulline concentration in critically

ill patients was recently studied by our team. We found that 44% (24/55) of critically ill patients had a plasma citrulline concentration ≤10 μmol/L, 24 h after their admission to the ICU [46]. Low plasma citrulline at 24 h was an independent factor of mortality. In addition, patients with low plasma citrulline concentrations had higher serum CRP concentration and nosocomial infection rate, and a lower plasma arginine concentration. Whereas plasma citrulline concentrations were constant among patients without shock, in patients with shock plasma citrulline concentration decreased rapidly. Plasma citrulline concentration is a continuous variable, which may measure the functional enterocyte mass in acute conditions, such as factor V for the liver. Enterocytes have a turnover of 3–5 days, and using a marker of enterocyte mass which is correlated with small bowel length, villi length, and absorptive capacity to evaluate small bowel function appears relevant. Plasma citrulline determination can be performed on usual blood samples. It is therefore easy for clinicians to perform and minimally invasive for patients.

Theoretical limits of plasma citrulline concentration in critically ill patients

Under physiological conditions, plasma citrulline concentration reflects gut citrulline synthesis.

However, in critically ill patients two conditions may induce greater plasma citrulline concentration (Fig. 1): first, inducible NOS in SIRS may increase extra-intestinal citrulline synthesis from arginine [47]; second, acute renal failure, a frequent condition in critically ill patients, may decrease kidney arginine synthesis from citrulline, and may cause falsely high plasma citrulline concentration. Therefore, normal plasma citrulline concentration (≥20 μmol/L) observed in critically ill patients cannot rule out a decreased gut citrulline synthesis, because it can be masked by extra-intestinal citrulline synthesis, or renal accumulation. In contrast, low plasma citrulline concentrations observed in critically patients are likely to reflect decreased gut citrulline synthesis. Indeed, two recent studies found that the low plasma citrulline concentration observed in critically ill patients is the result of a decreased citrulline synthesis [48, 49]. This suggests that despite SIRS and acute renal failure, critically ill patients with shock have less gut citrulline synthesis causing low plasma citrulline concentration. Reduced bioavailability of glutamine, the main precursor of citrulline, could also be responsible for decreased gut citrulline synthesis.

Other limitations are the accessibility to automated ion-exchange chromatography and the duration of the analysis [50]. However, new techniques are being developed that are capable of determining plasma citrulline concentration within 30 min [51]. This could allow clinicians to have the result in real time. The accuracy of plasma citrulline concentration has been validated in various contexts of chronic and acute reduction of enterocyte mass, and this concentration needs to be further evaluated with ICU patients in whom acute renal failure and SIRS are frequent conditions.

Definition of acute intestinal failure based upon enterocyte mass reduction and/or enterocyte dysfunction

Taking into account previous studies, a definition of acute intestinal failure based upon enterocyte mass reduction and/or enterocyte dysfunction, associated or not with loss of gut barrier function, may be proposed. Even if the gut hypothesis of multiple organ failure still requires confirmation, recent literature reinforces such a model: critically ill patients with shock have an epithelial lifting of villi [16, 17], enterocyte necrosis explaining the increased I-FABP concentration observed in this context [21], acute reduction of enterocyte mass explaining the lower gut citrulline synthesis and therefore the rapid decrease of plasma citrulline concentration [46, 48, 49]; acute dysfunction of enterocytes associated with SIRS [45], possibly by mitochondrial dysfunction, might also be involved in the reduction of citrulline synthesis observed in septic patients [48, 49]; loss of gut barrier function associated with denuded villi might account for the higher prevalence of sepsis [48, 49, 52], and mortality [46] observed in critically ill patients with low plasma citrulline concentration. Both acute reduction of enterocyte mass and enterocyte dysfunction could coexist, representing the organic and functional aspects of acute intestinal failure. Decreased arginine bioavailability secondary to diminished citrulline synthesis might also explain in part the higher mortality [48, 53, 54].

Clinical contexts of acute intestinal failure and biological interpretation

- Acute reduction of enterocyte mass may occur (a) in cases of small bowel ischemia: shock states, hypoxemia, and in the case of occlusive mesenteric ischemia; (b) in cases of small bowel toxicity with enterocyte damage: chemotherapy, and radiotherapy; (c) in cases of immune enterocyte destruction: acute graft-versus-host disease, and acute rejection of small bowel allograft. In these contexts, plasma citrulline concentration should be low, and plasma I-FABP concentration should be high, reflecting enterocyte necrosis.
- Acute dysfunction of enterocytes may occur in contexts of systemic inflammation or sepsis, maybe by mitochondrial dysfunction. In this context, plasma citrulline concentration should be low, reflecting low enzymatic

cellular activity, and plasma I-FABP concentration should be normal because enterocytes are conserved.
- Combined acute reduction of enterocyte mass and acute dysfunction of enterocytes may exist, e.g., during septic shock.

Conclusions

Although often occult or misdiagnosed, small bowel dysfunction is a common condition in critically ill patients and must be actively sought out because it is associated with a worse prognosis. Even if the gut hypothesis of multiple organ failure still requires confirmation, acute intestinal failure could be defined as a rapid reduction of enterocytic function by acute reduction of enterocyte mass and/or acute dysfunction of enterocytes responsible for decreased absorptive capacity and reduced citrulline synthesis; enterocyte mass reduction could be associated with morphological changes causing a loss of gut barrier function. Enterocyte mass reduction and enterocyte dysfunction could be the organic and functional aspects of acute intestinal failure. The influence of SIRS and acute renal failure on plasma citrulline concentration must be further evaluated.

Conflicts of interest None.

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