Gut rest strategy and nutritional support in the acute phase of critical illness

Abstract In critically ill patients, the intestine is a vulnerable organ and gastrointestinal ~~(GI)~~ dysfunction is common. Although guidelines recommend the use of enteral nutrition (EN) within 24–48 hours in the critically ill patient who needs nutritional support, this may be contraindicated in patients with acute gastrointestinal injury (AGI), as overuse of the gut in the acute phase of critical illness may be harmful to prognosis. While some evidence suggests that EN may favorably impact outcomes in critically ill patients~~There is a contradiction with injury GI and utilization of GI, which's form is mainly enteral nutrition (EN). EN has a positive role which can provides trophic effects to maintain intestinal physiology~~, we propose early and restrictive EN should be ~~performed~~ provided to~~in~~ critically ill patients, especially those with AGI, as an organ protective strategy.

批注 [JK1]: Throughout: please confirm that my interpretation of your text conveys your intended message.

Do you wish to focus on the Chinese population to increase the novelty of your review – if so you will need to expand your search to literature published in the Chinese language and only studies conducted in Chinese populations should be included – this may limit the generalizability of your review

In critically ill patients, theIn critically ill patients the intestine is susceptible to injury, and acute gastrointestinal (AGI) dysfunction is commoninjury is common [1]. Evidence suggests that an estimated 50% of patients have enterocyte damage at admission to the Intensive Care Unit (ICU), and gastrointestinal symptoms occur in approximately 62% of patients in the ICU [2]. The Working Group on Abdominal Problems (WGAP) of the European Society of Intensive Care Medicine (ESICM) identified four grades of AGI severity in intensive care patients: AGI grade I (risk of developing gastrointestinal dysfunction or failure), in which gastrointestinal symptoms occur after an insult; AGI grade II (gastrointestinal dysfunction), in which interventions are required to restore gastrointestinal function after acute occurrence of gastrointestinal symptoms; AGI grade III (gastrointestinal failure), in which interventions cannot restore gastrointestinal function; and AGI grade IV (gastrointestinal failure with severe impact on distant organ function), in which gastrointestinal failure is immediately life-threatening.

. In fact, an estimated 50% of patients have enterocyte damage at admission to the Intensive Care Unit (ICU) [2]. In contrast, gastrointestinal dysfunction can indicate a critical condition. Patients with gastrointestinal dysfunction have higher mortality rates [3-5]. One of functions onAs the –GIgastrointestinal tract is functions to ingest, digest, and absorb nutrients from food and waterdigesting and absorbing nutrients and water, disorders of which would be main manifestation while GI was injury name acute gastrotintestinal injury (AGI), AGI manifests as nausea and/or vomiting, absence of bowel sounds, diminished bowel motility, gastroparesis with high gastric residuals or reflux, paralysis of the lower gastrointestinal tract, diarrhea, intra-abdominal hypertension grade I (12–15 mmHg), and gastrointestinal bleeding, which shows mainly feeding intolerance in critically ill patients [6] and critically ill patients with AGI have higher mortality rates than those without AGI [3-5].. Although guidelines recommend early But in critically ill patients, the guideline recommend that enteral nutrition (EN) started within 24 – 48 hours of admission and is the preferred route of feeding over parenteral nutrition (PN) for the critically ill patient who requires nutrition support therapy, and enteral feeding should be started early within the first 24 – 48 hours following admission; the feedings should be advanced toward goal optimal nutritional goals over the next 48 –72 hours for nutritional support in critically ill patients [7]. Some, some questions emerge remain: 1): whether doesDoes the gastrointestinal tract need 'rest' –injuryfor recovery of gastrointestinal function in critically ill patients with –gut need be rest for recovery function when AGI is present? and 2) Is EN applicable in critically ill patients with gastrointestinal dysfunction - will they derive benefit from Patients could benefit from utilizationusing the of injury injured organ or enteral nutrition is applicable to patients with impaired gut? This review would The answers to these questions will betry to explored in this review the answer and rationale.

Gastrointestinal dysfunction in critical ill patients

The main function of the gastrointestinal tract is digesting and absorbing nutrients and water to meet the daily nutritional needs required for human survival. The gastrointestinal tract also performs excretory, immune, endocrine, and barrier functions. ~~The main function of GI tract is digesting and absorbing nutrients and water to meet the needs of "food" for survival as most animals and human being. Other function is including barrier control to modulate absorption of intraluminal microbes (and their products), endocrine and immune functions.~~

~~when GI was~~Injury to the gastrointestinal tract results in improper ~~injury and dysfunction, manifestations were~~ digestion and absorption ~~dysfunction~~ [6], impairment of the intestinal barrier ~~function impairment~~ [8], and dysregulation of the intestinal microbiota ~~dysregulation~~ [9]. In critically ill patients, the symptom profile of improper digestion and absorption ~~Digestion and absorption dysfunction was shown with~~is characterized by temporary self limiting gastrointestinal symptoms, which progress to –feeding intolerance syndrome as gastrointestinal dysfunction becomes more severe, ~~including:~~in which patients are intolerant of EN and ≥20 kcal/kg BW/day cannot be reached within 72 h of feeding attempts via the enteral route – ~~gastroesophageal reflux, intolerance to nasogastric feeding, slow gastric emptying, small intestinal dysmotility, and GI bleeding in critically illness~~ [1]~~, which were main target that was used to evaluate acute GI dysfunction or AGI~~ [6]. Small intestinal mucosal integrity may also be impaired in critically ill patients, leading to increased intestinal permeability, especially in patients intolerant to EN

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Another considering aspect was increased gut permeability while AGI, intestinal permeability was increased in the critically ill patients, especially in those intolerant to gastric feeding, and increased permeability may be part of the gastrointestinal dysfunction [10]. The dysbiosis ofFurthermore, critical illness alters the gut microbiota, whereby the gut microbiota of critically ill patients is gut microbiota characterized by low diversity, low abundance of key commensal genera, and overgrowth of one bacterial genera. This dysbiosis of the gut microbiota may be associated with in critical ill patients is associated with organ dysfunction [11], which should be as part of evaluatingand may be a useful marker of gastrointestinal function in critically ill patients GI function in future.

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Fig.1 Acute gastrointestinal dysfunction in critically ill patients

Adaptive metabolism in the acute phase of critical illness

Facing disease,Pathophysiological changes during illness cause the body to compensate in an attempt to restore stability within the internal environment body can try to compensate abnormal pathophysiologic changes and keep hemeostasis. The metabolic response to stress is part of the adaptive response to survive acute illness [12]T. Three phases of the metabolic response were described: the acute phase of critical illness has been variously (defined as the first hours after the onset of illness, to athe first few days after the onset of illness, or the, the first 5-7 days after admittance admission to the to ICU was used in recent clinical trials [13-15].): The adaptive response to acute critical illness includes a metabolic response to stress [12]the metabolic

~~response to~~, which ~~stress implies~~ involves neuroendocrine and inflammatory/immune mechanisms~~an~~ that cause uncontrolled catabolism and ~~the development of a~~ resistance to anabolic signals, including insulin~~, in order to reset the hierarchy of the delivery of energy substrates to~~. This prioritizes the delivery of glucose to the vital organs that are unable to use other substrates as energy~~vital tissues over the insulin-dependent organs, mainly fat and muscle~~ [16, 17]. ~~These changes~~These adaptive changes are complex and sequential, which has so far prohibited the successful development of targeted interventions to modulate the metabolic response to critical illness:~~ are hardly amenable to any fruitful intervention, and therapeutic interventions need to account for the complexity and sequential patterns of the metabolic response to critical illness~~ [17].

Enteral nutrition in the acute phase of critical illness

~~It is necessary to get~~Sufficient and appropriate nutrition is essential to sustain the ~~nutrition for~~ body's metabolism ~~which is essential condition to the living being. And~~ , such that malnutrition ~~increases~~ is associated with high morbidity and mortality in the ~~intensive care unit (~~ICU~~)~~ [18]. Evidence suggests that EN is ~~Enteral nutrition (EN) therapy has been shown to be~~ beneficial to critically ill patients, as it may reduce ~~in terms of reducing~~ disease severity, ~~diminishing~~ diminish infectious complications, and decrease~~decreasing~~ length of stay in the ICU, ~~and~~ favorably impacting patient outcomes [19, 20]. However, as ~~due to complicated metabolic changes~~the metabolic response to critical illness is complex, there is a high incidence of AGI ~~and~~

~~high proportion of GI injury~~ in the acute phase of critical illness [2]. Furthermore, as~~, and a~~ anorexia ~~is part of the~~is a component of the acute physiologic response to severe illness ~~that can be either adaptive or maladaptive~~ [21], it is uncertain when and how much EN should be ~~perform~~ provided ~~in the acute phase of critical illness~~at this time.

~~In a~~A large, retrospective, cohort study ~~found the~~showed that the initiation of ~~enteral nutrition~~EN within 48 hours of mechanical ventilation was associated with reduced rates of hospital mortality in critically ill hemodynamically unstable patients ~~was associated with a reduction in the rates of hospital mortality of critically ill hemodynamically unstable patients treated with mechanical ventilation~~ [22]. ~~Several meta-analyses~~A meta-analysis ~~aggregated data~~of data extracted from ~~from RCTs~~ randomized controlled trials (RCTs) showed early EN was associated with a significant reduction in mortality and infectious morbidity in critically ill patients in the ICU[23]. ~~But some~~In contrast, one RCT showed ~~trials showed early~~ EN within 24 hours of admission in ICU patients was not associated ~~with~~with a reduction in hospital discharge ~~mortality, even or with adverse clinical outcomes. A trial found early feeding and greater nutritional adequacy did not improve clinical outcomes in mixed patients in ICUs~~mortality or hospital or ICU length of stay [24], while another RCT demonstrated no difference in 30-day mortality or rates of adverse events in patients that received parenteral or EN ~~. Another trial found~~ within 36 hours ~~after a~~of an unplanned admission to the ICU ~~and continued for up to 5 days, either the parenteral or the enteral nutrition was no significantly differently in 30-day mortality and other adverse events~~ [14]. ~~In conclusion, no enough~~Taken together, these findings indicate that there is not enough data to determine the superiority of early EN vs. delayed EN or parenteral nutrition for critically ill patients data prove early EN is be superior to than delaying EN or PN. However, the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) 2016 guideline and the Working Group on Gastrointestinal Function within the Metabolism, Endocrinology and Nutrition (MEN) Section of the European Society of Intensive Care Medicine (ESICM) 2017 guideline recommend the use of EN within 24–48 hours in the critically ill patient who needs nutritional support vs. delaying EN or the use of early parenteral nutrition, as there may be a beneficial effect onconsidering potential benefit on mortaliymortality, and a reduced reduction in infection infectious complications, easy operation and decreased efficiency, new guidelines recommend that early EN be initiated within 24–48 hours in the critically ill patient who needs nutrition support therapy rather than delaying EN or early PN [23, 25].

Another problem is the dose of EN, which is complicated focus in the acute phase of critical illness also.Dosing of EN is in the ICU is complicated by a patient's nutrition risk, baseline nutrition status, and disease severity. One The single randomized, controlled trial (RCT) in critically ill patients showed permissive underfeeding in the first 7-days of an ICU stay may be associated with lower hospital mortality rates than target feeding in critically ill patients [26]. Two randomized, controlled trialsRCTs that evaluated initial minimal or trophic feedingtropic EN with about approximately 400 kcal per day (for up to 5 or 6 days after admission to the ICU) vs. full EN with approximately 1300 kcal per day over the first week of admission in patients with

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acute lung injury or acute respiratory failure ~~, compared with the full-feeding group with about 1300 kcal per day,~~ showed ~~initial trophic enteral nutrition resulted in~~ similar clinical outcomes, but ~~to those of early full-energy enteral nutrition but with~~ fewer episodes of gastrointestinal intolerance with initial tropic EN [15, 27]. ~~Then~~ Subsequently, a~~a multicenter, large~~large multicentre RCT was performed ~~for~~ to ~~evaluating~~ evaluate the effect of 2 weeks of permissive underfeeding, defined as 40 to 60% of calculated caloric –requirements vs. standard EN, defined as 70 to 100% of calculated caloric requirements, on mortality ~~compared with standard enteral feeding during 2 weeks~~ in critically ill patients after surgical, medical, or trauma admission to the ~~including~~ ICU ~~surgical, medical and trauma admission who were fed enterally within 48 hours after ICU admission [28]~~. [28]. Protein intake was similar in the two groups, but the permissive underfeeding group received less nonprotein calories than the standard EN group. ~~The result showed~~ Findings showed that receiving less nonprotein calories in the permissive underfeeding group –was not associated with lower mortality ~~than planned delivery of a~~compared to receiving a full amount of nonprotein calories in the standard EN group ~~(kilocalories (mean ±SD): 835±297 vs 1299±467)~~, but ~~associated with lower~~ blood glucose levels ~~and~~, ~~reduced~~ insulin requirements, need for renal-replacement therapy, and ~~low~~ daily fluid balance were lower in the permissive underfeeding group ~~and low incidence of renal placement therapy~~ [28]. ~~In conclusion~~These data suggest that~~,~~ permissive underfeeding may be applicable in the acute phase of critical illness, ~~although which is not applicable to~~ except in patients ~~who are~~ at high nutrition risk (~~eg~~e.g., Nutritional Risk Screening [NRS] 2002 ≥~~⩾~~5 [29] or Nutrition Risk in the Critically Ill [NUTRIC] score ≥~~⩾~~5 [19], without interleukin 6) or who are severely malnourished [23].

Gut rest strategy and enteral nutrition

Gastrointestinal blood flow is reduced in ~~patients in critical illnesses~~critically ill patients despite fluid replacement and interventions to normalize~~normalization of~~ blood pressure and cardiac output. This reduction in blood flow is associated with ischemic injury, bacterial translocation, and multiple organ failure[30]. Studies in dogs showed that~~, the study in animal found~~ enteral nutrients ~~could~~can increase blood flow to the gastrointestinal tract, a phenomenon referred to as the "postprandial hyperemic response~~",~~". This may preserve gut integrity and prevent gut-derived complications [31, 32]. ~~So enteral nutrients~~ Other evidence suggests that EN has ~~provide~~ trophic effects ~~to~~ that maintain intestinal physiology, prevent atrophy of gut ~~villi atrophy~~villi, ~~decrease~~reduce intestinal permeability, ~~stimulate intestinal perfusion to~~ protect against ischemia- reperfusion injury by stimulating intestinal perfusion~~, and~~, and that EN preserves gut immunity ~~through their effects on the~~by affecting gut-associated lymphoid tissue[33].

~~Although it is possible of~~Although some reports indicate that EN ~~support to restore of~~may restore gastrointestinal function in critically ill patients, ~~GI function, few studies~~studies investigating the influence of AGI on the prognosis of critically ill patients provided EN and the effect of ~~about nutrition support considered influence of AGI on prognosis and evaluated the~~

~~role of~~ EN on AGI in critically ill patients are scarce~~. So it is unclear how to perform,~~ and there are no guidelines for the provision of –EN ~~with~~ to patients with AGI~~, but~~. Theoretically, it seems reasonable to suggest that –excessive ~~usage~~ use ~~of injury GI tract~~of an injured gastrointestinal tract may ~~be not applicable in theory, "going too far is as bad as not going far enough~~have deleterious effects~~"~~. ~~The~~ Accordingly, one study found ~~that the~~a high frequency of ~~enteral nutrition~~EN-related gastrointestinal complications in critically ill patients~~.~~, ~~among which~~of which high gastric residuals was~~is~~ the most ~~frequent~~common, ~~in critically ill patients is high,~~ and ~~enteral feeding~~ gastrointestinal intolerance to EN ~~seems~~ seemed to ~~have an evolutive effect in~~ prolong~~ing the~~ ICU stay and ~~increasing~~ increase mortality [34]. ~~Early~~ In other studies, there was an association between early~~nutrition and~~ nutrition or ~~enteral feeding~~EN ~~were associated with~~and increased ~~ventilation~~ ventilator-associated pneumonia in patients with invasive mechanical ventilation and shock[35] ~~.~~, and EN resulted in ~~Another study also found when~~ upper ~~GI~~ digestive intolerance ~~occurred~~, which was associated with nosocomial pneumonia, a prolonged ICU stay, and a high ICU mortality in critically ill patients ~~there was a significantly higher occurrence of pneumonia longer ICU stay and higher ICU mortality~~ [36]. ~~And~~ Furthermore, overfeeding in critically ill patients may be associated with hypercapnia, increased risk of infection, metabolic disturbances such as hyperglyc~~a~~emia, liver dysfunction, and extended time on mechanical ventilation [12, 37], and~~. And in non-septic critically ill patients,~~ early energy overfeeding was associated with high~~er~~ mortality in non-septic critically ill patients [38].

批注 [JK2]: Do you want to mention Zhang et al (Ann Transl Med) and/or Li et al PLoS One. 2017 Aug 3;12(8):e0182393. doi: 10.1371/journal.pone.0182393 here - they stratified patients by serverity of AGI but used doifferent EN protocosl. AGI or III was not an independent predictor of 28 day mortality in these patients

In critically ill patients~~, when sever~~ with severe injury ~~occur~~, therapeutic approaches ~~must~~ focus on the ~~insult~~ pathology ~~itself~~ (e.g., trauma, necrotic, or infected tissue), ~~thereby interrupting the potentially fatal signaling cascade right at its root~~often allowing survival after a potentially lethal illness. While the adaptive metabolic response has evolved to be beneficial following minor trauma, it may become exaggerated and self-destructive causing secondary metabolic damage in patients surviving severe, potentially lethal conditions due to advances in modern medicine [39] ~~and medical therapy should not be with progressive harm~~. Effective treatment must prevent this secondary metabolic damage; however, these interventions must not cause progressive harm. In critical care, ~~studies found excessive usage of~~evidence suggests that excessive use of an injured organ ~~injury organ was associated with~~is associated with poor prognosis~~, r~~. Restrictive ~~therapy~~ or protective therapy ~~could~~ protects ~~injury~~the injured organ ~~organ, which can not afford normal workloads,~~ from progressive harm~~, at least no inferior liberal therapy with less cost, utilization of medical care, related complications~~. ~~For example, in~~In one study of patients with acute lung injury and ~~the~~ acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than is traditionally used ~~results in~~ was associated with reduced mortality and increased the number of days without ventilator use ~~decreased mortality~~ [40]. ~~Conservative~~ In another study, a conservative strategy of fluid management ~~in patients with acute lung injury improves~~ improved lung function and shorten~~s~~ the duration of mechanical ventilation in patients with acute lung injury [41]. Furthermore, a restrictive strategy of red-cell transfusion was shown to be at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients[43]. –Conversely, ~~The~~ the use of diuretics, ~~which means~~which causes –overuse of residual kidney function, ~~in critically ill patients with acute renal failure~~ was associated with an increased risk of death and nonrecovery of renal function in critically ill patients with acute renal failure [42]. ~~A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients[43].~~

Fig.2 Protective or restrictive therapy in critically ill patients

~~In addition~~Similarly, overuse of the gut may be harmful to prognosis in the acute phase of critical illness. ~~At least in the~~In the acute phase after a severe insult, ~~an~~ aggressive nutritional therapy (e.g., by guiding exogenous caloric support according to energy expenditure) may not ~~only be without~~ have beneficial effects~~,~~. In fact this approach is potentially~~but may be even~~ detrimental, as it may cause a ~~by causing a~~ metabolic overload and/or ~~by~~ suppress~~ing~~ the ubiquitin–proteasome pathway and related autophagy, which are potentially important for cellular repair and organ recovery [39, 44]. ~~And a recent~~In support of this, a recent ~~study has found~~study found that early isocaloric ~~enteral nutrition~~ EN did not reduce mortality or the risk of secondary infection ~~s~~in critically ill adults with shock, but it was associated with a greater risk of digestive complications compared with early isocaloric parenteral nutrition ~~in critically ill adults with shock~~ [45]. Efficacy of artificial nutritional support may increase and improve patient outcomes ~~Only if the~~when the immunologic and inflammatory metabolic triggers associated with

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the adaptive metabolic response, in the acute phase of critical illness have largely disappeared~~,~~ ~~efficacy of artificial nutritional support may increase thereby also improving outcome~~[46].

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~~So in~~Therefore, ~~critically ill patients with AGI,~~ we propose restrictive EN ~~should be better~~is the optimal choice ~~choice~~ for critically ill patients with AGI. ~~in theory~~ ~~, although no trials prove this hypothesis.~~ As trophic feeds (usually defined as 10–20 mL/h or 10–20 kcal/h) are a protective strategy, reducing gut burden and maintaining intestinal physiology, they ~~However, trophic feeds (usually defined as 10–20 mL/h or 10–20 kcal/h)~~ may be sufficient to prevent mucosal atrophy and maintain gut integrity in critically ill patients ~~without high~~at low nutrition risk (NUTRIC score ≥~~⩾~~5) [23]~~. Trophic feeds would be protective strategy of gut, keeping both reducing gut burden and maintaining intestinal physiology, and this~~and ~~strategy~~ may be ~~more~~ applicable to critically ill patients with AGI~~, which need to study in advance in future~~. To the authors' knowledge, there are no trials that prove this hypothesis; therefore, large scale studies are warranted to investigate this approach.

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Conclusions

Injury to the gastrointestinal tract manifests as improper digestion and absorption, impairment of the intestinal barrier, and dysregulation of the intestinal microbiota~~When GI was injury and dysfunction, manifestations were digestion and absorption dysfunction, intestinal barrier function impairment, and intestinal microbiota dysregulation~~**.** Early EN is believed to improve gastrointestinal function ~~In~~ in critically ill patients. However, in the acute phase of critical illness, we propose that ~~, it is believed that early enteral nutrition could improve gastrointestinal function, but~~ trophic feeding may be ~~applicable~~ the optimal strategy considering the adaptive metabolic response~~metabolism~~ and ~~acute gastrointestinal injury~~AGI.~~ in the acute phase of critical illness, and~~ T~~t~~rophic feeding may be ~~one kind of~~an organ protective strategy in critically ill patients, similar to the use of ~~such~~ low tidal volume, restrictive fluid resuscitation, and restrictive transfusion~~, etc in critically ill patients~~.

Competing interests

The authors declare that they have no competing interests.

Authors' details

Hongxiang Li produced the first draft of the manuscript. All authors critically revised the manuscript. All authors have seen and approved the final draft of the manuscript.

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