ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 10 | October - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PATIENTS WITH SHOCK ON INOTROPIC SUPPORT: WHAT IS THE IDEAL TIME WHEN WE CAN START EARLY ENTERAL NUTRITION.

Anaesthesiology

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ABSTRACT

Shock is a common critical illness characterised by microcirculatory disorders and insufficient tissue perfusion. Patients with shock and hemodynamic instability generally require vasopressors to maintain the target mean arterial pressure. Enteral nutrition (EN) is an important therapeutic intervention in critically ill patients and has unique benefits for intestinal recovery. Low-dose enteral nutrition can be safely started within 48 h after admission, even during treatment with small or moderate doses of vasopressor agents. A percutaneous access should be used when enteral nutrition is anticipated for ≥ 4 weeks. Energy delivery should not be calculated to match energy expenditure before day 4–7, and the use of energy-dense formulas can be restricted to cases of inability to tolerate full-volume iso caloric enteral nutrition or to patients who require fluid restriction. Low-dose protein (max 0.8 g/kg/day) can be provided during the early phase of critical illness, while a protein target of > 1.2 g/kg/day could be considered during the rehabilitation phase. The occurrence of refeeding syndrome should be assessed by daily measurement of plasma phosphate, and a phosphate drop of 30% should be managed by reduction of enteral feeding rate and high-dose thiamine. Vomiting and increased gastric residual volume may indicate gastric intolerance, while sudden abdominal pain, distension, gastrointestinal paralysis, or rising abdominal pressure may indicate lower gastrointestinal intolerance.However, the initiation of early EN in patients with shock receiving vasopressors remains controversial. Current guidelines make conservative and vague recommendations regarding early EN support in patients with shock. Increasing studies demonstrates that early EN delivery is safe and feasible in patients with shock receiving vasopressors; however, this evidence is based on observational studies. Changes in gastrointestinal blood flow vary by vasopressor and inotrope and are complex. Therefore, the current review aimed to summarise the evidence on the optimal and safe timing of early EN initiation in patients with shock receiving vasopressors to improve clinical practice.

KEYWORDS

INTRODUCTION

Shock is a critical and life-threatening illness in the intensive care unit (ICU) and is characterized by microcirculatory disorders and insufficient tissue perfusion. Splanchnic hypoperfusion and inadequate utilization of cellular oxygen result in important path- ophysiological changes in the gut (namely increased enterocyte necrosis, bacterial overgrowth and translocation, and an impaired barrier defence), which can be aggravated by subsequent reperfu- sion and vasopressors use . Moreover, gastrointestinal dysmotility is also present in patients with shock. In these pa- tients, persistent stress and high metabolism often cause energy deficiency.[1] In addition, high doses of vasopressors can exacerbate the already high metabolic status and gastrointestinal mobility disorders, further increase the energy requirements of intestinal epithelial cells.

The key non-nutritional benefits of EN include: 1) maintaining structural/functional gut integrity, thus attenuating intestinal permeability; 2) attenuated oxidative stress and inflammatory response, while maintaining humoral immune responses; and 3) Modulation of metabolism to decrease insulin resistance. Specific to prevention of dysbiosis- any period of starvation, lack of enteral nutrients and prebiotic fiber delivery, and the presence of exogenous/endogenous vasopressors will drive dysbiosis. Recent data shows provision of even 20% of nutrition via EN can prevent dysbiosis, attenuate loss of gut barrier function, and innate immunity. In addition a body of experimental and human critical care data demonstrates that EN can trigger activation of anti-inflammatory vagal-cholinergic pathway via CCK-mediated receptor stimulation in shock states. Thus, outside of the obvious need for protein/energy delivery to promote recovery, the mechanistic benefits of EN in critical care settings are long established. Currently, it is perceived that enteral nutrition (EN) should be initiated as soon as 24h to 48 h after ICU admission because critically ill patients face severe energy liabilities. Patients with shock are a special category of critically ill patients, and the use of EN in these patients is usually cautious.[2] A clinical concern is that the early EN-induced intestinal hemodynamic changes in patients with shock can be worsened by concurrently reduced blood flow and the imbalance of oxygen delivery/consumption in the gastrointestinal tract. This might lead to a high risk of developing mesenteric ischemia (MI) and necrosis.[3]

Guidelines recommend that EN should be delayed in patients with shock until the patient's circulation is fully resuscitated, and hemodynamic goals are achieved. However, the obscure definitions of “uncontrolled” and “controlled” hemodynamic status and unvalidated score make it difficult to determine the suitability of a patient EN initiation. Increasing evidence demonstrates that EN can be performed in patients with shock requiring vasopressors. The beneficial effects of early EN are more pronounced in the most severe patients receiving multiple vasopressors. The concept of early EN is ambiguous in patients with shock, and the early nutritional provisions in patients with shock usually mean within 72 h, mostly within 48 h.[4] It is reasonable to continue EN delivery for the patients receiving stable doses of vasopressors, assuming that the patients are hemodynamically stable, and the mean arterial blood pressure is sustained at 70 mm Hg. The reliability of the observational studies can be questioned, and interventional studies in this area are limited. However, as research evidence increases, recent guidelines and expert tips do not consider shock as a contraindication to EN support. It is recommended to apply low-dose EN in patients with controlled shock requiring small or moderate doses of vasopressor, consider EN only, or maintain EN at vasopressor dose equivalent scores >12.[5] However, vasopressor dose equivalent scores have not been validated in clinical practice. The questions, such as when to initiate EN in patients with shock who requiring vasopressors and under what circumstances it is safe, remain unanswered and are important topics in critical care nutrition therapy. This review was performed to evaluate the evidence regarding the optimal and safe time to initiate EN in patients with shock requiring vasopressors.[6]

Early EN May Be Preferred In Patients With Shock Who Can Be Fed Enterally

Highly metabolic and immune responses are common in pa- tients with shock. Delayed nutrition is associated with negative energy balance and fails to meet the increased metabolic and en- ergy consumption needs. [7]Moreover, this negative energy balance can worsen and persist

throughout the disease progression, thereby further deteriorating patient's outcomes. Nutritional sup- port not only provides nutrients to avoid "malnutrition", but it is also a major therapeutic intervention, achieving metabolic optimization and alleviating stress-induced immune responses.

Preclinical and clinical studies indicated that enteral fasting and delayed EN were associated with gastrointestinal barrier dysfunction. Recently, the authors of one study constructed an enterocutaneous fistula model and observed directly that early EN could alleviate intestinal mucosal injury, improve the intestinal immune milieu, and restore the intestinal barrier by decreasing the formation of neutrophil extracellular traps compared with total parenteral nutrition (PN).[8] Lack of EN alters the distribution of intestinal flora and PN cannot completely restore intestinal sym- biotes, even when specific nutrients are provided in PN. The interaction of intestinal microorganisms is an important part of intestinal immunity.[9] EN stimulation protects the mucosal immune system and preserves IgA and early antibiotic resistance. EN also promotes protein synthesis and regulates insulin resistance. Moreover, EN could increase cardiac output, decrease systemic vascular resistance, and increase mesenteric blood flow in patients with shock requiring vasopressors.[10]

Although preclinical studies have demonstrated the unique benefits of EN support for intestinal recovery, the risks, and benefits of initiating EN in patients with shock should be carefully evalu- ated. In critically ill patients, EN does not outperform PN in terms of survival benefit, although EN can reduce infection rates and ICU duration. In the FRANS study, investigators found that providing large amounts of macronutrients during the early ICU stay might be associated with poor outcomes.[11] Secondary analysis in the EFFORT study also demonstrated no survival benefit of nutritional support for the patients with high baseline inflammation (CRP >100 ng/mL). The NUTRIREA-2 and NUTRIREA-3 studies provided evidence against the risk of introducing EN in patients with shock; the results indicated that the early introduction of full-dose EN in patients with shock and hemodynamic instability was harmful. This might be because, on the one hand, the acute early phase of critical illness presents hyper-inflammation, oxidative stress, and mitochondrial dysfunction leading to anabolic resistance, while on the other hand, the excessive EN delivery increases intestinal loading and may further exacerbate the impaired visceral perfusion associated with shock.[12] The currently available studies also support the recommendation of the European Society for Clinical Nutrition and Meta- bolism (ESPEN) guidelines that early and progressive EN therapy should be administered to septic patients after hemodynamic stabilization. Overall, given the potential physiological, immune, and metabolic advantages of EN, as well as the risk of PN-associated infections, EN may be preferred for patients with shock, who can tolerate enteral feeding.[13] Of course, it is prudent and pragmatic to start partial (20%e50%) nutritional support as early as possible to"open" the enteral route and gradually increase the feeding volume according to feeding tolerance to achieve optimal nutritional support in the patients with shock. In order to assess feeding tolerance, a general clinical practice is to carefully monitor the patients for the development or exacerbation of gastrointestinal dysfunction symptoms, such as vomiting/reflux, diarrhoea, intestinal obstruction, and suspected MI/mesenteric perforation, after receiving EN before deciding on continuing the EN support.[14]

Effects Of Vasopressors/Inotropes On Gastrointestinal Perfusion

Using vasopressors is an important treatment for patients with shock. Combining vasopressors with inotropes is common in patients with shock to maintain target blood pressure and sufficient cardiac output. Changes in gastrointestinal blood flow vary by vasopressors/ inotropes; therefore, individual drug-related changes cannot be generalized. Vasopressors have dose response relationship with intestinal injury, with higher doses or multiple drug combinations associated with worse clinical outcomes, including MI.[15] The effects of vasopressors combined with inotropic drugs on intestinal perfusion and oxygen supply/consumption are more complex than with vasopressors only. Understanding the effects of vasopressors/ inotropes on the intestinal circulation requires further studies.

Norepinephrine has little effect on gastrointestinal perfusion; however, it is worth noting that using norepinephrine may lead to a redistribution of gastrointestinal blood flow.[16] An animal study indicated that the blood flow in the superior mesenteric artery and the microcirculation in the jejunal mucosa and pancreas. were significantly reduced during norepinephrine and epinephrine infusion. Epinephrine was also reported to impair gastrointestinal perfusion in patients with septic shock. In another study, epinephrine increased gastrointestinal mucosal perfusion, which might be related to increased cardiac output. The impairment of gastrointestinal perfusion induced by epinephrine might be in a dose response relationship. Several animal studies reported that phenylephrine impaired gastrointestinal microcirculatory perfusion. In contrast to previous animal studies, no reduction in gastrointestinal microcirculation was observed in patients after cardiac surgery, which might be due to blood redistribution, and the lower doses of norepinephrine do not represent the patients with shock requiring high dose vasopressor support. The effects of dopamine on gastrointestinal perfusion showed a dose response relationship. Low-dose of dopamine increases gastrointestinal microcirculation perfusion, while high-dose of dopamine decreases it.[17] Dobutamine increased gastrointestinal mucosal perfusion in septic shock. However, only norepinephrine or in combination with dobutamine showed completely opposite effects on MI. Vasopressin infusion diminished gastrointestinal mucosal perfusion. Exogenous vasopressin infusion reduced norepinephrine requirements in patients with shock and limited the adverse effects. However, available clinical studies suggested that the risk of acute MI in the patients receiving vasopressin infusion was similar to that in the patients receiving norepinephrine infusion. The use of vasopressors/ inotropes is complex for gastrointestinal circulation, especially when used in combination with different vasopressors/ inotropes[18] Early EN has been reported to improve gastrointestinal microcirculation perfusion ; however, in the case of complete intestinal artery occlusion, EN initiation can further aggravate MI and hypoxia. Therefore, for patients with shock, feeding tolerance should be carefully evaluated when receiving vasopressors/inotropes infusion, especially considering the complex effects of vasopressors/inotropes alone and in combination.

Evidenced-Based Methods to Address EN Feeding Patients on Vasopressors:

Vasopressor Choice	Vasopressor Dose	Resuscitation Markers and Suggestions for EN Delivery Safety	Feeding Strategy	Signs of Intolerance
Norepinephrine, Norepinephrine /Dobutamine and Phenylephrine > Epinephrine > Vasopressin/ Dopamine (Observational data and animal data supporting recommendation)	Keep Norepinephrine doses (equivalents) < 1.0 ug/kg/min- more optimal 1.0 – 3.0 ug/kg/min- may be acceptable > 0.5 ug/kg/min – significant risk – should not be done	1. Lactate normalized or falling rapidly 2. Vasopressor dose decreasing or stable 3. Mixed Venous 02-WNL or elevated 4. Fluid requirements stabilizing, no ongoing active bleeding. 5. Limit crystalloid fluid over-resuscitation to reduce bowel edema (especially in septic shock – with more pronounced vascular leak)	1. Start with ***gastric*** delivered trophic feeding (10–20 cc/h) (NO post-pyloric feeding) 2. Advance EN slowly and watch for signs of intolerance 3. Consider elemental or peptide formula to minimize gut O2 consumption for absorption	1. Increased gastric residual (> 500 cc's) 2. Abdominal distension 3. Nausea/ Vomiting 4. New abdominal pain 5. Unexplained elevation in lactate with feeding initiation or escalation 6. Intra-abdominal hypertension or abdominal compartment syndrome

The Risk Assessment Of Early EN In Patients With Shock

For patients with shock receiving vasopressors, an inadequate administration of early EN may aggravate gastrointestinal dysfunction and even lead to non-occlusive mesenteric ischemia (NOMI) or non-occlusive bowel necrosis (NOBN).[19] Using catecholamines during EN is a risk factor for feeding intolerance. Other factors, including sedatives and analgesics, hyperglycemia, elevated intra-abdominal pressure, and elevated serum lactate levels, are also associated with feeding intolerance. These factors should be carefully considered when deciding to initiate EN in patients with shock receiving vasopressors. NOMI and NOBN are rare but life-threatening complications with a high mortality rate of 50% to 85%. The NUTRIREA-2 study reported that early EN during vasoactive drug support in patients with shock could increase the risk of NOMI with an incidence rate of MI was 2% . In our previous observational study, one patient (1.5%) developed MI.[20] The NUTRIVAD study reported an incidence of suspected MI (diagnosed based on clinical symptoms) and confirmed MI (confirmed by computed tomography) during EN support in patients with shock requiring vasopressors, with incidence rates of 4.5% and 0.5%, respectively. In another study by our team, the incidence rates of suspected and confirmed MI were 1.9% and 1.0% in all 210 patients with shock requiring vasopressors, and the incidence rate of suspected MI in the category of patients with rapidly increasing vasopressor doses within 7 days of EN initiation was 11.76%.[21] In fact, the prevalence of NOMI may be underestimated due to the insidious onset, late presentation, and lack of abdominal computed tomography findings confirming such diagnosis after death. The risk of NOMI is probably higher in patients receiving vasopressors combined with inotropes than those receiving vasopressors alone.[22]

Another important point to consider is the delivery of EN doses.The risk of developing MI may be different in the case of EN delivered at

low doses as compared to EN delivered at full doses. In the NUTRIREA-2 study, patients in the early EN group were introduced to full-dose EN (25 kcal/kg/day) after 24 h of enrolment while receiving a higher dose of vasopressors, and they exhibited a significantly higher incidence of MI as compared to those receiving early PN. A subsequent post-hoc analysis of the NUTRIREA-2 study also reported that EN was independently associated with MI in the patients with shock receiving either EN or PN. Most of the early EN benefits are obtained with only 30%e50% of the nutritional target.[23] The NUTRIREA-3 study compared the effects of receiving low-calorie and low-protein targets with those of the standard-calorie and standard-protein targets in the acute phase of patients with shock. The results demonstrated that compared to the standard group, the low group had fewer MI events (1.8% vs.0.9%, P 1⁄4 0.03). In the NUTRIVAD study, the patients receiving vasoactive medications reached target feeding within 3 days of initiation of feeding and showed that limited provision of early EN was safe and not associated with serious complications. These studies illustrate that excessive nutrient delivery in the presence of higher vasopressor doses further increases the occurrence of MI.

Early recognition and diagnosis of NOMI is very crucial but difficult. The occurrence of NOMI/NOBN should be highly suspected in the presence of sudden abdominal pain, abdominal distention, peritonitis/muscular defense, gastrointestinal bleeding, multiple organ dysfunction/multiple organ failure, and positive radiographic signs, such as expanded and thickened loops of the intestine with thumb printing, air in the intestinal wall, portal gas and air in the peritoneal cavity. In addition, sufficient oxygen supply is also needed to avoid MI.[24] The risk of MI has been reported in patients with acute respiratory distress syndrome receiving conservative oxygen therapy, with a peripheral oxygen saturation of 88% to 92%. Interestingly, most of the MI cases associated with EN were described in trauma burn and surgery patients fed with jejunal tubes. Most studies support that EN-related NOBN occurs via post-pyloric feeding rather than gastric feeding . This might suggest that delayed gastric emptying could be protective in the case of a poorly perfused bowel; therefore, large gastric residuals should not be interpreted as a sign to attempt post-pyloric feeding. Post-pyloric feeding should be avoided until there is sufficient evidence of its safety in patients with shock.

For patients with shock, systemic circulatory and microcirculatory parameters, arterial blood gas analysis, and symptoms of gastrointestinal complications, gastrointestinal residuals, and intra-abdominal pressure should be closely evaluated during EN support.[25] However, laboratory data specifically predicting gastrointestinal complications are lacking. Several novel and potential biomarkers have been investigated in association with NOMI, namely intestinal fatty acid binding protein, a-glutathione S-transferase, D-dimer, L- and D-lactate, and citrulline; however, no clinically useful biomarkers have been identified yet.

Early En Initiation In Patients With Shock In Current Guidelines

Early and effective fluid resuscitation is the first-line treatment to improve tissue perfusion in patients with shock [85]. Sufficient blood perfusion and active gastrointestinal motility are pre- requisites for the safe starting of early EN.[26] For patients with shock with hemodynamic instability, early EN is indeed considered a relative contraindication. Guidelines offer conservative recommendations, which are based on expert consensus and are quite subjective (Table 1). The Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN) suggest not to initiate EN until the achievement of complete hemodynamic resuscitation and/or stability. The European Society of Intensive Care Medicine suggests delaying EN if the shock is uncontrolled, and hemodynamic and tissue perfusion goals are not met; however, low-dose EN should be started as soon as the shock is controlled with fluid resuscitation and vasopressors/inotropes support. In contrast, according to the ESPEN guidelines, there is no sufficient evidence available as no interventional studies have been published, to date.[27] These guidelines do not identify a clear definition of “uncontrolled” and “controlled” hemodynamic status, which may confuse clinicians regarding when to start EN in patients with shock. The Surviving Sepsis Campaign suggests early EN as the preferred route of administration rather than early PN alone or PN combined with EN in patients with shock who can be fed enterally. The German Society for Nutritional Medicine (DGEM) suggests that EN should not be used until he modynamics have stabilized in patients with hemodynamic instability. According to DGEM guideline, early EN may be harmful for patients receiving high doses of norepinephrine beyond 0.5 mg/kg/min and EN can be resumed in those who require a stable or declining dose of vasopressors. Initiating early EN did not appear to be contraindicated, but the reports recommended beginning EN at a low flow rate and with caution.[28] A recent guide recommends initiating low-dose EN within 48 h of ICU admission in patients with controlled shock requiring small or moderate doses of vasopressor and delaying EN in those who are actively being resuscitated or are unstable. In the practice guidelines for nutritional therapy in critically ill patients with coronavirus disease 2019 (COVID-19), this guideline also recommended that circulatory shock associated with COVID-19 should not be considered a contraindication to EN unless an increased dose of vasopressors and/or feeding intolerance occurs. The Board of Directors of ASPEN established the Enteral Nutrition Committee attempting to establish borderline values for the initiation of EN in patients with hemodynamic instability using a vasopressor dose equivalent score.[29]

According to the committee's consensus recommendations, if the vasopressor dose equivalent score is > 12, the administration of trophic only or holding EN should be considered. However, this score has not been proven in clinical practice, which may limit its application. Although current guideline recommendations and expert consensus are moving toward the possibility of initiating EN in patients with shock receiving low to moderate doses of vasopressors, vague definitions of vasopressor doses and the use of unvalidated scoring systems make these guidelines and expert consensus less accurate for clinical practice. It is clear that the timing, dosage, and aspects of EN delivery all determine the “window of opportunity” for patients with shock to benefit from this therapy. However, a vague definition of the timing for early EN in most guidelines may limit its benefit regarding the “window of opportunity".

Safe Threshold Dose Of Vasopressors For Initiating Early EN

Vasoactive drug therapy is not a contraindication for the early introduction of EN in patients with shock monitored carefully; one of the difficulties lies in weighing when it is safe to introduce it. In patients with shock, the tolerability of early EN is associated with the maximum cumulative dose of vasopressors and might be related to the administration of specific vasopressors. Early EN may be harmful for patients with shock receiving high doses of norepinephrine beyond 0.3 mg/kg/min. A study reported that early EN had no survival benefits for patients receiving high doses of norepinephrine exceeding 0.3 mg/kg/min. Piton et al. reported that a dose of epinephrine and/or norepinephrine of 0.48 mg/kg/min was associated with high concentrations of the enterocyte damage biomarker, intestinal fatty acid binding protein, reflecting the degree of severity of hemodynamic instability. The NUTRIREA-2 and NUTRIREA- 3 studies indicated that early full EN was harmful in ventilated patients with shock who received a high dose of norepinephrine up to 0.5 mg/kg/min, with a higher risk of adverse gastrointestinal consequences.[30]

The suggested cutoff dosage of norepinephrine or equivalent might b below 0.3 mg/kg/min. Merchan et al. reported that 62% of 120 patients with septic shock tolerated early EN with norepinephrine-equivalent doses of <0.14 mg/kg/min. Ohbe et al. divided ventilated adults with shock undergoing early EN and late EN into three groups: low-dose (<0.1 mg/kg/min), medium-dose (0.1e0.3 mg/kg/min), and high-dose (0.3 mg/kg/min) norepinephrine groups. The results suggested that a cutoff norepinephrine dose of <0.3 mg/kg/min might guide early EN use in these patients and benefit patients 'outcomes. Our previous study results suggested that the threshold of 0.2 mg/kg/min of norepinephrine-equivalent doses was feasible and safe to initiateEN in patients with shock [68]. In a multicenter pragmatic clinical trial, Ortiz-Reyes et al. reported that early EN was associated with improved outcomes in mechanically ventilated patients with circulatory shock requiring a norepinephrine dose of 0.3 mg/kg/min.[31]

In addition, the temporal effects of changes in vasopressors dose and intestinal injury should also be considered. The NUTRIVAD study suggested that even for the patients with shock receiving high doses (>0.5 mg/kg/min) of vasopressors in the first 48 h of ICU admission, EN was still feasible and safe for them if the dose could be reduced to a safe dose range in subsequent days. However, the study did not report data on the changes in the dose of vasopressors after EN initiation. Recently, our team characterized the norepinephrine-equivalent doses trajectories in patients with shock and demonstrated that the initiation of EN in patients with shock at a stable maintenance of

norepinephrine-equivalent doses below 0.2 mg/kg/min was associated with a reduced risk of gastrointestinal adverse events and mortality. Although our previous study attempted to characterize the temporal effects of changes in vasoactive drug dose with intestinal adverse events, this is still an exploratory work. Moreover, it would be meaningful to take the temporal effects of vasoactive drugs into account in future studies focusing on nutritional interventions for critically ill patients.[32]

Based on the current literature, the threshold dose of vasopressors for initiating early EN remains inconclusive in patients with shock. Low- to moderate-dose vasopressor infusions are likely associated with low risks of gastrointestinal complications during early EN support; however, there is no clear evidence or recommendations regarding validated management strategies to safely guide this common clinical scenario [90]. Clearly, vasopressor dose and EN delivered dose coexist in the equation of gastrointestinal risk in patients with shock. However, it is unclear in what form these two variables should be characterized and applied to nutritional practices in critically ill patients. A more detailed discussion of the effects of EN dose on gastrointestinal risk in patients with shock can be found in the review by Patel JJ et al. [38]. Our previous study attempted to use mean arterial pressure/ norepinephrine equivalent dose index to define the optimal time of early EN initiation in patients with shock and demonstrated that it may be abetter potential indicator for guiding early EN initiation in patients with shock. In addition to finding new indicators to define and guide early initiation of EN in patients with shock, another important point of interest could be the temporal effects of vasopressors use. The different subgroups of patients with shock who require vasopressors might require different EN strategies, and the optimal nutritional strategy for different categories of patients with shock should be further explored in the future.

CONCLUSIONS

There is currently no sufficient and definitive evidence to clarify the optimal time to initiate early EN; however, recent observational studies have indicated that early EN can be delivered safely, which can benefit critically ill patients. Although the current consensus is that EN support is not incompatible with vasopressors, the complex effects of vasopressors on the gut should also be considered. The risks and benefits of early EN should be weighed carefully for each patient with shock requiring vasopressors. In addition to vasopressor dose, the factors, such as EN delivery dose, disease severity, and route of nutritional support, also affect nutritional provision in patients with shock. The temporal effects of vasopressor dosage on intestinal circulation should also be considered. A norepinephrine dose of <0.3 mg/kg/min may be considered a safe zone for initiating EN in patients with shock, who are hemodynamically unstable, and better metrics may be available in the future to define the safe zone for EN initiation. Future studies should determine when can patients with shock start early EN support to greatly benefit from it.

REFERENCES

1. Allen JM. Vasoactive substances and their effects on nutrition in the critically ill patient. Nutr Clin Pract 2012;27(3):335e9.
2. Berger MM, Chiolero RL. Enteral nutrition and cardiovascular failure: from myths to clinical practice. JPEN - J Parenter Enter Nutr 2009;33(6):702e9.
3. Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutri- tion support therapy in the adult critically ill patient. Crit Care Med 2016;44(2):390e438.
4. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med 2017;43(3):380e98.
5. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38(1):48e79.
6. Merchan C, Altshuler D, Aberle C, Papadopoulos J, Schwartz D. Tolerability of enteral nutrition in mechanically ventilated patients with septic shock who require vasopressors. J Intensive Care Med 2016;32(9):540e6.
7. Ohbe H, Jo T, Matsui H, Fushimi K, Yasunaga H. Differences in effect of early enteral nutrition on mortality among ventilated adults with shock requiring low-, medium-, and high-dose noradrenaline: a propensity-matched analysis. Clin Nutr 2020;39(2):460e7.
8. Flordelís Lasierra JL, Perez-Vela JL, Umezawa Makikado LD, Torres Sanchez E, Colino Gomez L, Maroto Rodríguez B, et al. Early enteral nutrition in patients with hemodynamic failure following cardiac surgery. J Parenter Enteral Nutr 2013;39(2):154e62.
9. Ohbe H, Jo T, Yamana H, Matsui H, Fushimi K, Yasunaga H. Early enteral nutrition for cardiogenic or obstructive shock requiring venoarterial extra- corporeal membrane oxygenation: a nationwide inpatient database study. Intensive Care Med 2018;44(8):1258e65.
10. Mancl EE, Muzevich KM. Tolerability and safety of enteral nutrition in criti- cally ill patients receiving intravenous vasopressor therapy. JPEN - J Parenter Enter Nutr 2013;37(5):641e51.
11. Patel JJ, Kozeniecki M, Peppard WJ, Peppard SR, Zellner-Jones S, Graf J, et al. Phase 3 pilot randomized controlled trial comparing early trophic enteral nutrition with "No enteral nutrition" in mechanically ventilated patients with septic shock. JPEN - J Parenter Enter Nutr 2020;44(5):866e73.
12. Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of criti- cally ill patients treated with vasopressors and mechanical ventilation. Am J Crit Care 2010;19(3):261e8.
13. McClave SA, Chang W-K. Feeding the hypotensive patient: does enteral feeding precipitate or protect against ischemic bowel? Nutrition in clinical practice. Off Pub Am Soci Paren Ent Nutr 2003;18(4):279e84.
14. Preiser JC, Arabi YM, Berger MM, Casaer M, McClave S, Montejo-Gonzalez JC, et al. A guide to enteral nutrition in intensive care units: 10 expert tips for the daily practice. Crit Care 2021;25(1):424.
15. Bechtold ML, Brown PM, Escuro A, Grenda B, Johnston T, Kozeniecki M, et al. When is enteral nutrition indicated? JPEN -. J Parenter Enter Nutr 2022;49(7): 1470e96.
16. Martindale R, Patel JJ, Taylor B, Arabi YM, Warren M, McClave SA. Nutrition therapy in critically ill patients with coronavirus disease 2019. JPEN - J Parenter Enter Nutr 2020;44(7):1174e84.
17. McClave SA, Martindale RG, Rice TW, Heyland DK. Feeding the critically ill patient. Crit Care Med 2014;42(12):2600e10.
18. Hamarneh SR, Mohamed MM, Economopoulos KP, Morrison SA, Phupitakphol T, Tantillo TJ, et al. A novel approach to maintain gut mucosal integrity using an oral enzyme supplement. Ann Surg 2014;260(4):706e14. discussion 14-5.
19. Buchman AL, Moukarzel AA, Bhuta S, Belle M, Ament ME, Eckhert CD, et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. JPEN - J Parenter Enter Nutr 1995;19(6):453e60.
20. Hernandez G, Velasco N, Wainstein C, Castillo L, Bugedo G, Maiz A, et al. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. J Crit Care 1999;14(2):73e7.
21. Nguyen NQ, Besanko LK, Burgstad C, Bellon M, Holloway RH, Chapman M, et al. Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients. Crit Care Med 2012;40(1):50e4.
22. Hu Q, Ren H, Hong Z, Wang C, Zheng T, Ren Y, et al. Early enteral nutrition preserves intestinal barrier function through reducing the formation of neutrophil extracellular traps (NETs) in critically ill surgical patients. Oxid Med Cell Longev 2020;2020: 8815655.
23. Fukatsu K. Impact of the feeding route on gut mucosal immunity. Curr Opin Clin Nutr Metab Care 2014;17(2):164e70.
24. Heneghan AF, Pierre JF, Tandee K, Shanmuganayagam D, Wang X, Reed JD, et al. Parenteral nutrition decreases paneth cell function and intestinal
25. L. Wang, X. Zhong, H. Yang et al. Clinical Nutrition ESPEN 61 (2024) 28e36 bactericidal activity while increasing susceptibility to bacterial enter- oinvasion. JPEN - J Parenter Enter Nutr 2014;38(7):817e24.
26. Ikeda S, Kudsk KA, Fukatsu K, Johnson CD, Le T, Reese S, et al. Enteral feeding preserves mucosal immunity despite in vivo MAdCAM-1 blockade of lymphocyte homing. Ann Surg 2003;237(5).
27. Martindale RG, Warren M. Should enteral nutrition be started in the first week of critical illness? Curr Opin Clin Nutr Metab Care 2015;18(2):202e6.
28. Revelly JP, Tappy L, Berger MM, Gersbach P, Cayeux C, Chiolero R. Early metabolic and splanchnic responses to enteral nutrition in postoperative cardiac surgery patients with circulatory compromise. Intensive Care Med 2001;27(3):540e7.
29. Elke G, van Zanten AR, Lemieux M, McCall M, Jeejeebhoy KN, Kott M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated sys- tematic review and meta-analysis of randomized controlled trials. Crit Care 2016;20(1):117.
30. Pardo E, Lescot T, Preiser JC, Massanet P, Pons A, Jaber S, et al. Association between early nutrition support and 28-day mortality in critically ill patients: the FRANS prospective nutrition cohort study. Crit Care 2023;27(1):7.
31. Merker M, Felder M, Gueissaz L, Bolliger R, Tribolet P, Kaegi-Braun N, et al. Association of baseline inflammation with effectiveness of nutritional support among patients with disease-related malnutrition: a secondary analysis of a randomized clinical trial. JAMA Netw Open 2020;3(3):e200663.
32. Reignier J, Boisrame-Helms J, Brisard L, Lascarrou J-B, Ait Hssain A, Anguel N, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet 2018;391(10116):133e43.