



Published in final edited form as:

Crit Care Med. 2020 January ; 48(1): 122–125. doi:10.1097/CCM.0000000000003965.

Enteral Nutrition Can Be Given To Patients On Vasopressors

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The gut has long been felt to play a central role in the progression and pathogenesis of critical illness. In fact, seminal papers have described the gut as the “motor for systemic inflammation and organ failure” (1). Perturbations of intestinal epithelial homeostasis in critical illness can lead to increased pro-inflammatory cytokine production, gut barrier dysfunction, and cellular apoptosis which is felt to contribute to multiple organ failure (MOF) (1). This is felt to be driven by a range of factors including rapid change in the microbiome, known as dysbiosis(2), and intestinal permeability changes(1). Further, inflammatory signalling changes via the vagus nerve (3) and effects on mesenteric lymph(4) are believed to drive systemic inflammation and can lead to gut-related downstream organ dysfunction in the critically ill patient. Finally, the gut’s fate, and we believe short and long-term outcomes from critical illness will ultimately depend on successful delivery of nutrients to ensure nutritional delivery to promote recovery (5). Enteral nutrition (EN) has been shown to be beneficial in achieving all of these goals. 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 (6). 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 (2, 7). Recent data shows provision of even 20% of nutrition via EN can prevent dysbiosis, attenuate loss of gut barrier function, and innate immunity (7). 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 (3). 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.

Specific to the effects of nutrition delivery on gut blood flow during shock, benefits of EN on splanchnic ischemia due to shock have been long-described in laboratory models of shock (8). Human studies of cardiogenic shock reveal EN increases cardiac index, splanchnic blood flow, and preserves bowel absorption capacity during vasopressor delivery (9). Despite this, concerns around early EN in patients on vasopressors are still present and valid due to concern for mesenteric ischemia and non-occlusive bowel necrosis ((NOBN)-

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where bowel ischemia occurs in patchy, non-contiguous areas) (10). Without question, vasopressor administration can be associated with bowel injury when doses are sufficient. A recent study of patients receiving epinephrine and/or norepinephrine compared this group with a control population not receiving vasopressors. In patients receiving increasing doses of catecholamines, an increase in intestinal fatty acid-binding protein concentration (IFABP) (marker of intestinal injury), lactate, and 28-day mortality was observed (11). It is key to note the magnitude of effect on the gut may be vasopressor drug-dependent. In animal (porcine) models, epinephrine treatment of septic shock leads to impaired bowel microcirculatory flow and early evidence of gut mucosal injury(12). However, data for norepinephrine is conflicting in similar animal shock models(12). Specific to phenylephrine administration, a porcine septic peritonitis model showed an increase in jejunal blood flow to the muscularis with no changes in splanchnic gut oxygen extraction before and after phenylephrine administration (12).

Human studies have examined effect of specific vasopressors on gut blood flow as well. In a small study of septic shock patients, data showed despite similar hemodynamic measures in patients receiving dobutamine/norepinephrine and epinephrine alone, those on epinephrine had lower splanchnic blood flow (13). Epinephrine receiving patients also had lower splanchnic oxygen consumption, higher lactates, and lower gastric pH levels. Specific to phenylephrine, a small cardiothoracic ICU trial examined phenylephrine versus norepinephrine (14). Specifically, phenylephrine increased splanchnic oxygen extraction versus norepinephrine, with no difference in jejunal small bowel perfusion. A range of investigators have shown that the administration of vasopressin to patients in septic shock leads to enteric and gastric hypoperfusion (10). Interestingly, most of the cases of EN-related mesenteric ischemia are described in trauma burn and surgery patients fed via jejunostomy tubes (mainly placed surgically) (15).

Recent Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition Guidelines suggest *“Based on expert consensus, we suggest in setting of hemodynamic compromise or instability, EN should be withheld until patient is fully resuscitated and/or stable. Initiation/reinitiation of EN may be considered with caution in patients undergoing withdrawal of vasopressor support.”*(16) The stated concern for feeding on vasopressors is NOBN from feeding that increases gut oxygen demand beyond delivery. As recently reported, the incidence of bowel ischemia and NOBN ranges between 0.3% and 8.5%, with mortality ranging from 46% to 100% (10). Table 1 describes key markers associated with NOBN and bowel ischemia. It is interesting to note, most patients present late in their feeding course, rather than during or following initial resuscitation (10). This is contrary to belief that bowel ischemia occurs at initiation of EN feeds in under-resuscitated shock patients. It also implies patients developing NOBN may have impaired GI mucosal perfusion without demonstrating overt signs of systemic shock. One potential intervention to avoid gut hypoperfusion in the ICU setting may include limiting crystalloid resuscitation. In Surgical Enhanced Recovery Programs (ERAS) this has been thought to minimize bowel edema and may improve gut perfusion (17). Interestingly, most literature reports describe NOBN occurring primarily in post-pyloric small bowel feeding and not gastric-delivered EN(10). The role of monitoring GI residuals in patients receiving early EN when on vasopressors cannot be overstated. Thus, post-pyloric feeding should be avoided and

discouraged in shock patient receiving vasopressors until more data showing safety of this practice are available.

Clinical Data Describing and Defining Potential Safe Feeding Practices on Vasopressors:

A range of recent trials have demonstrated safety and clinical outcome benefit of early EN feeding on vasopressors. These trials also provide guidance on to how to potentially optimize which patients and what vasopressor doses may be more safely fed and which patients should not receive EN while in shock. The primary original trial cited in support of clinical outcomes benefits in patients receiving early EN in vasopressors is the retrospective observational study from Khalid et al (18). This study examined mechanically ventilated ICU patients requiring vasopressors within first 2 days of admission. Patients were divided into those who received EN within 48 hours of start of mechanical ventilation or after 48 hours. There were 707 patients in early EN and 467 in late EN group. Even following correction via multivariate modeling for confounders, hospital mortality was significantly less in ICU patients on vasopressors receiving early EN (18). In fact, patients on multiple vasopressor agents appeared to show greater benefit of receiving early EN. A recent trial by Patel et al retrospectively studied adult medical ICU patients examining role of trophic EN in septic shock patients all receiving vasopressors (19). Trophic feeding was defined as <600 kcal/d (~20 mL/h). After controlling for confounders and multivariate logistic regression, a shorter length of stay and shorter mechanical ventilation time was seen in patients receiving trophic EN versus full EN support *and/or* those on no EN. An additional retrospectively study of 259 adult ICU patients receiving simultaneous vasopressor therapy for at least 1 hour with EN was recently reported(20). Overall, 75% of EN attempts were tolerated. Intolerance events included following key markers: rising lactate >2 mmol/L (50%), positive abdominal radiographs findings or CT scan imaging (18/55 ordered, 32.7%), 1 episodes of GRV > 300 mL (14.5%), 1 vomiting episodes (9%), and 3 episodes of bowel perforation/ ischemia (0.9%). Patients tolerating EN received a lower maximum dose of norepinephrine versus patients not tolerating EN (12.5 vs 19.4 mcg/min)(20). Key factors associated with EN tolerance included vasopressor agents chosen and dose used. Specifically, norepinephrine at <12.5 mcg/min, phenylephrine use, and exclusion of vasopressin and dopamine were associated with EN tolerance. Specific to CT ICU patients with circulatory failure (2 vasopressor agents and/or mechanical circulation support), a recent study looked at EN tolerance. EN was initiated in severely hemodynamically impaired patients with no episodes of mesenteric ischemia complications observed (21). 62% of patients experienced EN-related issues, with 46% being constipation. The authors conclude “that in hemodynamically compromised CT surgery patients, EN is safe, although only 40% of patients reached EN nutrition goals.” A very recent 2017 study by Merchan et al retrospectively examined 120 adult ICU patients with septic shock and on EN (15). 62% of patients tolerated EN successfully. The most common reason for EN intolerance was GRV’s > 250 mL (74%). No mesenteric ischemia was observed. Multivariate analysis demonstrated that in patients with septic shock initiating EN within 48 hours and receiving norepinephrine-equivalent doses of 0.14 mg/kg/min were more likely to tolerate EN. Authors concluded early EN may be tolerated and safely administered in patients with septic

shock who are adequately fluid resuscitated and receive doses of < 0.14 mg/kg/min of norepinephrine equivalents (15). Finally, recently a large health outcomes study showed safety and benefit of early EN (EEN) on vasopressors. This study compared outcomes between EEN and late enteral nutrition (LEN) in ventilated patients with shock requiring low- (<0.1 $\mu\text{g}/\text{kg}/\text{min}$), medium-(0.1 – 0.3 $\mu\text{g}/\text{kg}/\text{min}$), or high-dose (>0.3 $\mu\text{g}/\text{kg}/\text{min}$) norepinephrine(22). 52,563 eligible patients were identified and matched via propensity score matching. The 28-day mortality rate was significantly lower in EEN versus LEN group in the low-dose norepinephrine group (risk-difference, 2.9%; 95% confidence interval [CI], 4.5% to 1.3%) and in the medium-dose norepinephrine group (risk-difference, 6.8%; 95% CI, 9.6% to 4.0%). In the high-dose norepinephrine group, 28-day mortality did not differ significantly between EEN and LEN groups (risk-difference, 1.4%; 95% CI, 7.4%,–4.7%). The authors conclude that results suggest EEN is associated with a reduction in mortality in ventilated adults treated with low- or medium-dose norepinephrine but not high-dose norepinephrine. The one key study which demonstrated concern for bowel ischemia with EN is the NUTRIREA-2 trial (23), in which 2,410 mechanical ventilated adults receiving vasopressor agents were randomized to PN or EN with a goal to achieve early nutrition goals within 24 hours (24). It is key to note the patients received an exceedingly high norepinephrine dose, with a mean of 0.53 $\mu\text{g}/\text{kg}/\text{min}$, a dose that was higher than the exclusion limits for both most similar large nutrition RCTs (including PermiT and EDEN trials). Results showed no differences in primary 28-day mortality or ICU-acquired infections. Unfortunately, a significant increase in bowel ischemia (2% vs $< 1\%$; HR 3.84 [95% CI, 1.43–10.3]; $p = 0.007$), and acute colonic pseudoobstruction (1% vs $< 1\%$; HR 3.7, 95% CI, 1.03–13.2; $p = 0.04$) with EN was observed. This study is the first evidence describing an association of EN with bowel ischemia. The authors conclude full-feeding with EN should be avoided until patients are hemodynamic stable. This trial also implied that early in shock, PN may be a better option versus full dose EN.

In summarizing this data, most all recent studies show EN can be delivered safely to patients on vasopressors. In fact, many studies show an outcome benefit of early EN in ICU patients who are receiving vasopressors. It appears that there are doses of norepinephrine (or equivalent) that are safer, and perhaps beneficial, in which to provide EN. Based on existing data, a suggested this cut-off appears to lay between 0.14 and 0.3 $\mu\text{g}/\text{kg}/\text{d}$ norepinephrine or equivalent. It is also essential to realize that slow advance of trophic feeds, perhaps with maintenance of trophic feeding with supplemental parenteral nutrition until full stability is achieved. Suggestions for safety and optimization of EN delivery in ICU patients receiving vasopressors are summarized in Table 1. Without doubt, patients exhibiting signs of feeding intolerance as described in Table 1 here and patients who are not resuscitated should not receive EN until patient is stabilized further. Future meaningful randomized controlled data is needed in this field as most all existing studies are retrospective observational studies or large health outcome databases trials. However, the reasonably large body of existing data cannot be ignored and can teach us much, especially since virtually all existing data supports safety and benefit to early EN, especially trophic EN, in ICU patients on vasopressors. It is likely the mechanistic explanations for the potential clinical benefits of early EN include both non-nutrition related gut protective pathways (as described previously) and nutritional benefits. In closing, we must continue to look for improved methods to address the silent

epidemic of *preexisting malnutrition in ICU patients- with as many as 1 in 2 (30–50%) patients being malnourished at ICU admission*(24). Further, ubiquitous and unacceptable starvation occurs not just for the early few days ICU patients may be in shock, but for over 10 days in ICU's around the world(25). Thus, it is imperative we look for data-driven methods to feed early and safely rather than additional methods to continue the ongoing iatrogenic starvation of ICU patients worldwide.

Acknowledgments

Financial support and sponsorship: None

Conflicts of Interest: PEW- Has received grant funding related to this work from NIH, Canadian Institutes of Health Research, Abbott, Baxter, Fresenius, and Takeda. Dr. Wischmeyer has served as a consultant to Abbott, Fresenius, Baxter, Cardinal Health, Nutricia, and Takeda for research related to this work. Dr. Wischmeyer has received unrestricted gift donation for surgical nutrition research from Musclesound and Cosmed. Dr. Wischmeyer has received honoraria or travel expenses for CME lectures on improving nutrition care from Abbott, Baxter and Nutricia.

Copyright form disclosure: Dr. Wischmeyer's institution received funding from Abbott, Fresenius, and the National Institutes of Health (NIH); he has received grant funding related to this work from NIH, Canadian Institutes of Health Research, Abbott, Baxter, Fresenius, and Takeda; he has served as a consultant to Abbott, Fresenius, Baxter, Cardinal Health, Nutricia, and Takeda for research related to this work; he has an unrestricted gift donation for surgical nutrition research from Musclesound and Cosmed, he has received honoraria or travel expenses for CME lectures on improving nutrition care from Abbott, Baxter and Nutricia; and he received support for article research from the NIH.

References:

1. Clark JA, Coopersmith CM. Intestinal crosstalk: a new paradigm for understanding the gut as the "motor" of critical illness. *Shock* 2007;28(4):384–393. [PubMed: 17577136]
2. Wischmeyer PE, McDonald D, Knight R. Role of the microbiome, probiotics, and 'dysbiosis therapy' in critical illness. *Curr Opin Crit Care* 2016;22(4):347–353. [PubMed: 27327243]
3. Lubbers T, de Haan JJ, Luyer MD, et al. Cholecystokinin/Cholecystokinin-1 receptor-mediated peripheral activation of the afferent vagus by enteral nutrients attenuates inflammation in rats. *Ann Surg* 2010;252(2):376–382. [PubMed: 20585240]
4. Magnotti LJ, Upperman JS, Xu DZ, et al. Gut-derived mesenteric lymph but not portal blood increases endothelial cell permeability and promotes lung injury after hemorrhagic shock. *Ann Surg* 1998;228(4):518–527. [PubMed: 9790341]
5. Wischmeyer PE. Tailoring nutrition therapy to illness and recovery. *Crit Care* 2017;21(Suppl 3):316. [PubMed: 29297385]
6. McClave SA, Martindale RG, Rice TW, et al. Feeding the critically ill patient. *Crit Care Med* 2014;42(12):2600–2610. [PubMed: 25251763]
7. Krezalek MA, Yeh A, Alverdy JC, et al. Influence of nutrition therapy on the intestinal microbiome. *Curr Opin Clin Nutr Metab Care* 2017;20(2):131–137. [PubMed: 27997410]
8. Gosche JR, Garrison RN, Harris PD, et al. Absorptive hyperemia restores intestinal blood flow during *Escherichia coli* sepsis in the rat. *Arch Surg* 1990;125(12):1573–1576. [PubMed: 2123086]
9. Revelly JP, Tappy L, Berger MM, et al. Early metabolic and splanchnic responses to enteral nutrition in postoperative cardiac surgery patients with circulatory compromise. *Intensive Care Med* 2001;27(3):540–547. [PubMed: 11355123]
10. Bruns BR, Kozar RA. Feeding the Postoperative Patient on Vasopressor Support: Feeding and Pressor Support. *Nutr Clin Pract* 2016;31(1):14–17. [PubMed: 26703957]
11. Piton G, Cypriani B, Regnard J, et al. Catecholamine use is associated with enterocyte damage in critically ill patients. *Shock* 2015;43(5):437–442. [PubMed: 25565647]

12. Krejci V, Hildebrand LB, Sigurdsson GH. Effects of epinephrine, norepinephrine, and phenylephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis. *Crit Care Med* 2006;34(5):1456–1463. [PubMed: 16557162]
13. Meier-Hellmann A, Reinhart K, Bredle DL, et al. Epinephrine impairs splanchnic perfusion in septic shock. *Crit Care Med* 1997;25(3):399–404. [PubMed: 9118653]
14. Nygren A, Thoren A, Ricksten SE. Vasopressors and intestinal mucosal perfusion after cardiac surgery: Norepinephrine vs. phenylephrine. *Crit Care Med* 2006;34(3):722–729. [PubMed: 16505658]
15. Merchan C, Altshuler D, Aberle C, et al. Tolerability of Enteral Nutrition in Mechanically Ventilated Patients With Septic Shock Who Require Vasopressors. *J Intensive Care Med* 2017;32(9):540–546. [PubMed: 27377392]
16. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016;40(2):159–211. [PubMed: 26773077]
17. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg* 2017;152(3):292–298. [PubMed: 28097305]
18. Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *Am J Crit Care* 2010;19(3):261–268. [PubMed: 20436064]
19. Patel JJ, Kozeniecki M, Biesboer A, et al. Early Trophic Enteral Nutrition Is Associated With Improved Outcomes in Mechanically Ventilated Patients With Septic Shock: A Retrospective Review. *J Intensive Care Med* 2016;31(7):471–477. [PubMed: 25315218]
20. Mancl EE, Muzevich KM. Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy. *JPEN J Parenter Enteral Nutr* 2013;37(5):641–651. [PubMed: 23270986]
21. Flordelis Lasierra JL, Perez-Vela JL, Umezawa Makikado LD, et al. Early enteral nutrition in patients with hemodynamic failure following cardiac surgery. *JPEN J Parenter Enteral Nutr* 2015;39(2):154–162. [PubMed: 24096266]
22. Ohbe H, Jo T, Matsui H, et al. 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* 2019.
23. Reignier J, Boisrame-Helms J, Brisard L, 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):133–143. [PubMed: 29128300]
24. Norman K, Pichard C, Lochs H, et al. Prognostic impact of disease-related malnutrition. *Clin Nutr* 2008;27(1):5–15. [PubMed: 18061312]
25. Cahill NE, Dhaliwal R, Day AG, et al. Nutrition therapy in the critical care setting: what is “best achievable” practice? An international multicenter observational study. *Critical Care Medicine* 2010;38(2):395–401. [PubMed: 19851094]

Table 1:

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) lower: < 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 O2-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

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