

Early Enteral Nutrition in Shock: Do the Benefits Outweigh the Risks?

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Disclosure

I do not have any financial relationships or any conflicts of interest to disclose



Learning Objectives

1. Review early enteral feeding strategies in critically ill patients with shock
2. Discuss the risks and benefits of early enteral feedings in shock

Learning Assessment Questions

1. According to the current ASPEN/SCCM and Surviving Sepsis Guidelines, which of the following could be stated regarding enteral nutrition?
 - a) Enteral nutrition should get to goal within 72 hours of ICU admit
 - b) Early enteral nutrition should be initiated within 24-48 hours for patients able to receive enteral nutrition after resuscitation and hemodynamic stability is achieved
 - c) Trophic enteral nutrition should be initiated in septic shock patients during resuscitation to aid with resuscitation efforts
 - d) Enteral nutrition should be held during the first 24-48 hours of ICU admission
2. Which of the following is not considered a benefit of early enteral nutrition in critically ill patients?
 - a) Maintains gut integrity
 - b) Role in reducing insulin resistance
 - c) Reduction of infection
 - d) Increase in lean body mass

Current Guidelines for Nutrition in Sepsis/Septic Shock

Time of Initiation

2016 ASPEN/SCCM Guidelines¹

- ▶ Suggest that critically ill pts receive EN therapy within 24-48 hours of making the dx of severe sepsis/septic shock as soon as resuscitation is complete and the patient is hemodynamically stable. (N1)
- ▶ In the setting of hemodynamic compromise or instability, EN should be withheld until the patient is fully resuscitated and/or stable. Initiation of EN may be considered with caution in pts undergoing withdrawal of vasopressor support. (B5)
- ▶ While EN may be provided with caution to pts on chronic, low doses of vasopressors, EN should be withheld in pts who are hypotensive (MAP < 50 mm Hg), in pts for whom catecholamine agents are being initiated or in pts for whom escalating doses are required to maintain hemodynamic stability. (B5)

2016 Surviving Sepsis Campaign²

- ▶ Suggest the early initiation of EN rather than a complete fast or only IV glucose in critically ill pts with sepsis/septic shock who can be fed enterally. (T3)
- ▶ Current evidence did not specifically address patients with high vasopressor requirements, and the decision about withholding the feeds should be individualized. (T3)

¹SA McClave, BE Taylor, et al (JPEN 2016;40:159-211); ²A Rhodes, LE Evans, et al (Intensive Care Med 2017; 43:304-377)
N1/B5: expert opinion; T3: weak recommendation, low quality of evidence

Current Guidelines for Nutrition in Sepsis/Septic Shock

Trophic vs Full Feeds

2016 ASPEN/SCCM Guidelines¹

- ▶ Suggest the provision of trophic feeding (defined as 10-20 kcal/hr or up to 500 kcal/d) for the initial phase of sepsis, advancing as tolerated after 24-48 hours to >80% of target energy goal over the first week (N4)
 - ▶ Also states 60-70% of target over the first week may be optimal

2016 Surviving Sepsis Campaign²

- ▶ Suggest either early trophic/hypocaloric or early full EN in critically ill pts with sepsis/septic shock. If trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to pt tolerance (T4)
 - ▶ Trophic/hypocaloric defined as 70% or less of standard caloric target goals for at least 48 hr before titrated to goal

¹SA McClave, BE Taylor, et al (JPEN 2016;40:159-211); ²A Rhodes, LE Evans, et al (Intensive Care Med 2017; 43:304-377)
N4: expert opinion; T4: weak recommendation, moderate quality of evidence

Current Guidelines for Nutrition in Sepsis/Septic Shock

EN vs PN

2016 ASPEN/SCCM Guidelines¹

- ▶ Suggest not using exclusive PN or supplemental PN in conjunction with EN early in the acute phase of severe sepsis or septic shock, regardless of pt degree of nutrition risk (N2)

2016 Surviving Sepsis Campaign²

- ▶ Recommend against the administration of early PN alone or PN in combination with EN (but rather initiate early EN) in critically ill pts with sepsis or septic shock who can be fed enterally (T1)
- ▶ Recommend against the administration of PN alone or in combination with EN (but rather to initiate IV glucose and advance EN as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock for whom early EN is not feasible. (T2)

Current Guidelines for Nutrition in Sepsis/Septic Shock

▶ 2017 ESICM Guidelines¹

- ▶ Suggest delaying EN if shock is uncontrolled and hemodynamic and tissue perfusion goals are not reached, but start low dose EN as soon as shock is controlled with fluids and vasopressors/inotropes*
 - ▶ Concern regards applying EN when very high doses of vasopressors are required and hyperlactatemia is persisting or other signs of end organ hypoperfusion are present
- ▶ Suggest delaying EN in uncontrolled life-threatening hypoxemia, hypercapnia, or acidosis, but using early EN in patients with stable hypoxemia, and compensated or permissive hypercapnia and acidosis*

▶ 2013²/2015³ Canadian Guidelines

- ▶ Recommend early enteral nutrition (within 24-48 hours following admission to ICU) in critically ill patients.

¹AR Blaser, J Starkopf, et al (Intensive Care Med 2017; 43:380-398); *conditional recommendation based on expert opinion;

²R Dhaliwal, N Cahill, et al (Nutr Clin Pract 2014;29:29-43); ³criticalcarenutrition.com

Risks of Early Enteral Feeding in Shock

Mesenteric Ischemia

- ▶ In hypotensive state blood is shunted from the gut + pressors increase gut vasoconstriction which increases the risk of nonocclusive mesenteric ischemia (NOMI)
- ▶ Volume resuscitation does not immediately reverse blood flow to the gut
- ▶ Difficult to estimate the risk of intestinal ischemia with different types of vasoactive agents

Bowel Necrosis

- ▶ Nonocclusive bowel necrosis (NOBN): considered rare but high morbidity/mortality so important - most feared!
- ▶ Mostly reported in jejunal feeds



Early EN and GI Complications

NUTRIREA-2 study

- ▶ RCT with 44 French ICUs - EN vs PN in MICU adults with shock on pressors and MV
- ▶ Primary outcome: 28d mortality
- ▶ Nutrition support was started within 24 hours of MV and started at the rate (mL/hr) required to achieve the calorie target on day 1

Baseline	EN (n=1202)	PN (n=1208)
M/F	67% / 33%	67% / 33%
Age	66 ± 14	66 ± 14
BMI	28.0 ± 7.2	27.7 ± 6.8
SOFA	11 ± 3	11 ± 3
Type of Shock	61% sepsis 19% cardiac	64% sepsis 19% cardiac
NE alone	978 (81%)	973 (81%)
Epinephrine alone	43 (4%)	48 (4%)
Dobutamine alone	28 (2%)	37 (3%)
At least 2 pressors	144 (12%)	138 (11%)
NE Dose (µg/kg/min)	0.56 (0.3-1.2)	0.5 (0.25-1.03)

NUTRIREA-2 Results

Results	EN (n=1202)	PN (n=1208)	P value
Daily kcal intake (kcal/kg/d)	17.8 ± 5.5	19.6 ± 5.3	<0.0001
Daily protein intake (g/kg/d)	0.7 ± 0.2	0.8 ± 0.2	<0.0001
Vomiting	406 (34%)	246 (24%)	<0.0001
Diarrhea	432 (36%)	393 (33%)	0.009
Acute Colonic Pseudo-obstruction	11 (1%)	3 (<1%)	0.04
Bowel Ischemia	19 (2%)	5 (<1%)	0.007
28d mortality	443 (37%)	422 (35%)	0.33
ICU mortality	429 (33%)	405 (31%)	0.17
ICU LOS (d)	9 (5-16)	10 (5-17)	0.08

**Impact of
aggressive
EN vs early
EN?**

CALORIES study

RCT with 33 UK adult ICUs - EN vs PN

Baseline/Results	EN (n=1197)	PN (n=1191)	P value
M/F	61% / 39%	58% / 42%	Not stated
Age	62.9 ± 15.4	63.3 ± 15.1	Not stated
BMI	28.2 ± 7.5	27.7 ± 7.4	Not stated
SOFA	9.6 ± 3.3	9.5 ± 3.4	Not stated
High degree of malnutrition	81 (7%)	74 (6.4%)	Not stated
Pts receiving vasoactive agents	1007 (84.6%)	958 (80.9%)	Not stated
30d mortality	409 (34.2%)	393 (33.1%)	0.57
ICU mortality	352 (29.4%)	317 (26.6%)	0.13
ICU LOS (d)	7.3 (3.9-14.3)	8.1 (4-15.8)	0.15
Bowel ischemia	11 (0.9%)	8 (0.7%)	Not stated

Tolerance of Early EN in Shock+Pressors

- ▶ Tolerability of EN by Merchan, et al 2017¹
 - ▶ Retrospective - vent, septic shock on a pressor. n=150
 - ▶ 62% tolerated EN (primary outcome). No reports of mesenteric ischemia
 - ▶ Median EN in tolerance group: 16 (11-24) kcal/kg/d
 - ▶ Pts who tolerated were more likely to have EN initiated within 48 hours and NE dose $\leq 0.14 \mu\text{g}/\text{kg}/\text{min}$
- ▶ Tolerability of EN by Mancl, et al 2013²
 - ▶ Retrospective - EN + pressors >1hr, multiple types of shock. n=259
 - ▶ Overall tolerability 74.9%; 3 episodes of bowel ischemia or perforation (0.9%)
 - ▶ Mean EN in tolerance group: 22 (16-28) kcal/kg/d
 - ▶ Pts who tolerated had a NE dose $\leq 0.157 \mu\text{g}/\text{kg}/\text{min}$
 - ▶ Inverse relationship between max NE dose and EN tolerability; those who tolerated EN were less likely to have received dopamine or vasopressin

Risks of Early Enteral Feeding in Shock

Overfeeding

- ▶ Early phase of sepsis brings a massive catabolic response
 - ▶ Can generate 50-75% of glucose needs during illness - not suppressed by feeding or IV glucose¹
 - ▶ Not a hypermetabolic response - the more severe the septic shock, the lower the REE as the body hibernates and reduces metabolism²
- ▶ Overfeeding in ICU pts can occur when EN is added to hepatic endogenous glucose production²
- ▶ Overfeeding + altered glycogen metabolism and profound insulin resistance can lead to hyperglycemia → impaired immune function → increased risk of infection³
 - ▶ Hyperglycemia = Independent predictor of adverse outcomes in critically ill pts

¹P Wischmeyer (Crit Care Clin 2018;34:107-125); ²V Fraipont, JC Preiser (J Parenter Enteral Nutrition 2013; 37(6)705-713);

³JA Englert, AJ Rogers (Clin Chest Med 2016;37(2):321-331)

Nutritional Benefits of Early EN

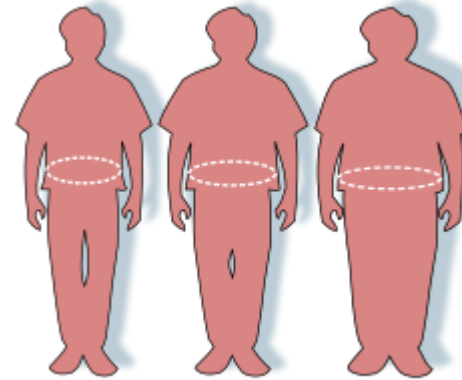
- ▶ Provision of energy, protein, micronutrients, antioxidants
- ▶ Maintain LBM, stimulate protein synthesis, enhance muscle function and mobility

Benefit is seen the most in high risk patients

- ▶ Greater risk for malnutrition in sepsis pts
 - ▶ Early phase of sepsis contributes to rapid loss of LBM → muscle wasting and weakness
 - ▶ ASPEN/SCCM Guidelines¹: “The combination of compromised GI function and hypermetabolism from an exaggerated acute phase response likely leads to a greater risk for malnutrition in this subpopulation of critically ill patients. Nutrition therapy, therefore, would be expected to offer a benefit for improved clinical outcomes”
 - ▶ Surviving Sepsis Campaign²: “Critical illness is associated with loss of skeletal mass it is possible that not administering adequate protein may lead to challenges weaning from the ventilator and more general weakness”

Nutrition Risk/Malnutrition

- ▶ NUTRIC, NRS 2002, NFPA, CT LBM analysis
- ▶ Nutritional status + disease severity
- ▶ High nutrition risk more likely to benefit from early EN with improved outcome than low nutrition risk¹
 - ▶ Reduced mortality and nosocomial infection



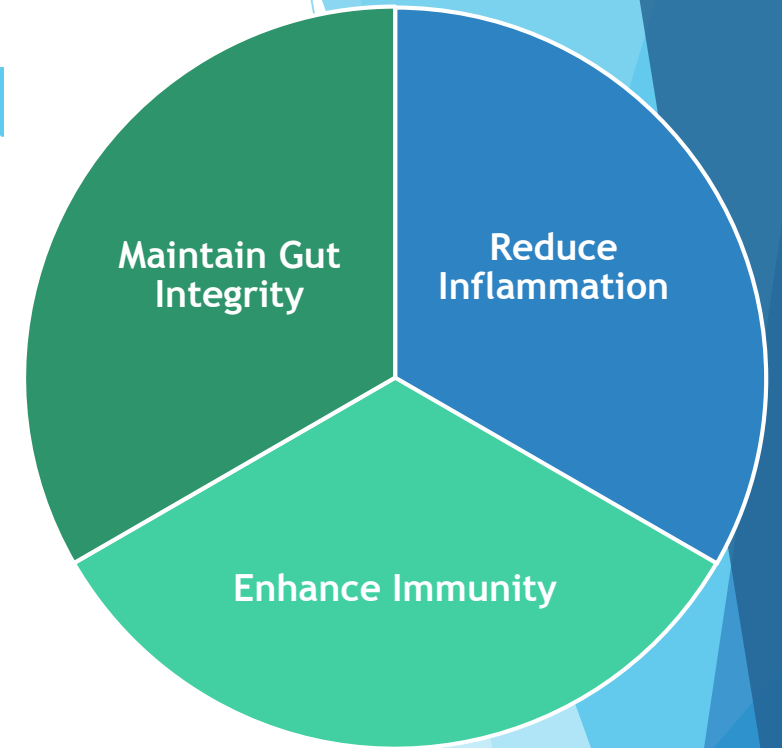
Mortality in higher risk critically ill pts²

- ▶ 202 ICUs, observational study
- ▶ Greater nutrition intake is associated with lower mortality and faster time to discharge alive in high risk, longer stay patients but not low risk patients

¹SA McClave, BE Taylor, et al (JPEN 2016;40:159-211); ²AC Compher, J Chittams, et al (Crit Care Med 2017;45:156-163)

Non-Nutritional Benefits of Early EN

- ▶ Maintain Gut Integrity and & Support Gut Microbiome
 - ▶ Decrease gut permeability
 - ▶ Increase gut absorptive capacity, gut motility and contractility
 - ▶ Support commensal bacteria
- ▶ Reduce Inflammation
 - ▶ Attenuate oxidative stress
 - ▶ Reduce gut/lung axis of inflammation
- ▶ Preserve and Enhance Immunity
 - ▶ Maintain MALT tissue and increase secretory IgA
 - ▶ Increase anti-inflammatory Th-2 response
 - ▶ Preserve enterocyte function, reducing infectious complications
 - ▶ Increase in incretin, reduce insulin resistance and hyperglycemia



May be able to get with just trophic TF

Early EN Outcomes

- ▶ Early EN in vasopressors and MV
 - ▶ Prospective, multi-institutional MICU
 - ▶ Early EN within 48 hrs of MV (n=707); remainder of patients were late EN (n=467)
 - ▶ Early EN: Decreased ICU mortality (22.5% vs 28.3%, $p = .03$) and decreased hospital mortality (34% vs 44%, $p < .001$)
 - ▶ Benefit more evident in the sickest patients: on multiple pressors and those without early improvement who required pressors for longer than 2 days
 - ▶ Not reported: BMI, dose of vasopressors, amount of feeding provided, rate of advancement of feeding, or occurrence of bowel ischemia

How Much is Needed for Benefit?

Early Trophic EN in MV + septic shock

Baseline/Results	No EN (n=15)	<600 kcal/d (n=37)	≥600 kcal/d (n=14)	P value
M/F	53% / 47%	68% / 32%	57% / 43%	0.57
Age	59 (35-64)	58 (48-76)	50 (37-75)	0.53
BMI	28 (25-40)	26 (22-35)	25 (23-46)	0.57
APACHE	21 (16-27)	23 (18-28)	21 (15-24)	0.36
Multiple pressors	40%	13.5%	21.4%	Not stated
ICU LOS	12 (7-30)	5 (5-11)	13 (7-20)	<0.025
Days on MV	7 (5-27)	3 (2-4)	7.5 (3-15)	<0.025
Mortality	33.3%	21.6%	21.4%	0.64
Ischemia/Necrosis	0	0	0	N/A

How Much is Needed for Benefit?

- ▶ EAT-ICU Trial¹
 - ▶ RCT n=199; BMI 22 kg/m². On MV, expected to stay in ICU >3d
 - ▶ 100% of REE on day one vs gradual increase via EN ± PN; full protein for both groups
 - ▶ No difference in outcomes when 60% or 90% REE during first 7 days in ICU

- ▶ REE in Critically Ill²
 - ▶ Retrospective n=6994; BMI 28 kg/m²
 - ▶ 70% of REE reduced mortality; >70% increased mortality, LOS, and length of MV; <70% also increased mortality
 - ▶ Higher protein intake decreased mortality



How Much is Needed for Benefit?

▶ EDEN trial¹

- ▶ RCT n=1000. BMI 30 kg/m². Pts with ARDS, many had sepsis (pressor use in ~38%)
- ▶ Trophic or full enteral feeds for first 6 days (400 kcal vs 1300 kcal)
- ▶ No difference in MV, infectious complications, 60 day mortality, or physical/cognitive fxn 1 year after D/C

▶ PERMIT Trial²

- ▶ RCT n=894; BMI 29 kg/m²
- ▶ Permissive underfeeding (40-60%) vs standard (70-100%) however full protein - no difference in 90d mortality



Limitations

- ▶ Limitations of research studies/research needed
 - ▶ No studies found comparing early with delayed EN in shock
 - ▶ Sepsis/shock typically happens in conjunction with other illnesses
 - ▶ Often those receiving high dose pressors and malnourished pts are excluded from studies
- ▶ Data can be difficult to interpret
 - ▶ We're improving critical care - innovations in ICU care have led to [almost yearly] reduction of hospital mortality from sepsis¹
 - ▶ Do we need to look at calories and protein separately?
 - ▶ Poor outcomes in septic shock patients could be due to severity of illness vs early EN

As always...“more research needed”

¹P Wischmeyer (Crit Care Clin 2018;34:107-125)

Surviving Sepsis Campaign:

“There is insufficient evidence to confirm that a trophic/hypocaloric feeding strategy is effective and safe in patients who are malnourished (body mass index <18.5) because these patients were either excluded or rarely represented in the clinical trials from our systematic review. Until further clinical evidence is generated for this subpopulation, the clinician may consider titrating enteral feeds more aggressively in accordance with patient tolerance while monitoring for re-feeding syndrome.”



Where Do We Go From Here?

- ▶ Early EN when stable: low to moderate doses of vasopressors, doses stable or decreasing
- ▶ Slow ramp up over the first week (or the early acute phase of critical illness)
 - ▶ Able to closely monitor tolerance
 - ▶ Avoid overfeeding
 - ▶ Obtain trophic benefits without aggressive nutrition support
 - ▶ Trophic/underfeeding have similar outcomes to full feeding and may actually have better outcomes for low nutrition risk septic shock patients
- ▶ Avoid early EN in unstable hemodynamics, high or escalating doses of vasopressors, conditions that compromise mesenteric blood flow, worsening lactic acidosis, s/s of GI intolerance
- ▶ Consider titrating EN more quickly in high nutrition risk patients who are stable



Learning Assessment Questions

1. According to the current ASPEN/SCCM and Surviving Sepsis Guidelines, which of the following could be stated regarding enteral nutrition?
 - a) Enteral nutrition should get to goal within 72 hours of ICU admit
 - b) Early enteral nutrition should be initiated within 24-48 hours for patients able to receive enteral nutrition after resuscitation and hemodynamic stability is achieved
 - c) Trophic enteral nutrition should be initiated in septic shock patients during resuscitation to aid with resuscitation efforts
 - d) Enteral nutrition should be held during the first 24-48 hours of ICU admission

Answer B is correct. Both the current ASPEN/SCCM and Surviving Sepsis Guidelines recommend initiation of early enteral nutrition provided that the septic shock patient is resuscitated and hemodynamically stable.

Learning Assessment Questions

2. Which of the following is not considered a benefit of early enteral nutrition in critically ill patients?
- a) Maintains gut integrity
 - b) Role in reducing insulin resistance
 - c) Reduction of infection
 - d) Increase in lean body mass

Answer D is correct. Enteral nutrition aids in the maintenance of gut integrity, modulation of metabolic responses that may reduce insulin resistance, and has been shown to decrease infection. Early enteral nutrition is not designed to increase lean body mass in a critically ill patient.