

Pressing On: Navigating Enteral Nutrition and Vasopressors in the ICU



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Disclosures

- No commercial relationships to disclose

Learning Objectives

- Discuss the guidelines for safe initiation of enteral nutrition in ICU patients receiving vasopressors
- Address the myths surrounding enteral nutrition in ICU patients receiving vasopressors
- Describe strategies for monitoring enteral nutrition tolerances in ICU patients requiring vasopressors
- Discuss the potential complications associated with vasopressors used in patients receiving enteral nutrition

Patient Case - DH



- ICU admission diagnosis:
 - Cardiogenic shock
- HPI:
 - 56M with hx of HTN, HLD, DM, CAD, and CHF who presented to OSH with acute decompensated HF exacerbation and sepsis secondary to likely legionella pneumonia. Escalating oxygenation and pressor/inotrope requirements led to intubation
- Current medications (ICU day 3):
 - Piperacillin-tazobactam, 4.5 g, intravenous, q8h
 - Epinephrine, 0.25 mcg/kg/min
 - Norepinephrine, 0.12 mcg/kg/min
 - Vasopressin, 0.04 Units/min
- Consult to initiate enteral nutrition (EN)



Is it safe to feed?

EN in Hemodynamically Unstable Patients

Clinical Guidelines

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.)

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for Parenteral and Enteral Nutrition
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Question: Is EN safe during periods of hemodynamic instability in adult critically ill patients?

“ **B5. Based on expert consensus, we suggest that in the setting of hemodynamic compromise or instability, EN should be withheld until the patient is fully resuscitated and/or stable. Initiation/reinitiation of EN may be considered with caution in patients undergoing withdrawal of vasopressor support.** ”

EN in Hemodynamically Unstable Patients

DOI: 10.1002/jpen.2267

CLINICAL GUIDELINES



Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and Enteral Nutrition

Charlene Compher PhD, RD¹ | Angela L. Bingham PharmD^{2,3} | Michele McCall MSc, RD⁴ | Jayshil Patel MD⁵ | Todd W. Rice MD, MSc⁶ | Carol Braunschweig PhD⁷ | Liam McKeever PhD, RDN⁷

- EN-related clinical outcomes were assessed for:
 - Higher or lower energy dose
 - Higher or lower protein dose
 - Exclusive isocaloric EN vs. PN
 - EN alone vs. supplemental PN + EN

EN in Hemodynamically Unstable Patients

CONSENSUS STATEMENT



When is enteral nutrition indicated?

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5. When to initiate early EN in hemodynamically unstable patients?

A. Vasopressor administration is not a contradiction to providing early EN with careful monitoring.

Safe EN Initiation and Vasopressors

- Factors to be considered:
 - Type of vasopressor agent(s)
 - Dosage of vasopressor agent(s)
 - Time of EN initiation
 - Feeding tube location
 - EN formula recommendation
 - Ongoing monitoring

Safe EN Initiation and Vasopressors

- Factors to be considered:
 - **Type of vasopressor agent(s)**
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Vasopressors 101: Type

Agents	 Receptor Profile Receptor location & hemodynamic effect with agonists 					
	V1 Vascular ↑ Constriction	V2  Kidney Fluid Retention	α-1  Vasculature ↑ Constriction ↑ SVR/MAP	β-1  Myocardium ↑ Chronotropy ↑ Inotropy	β-2  Pulmonary ↑ Bronchodilation	dopamine  Vascular & Kidney ↑ Dilation ↓ SVR/MAP
Norepinephrine	-	-	+++++	+++	+	-
Epinephrine	-	-	+++	++++	+++	-
Phenylephrine	-	-	+++++	-	-	-
Vasopressin	+++	+++	-	-	-	-
Dopamine*	**Shunt blood to the heart away from other organs like the gastrointestinal (GI) tract**					
2-5 mcg/kg/min	-	-	-	+	-	+++
5-10 mcg/kg/min	-	-	++	+++	++	+++
> 10 mcg/kg/min	-	-	+++	+++	+	++

*Inotropic agent, but consider as vasopressor when ≥ 5 mcg/kg/min for EN initiation

- = no significant receptor affinity; + through +++++ = minimal to maximal receptor affinity

Shi R, et al. *Ann Transl Med*. 2020;8(2):794-803.

<https://www.studyph.com/nclex-pharmacology-vasopressors-and-inotropes-cheat-sheet/>

Vasopressors 101: Their Effects

Agents	CO/CI	SVR	MAP	GI Blood Flow
Norepinephrine	↑↓	↑↑	↑↑	↓
Epinephrine	↑↑	↑	↑↑	↓
Phenylephrine			↑	↓
Vasopressin	↓	↑↑	↑↑	↓
Dopamine				
2-5 mcg/kg/min	-	-	-	↓
5-10 mcg/kg/min	↑	↑	↑	↓
> 10 mcg/kg/min	↑	↑	↑	↓

CI: cardiac index; CO: cardiac output; GI: gastrointestinal; MAP: mean arterial pressure; SVR: systemic vascular resistance

↓ GI blood flow → necrosis (~1%)

Vasopressors 101: Type

Septic Shock	Surgical ICU	Medical ICU	Cardiovascular ICU
First line	Norepinephrine	Norepinephrine	Norepinephrine
Second line	Vasopressin	Vasopressin	Dobutamine
Refractory	Epinephrine	Dobutamine	Vasopressin

Vasopressors	GI Blood Flow	Inotropic Agents	GI Blood Flow
Norepinephrine	↓	Dobutamine	↑
Vasopressin	↓	Milrinone	↑
Epinephrine	↓	Dopamine (low dose: 3-5 mcg/kg/min)	↑

Safe EN Initiation and Vasopressors

- Factors to be considered:
 - Type of vasopressor agent(s)
 - **Dosage of vasopressor agent(s)**
 - Time of EN initiation
 - Feeding tube location
 - EN formula recommendation

Vasopressors 101: Dosage

Medication	Dosing Unit	Initial Dose	Typical Dose Range
Norepinephrine	mcg/kg/min	0.01 to 0.04	0.04 to 1
Epinephrine	mcg/kg/min	0.02 to 0.05	0.005 to 0.2
Phenylephrine	mcg/kg/min	0.1 to 0.3	0.1 to 1.5
Vasopressin	<u>units/min</u>	0.01 to 0.03	0.01 to 0.04
Dopamine	mcg/kg/min	2 to 5 3 to 10 (inotropic) > 10 (vasopressor)	2 to 20

Vasopressors 101: Norepinephrine Dose Equivalent

Vasopressor Conversion Ratios			
Vasopressor	Range of Ratios	Suggested Ratio	Equivalent Dose
Norepinephrine	1	1	0.1mcg/kg/min
Epinephrine	0.7-1.4	1	0.1mcg/kg/min
Vasopressin	0.3-0.4	0.4	0.04U/min
Dopamine	75.2-144.4	100	10mcg/kg/min
Phenylephrine	1.1-16.3	10	1mcg/kg/min
Angiotensin II	0.07-0.13	0.1	0.01ug/kg/min

Norepinephrine Dose Equivalent = norepinephrine +
epinephrine +
vasopressin x 2.5 +
dopamine ÷ 100 +
phenylephrine ÷ 10 +
angiotensin II x10

Back to DH – ICU Day 3



- What is DH's Norepinephrine Dose Equivalent?
 - Epinephrine, 0.25 mcg/kg/min
 - Norepinephrine, 0.12 mcg/kg/min
 - Vasopressin, 0.04 Units/min



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Norepinephrine Dose Equivalent Calculation

- Pre-built Excel Sheet

Norepinephrine Dose Equivalent Calculation				
Norepinephrine (mcg/kg/min)		x	1 =	0
Epinephrine (mcg/kg/min)		x	1 =	0
Vasopressin (Unit/min)		x	2.5 =	0
Dopamine (mcg/kg/min)		÷	100 =	0
Phenylephrine (mcg/kg/min)		÷	10 =	0
Angiotensin II (ug/kg/min)		x	10 =	0
			Sum	0

OpenEvidence®

calculate norepinephrine dose equivalent for ...

>

Back to DH – ICU Day 3

OpenEvidence®

calculate norepinephrine dose equivalent for Epinephrine, 0.25 mcg/kg/min
Norepinephrine, 0.12 mcg/kg/min
Vasopressin, 0.04 Units/min



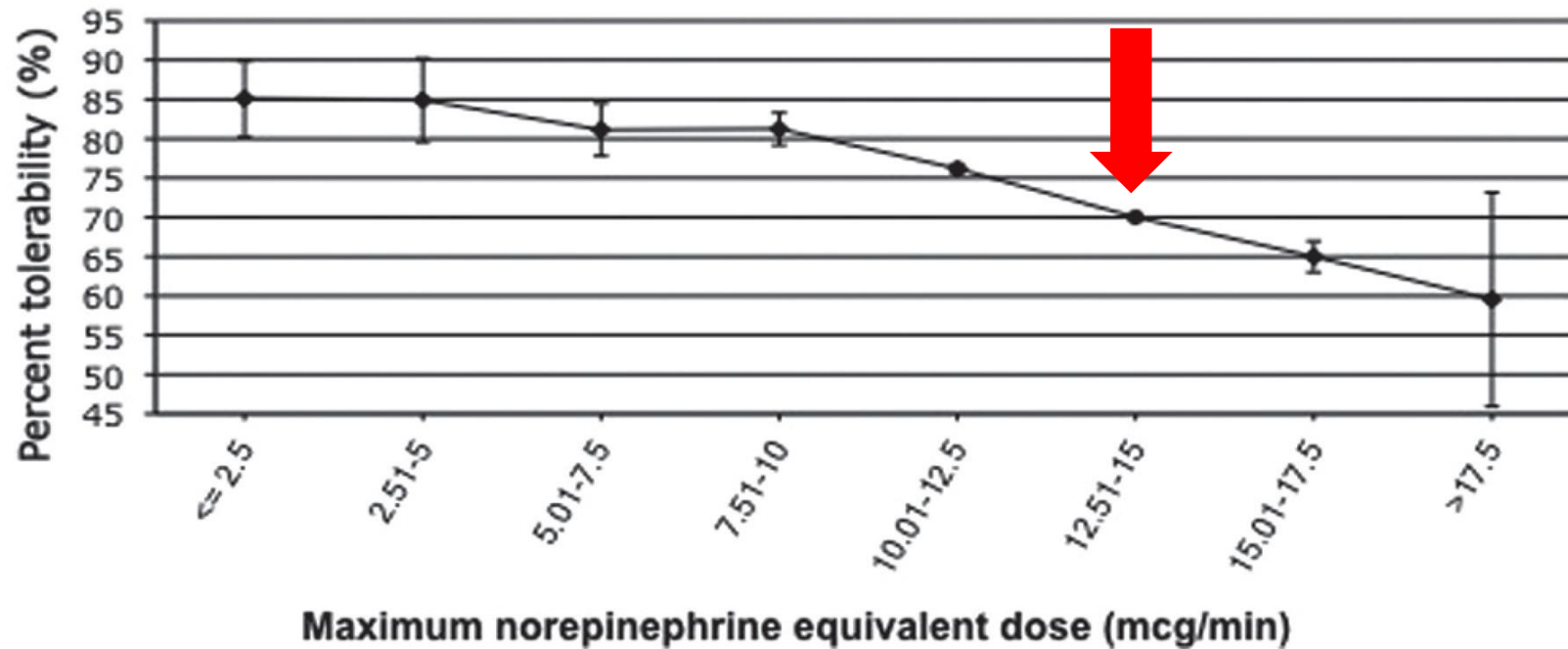
Plugging these values into the formula:

$$NEE = 0.12 + 0.25 + (0.04 \times 2.5) = 0.12 + 0.25 + 0.10 = \mathbf{0.47 \text{ mcg/kg/min}}$$

This calculation provides a standardized way to compare total vasopressor support, as recommended in the critical care literature. The Surviving Sepsis Campaign, published by the Infectious Diseases Society of America and the Society of Critical Care Medicine, also recognizes the need for such standardization in reporting vasopressor dosing in shock management.^[3]

Filters		Export	
Vasopressor	Dose	Norepinephrine Equivalent Contribution (mcg/kg/min)	References
Epinephrine	0.25 mcg/kg/min	0.25	[1-2]
Norepinephrine	0.12 mcg/kg/min	0.12	[1-2]
Vasopressin	0.04 units/min	0.10 (0.04 × 2.5)	[1-2]
Total NEE		0.47	[1-2]

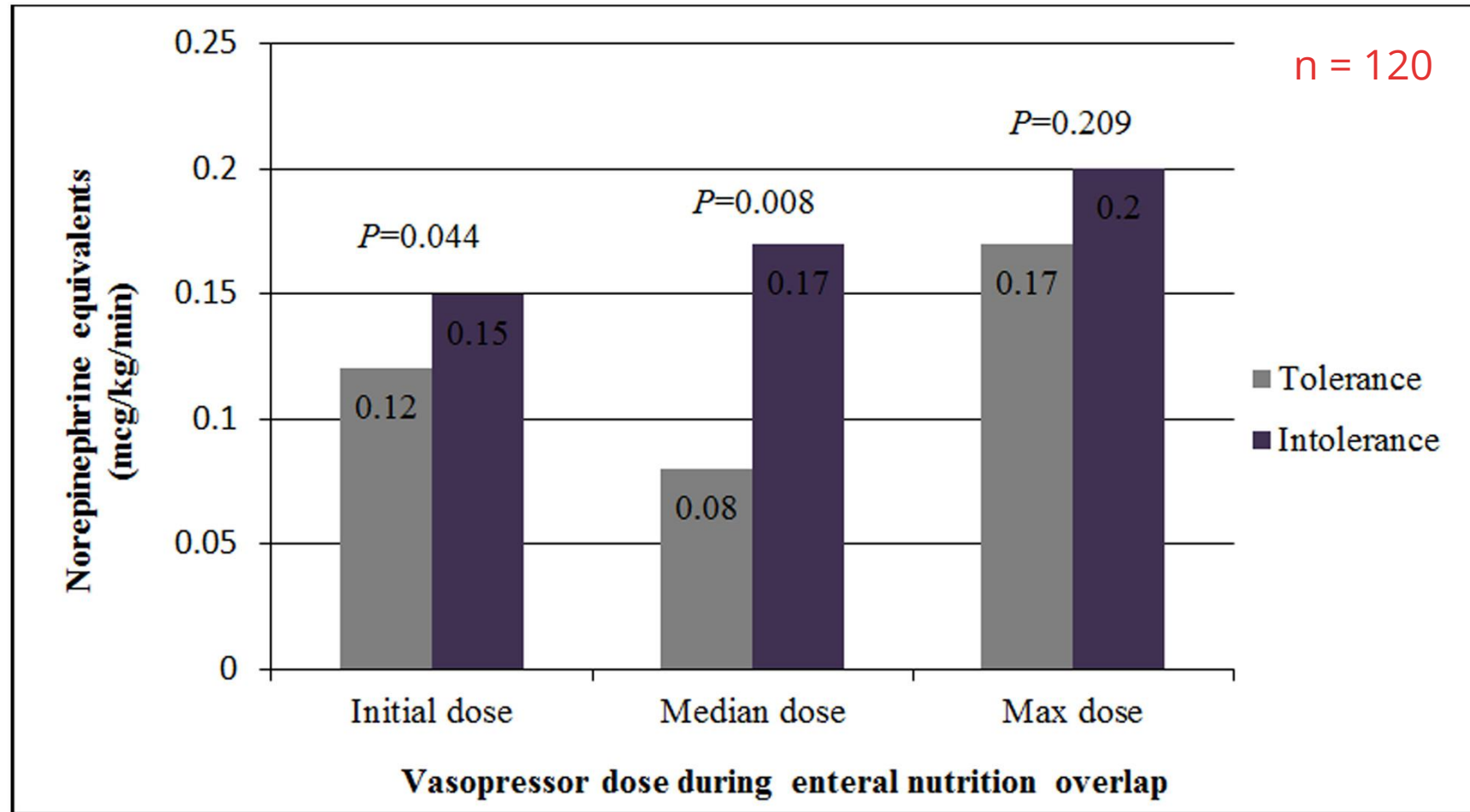
EN Tolerability and Vasopressor Dosage Impact



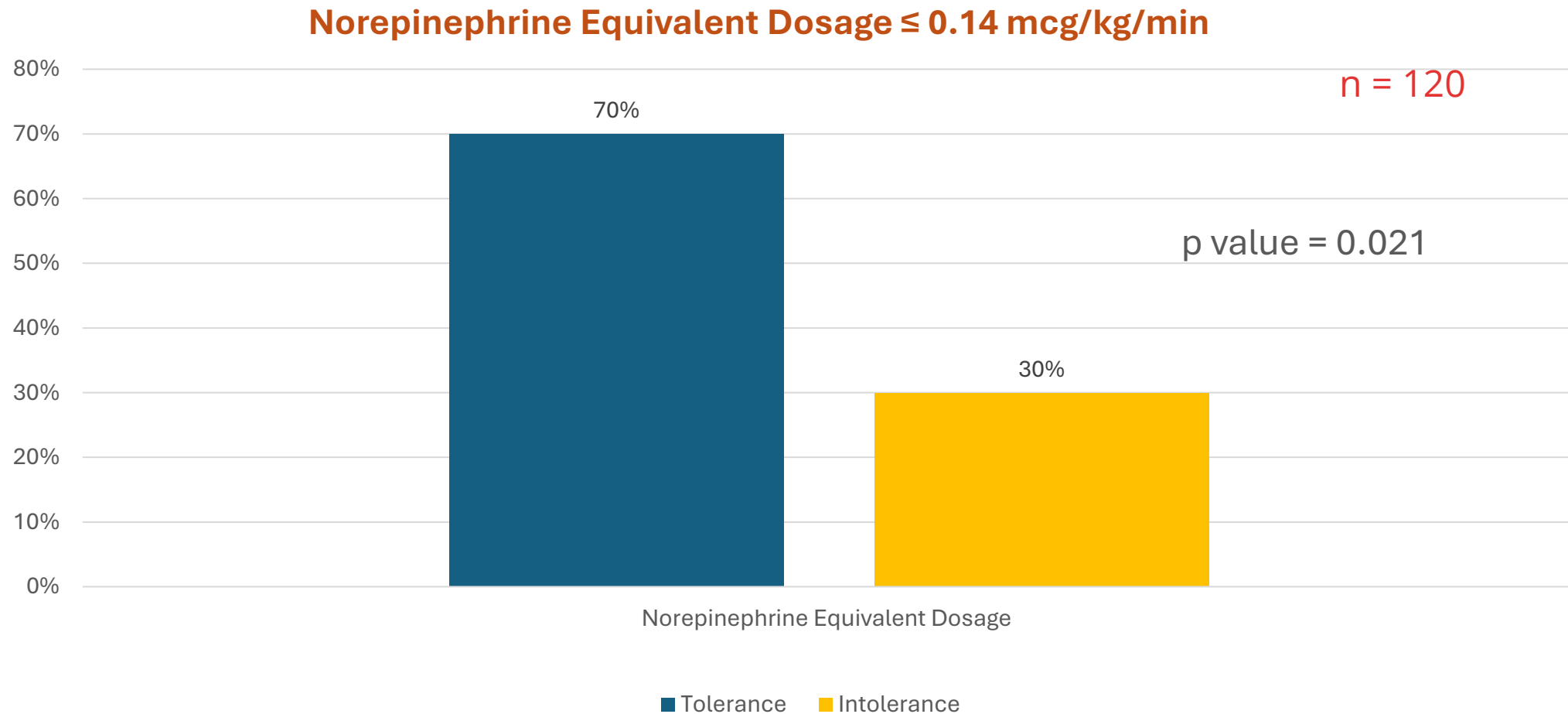
**Maximum
norepinephrine
equivalent dose:
12.5 vs. 19.4 mcg/min
(p = 0.0009)**

- EN is safe and well tolerated in patients receiving vasopressor equivalent to ≤ 12.5 mcg/min of norepinephrine

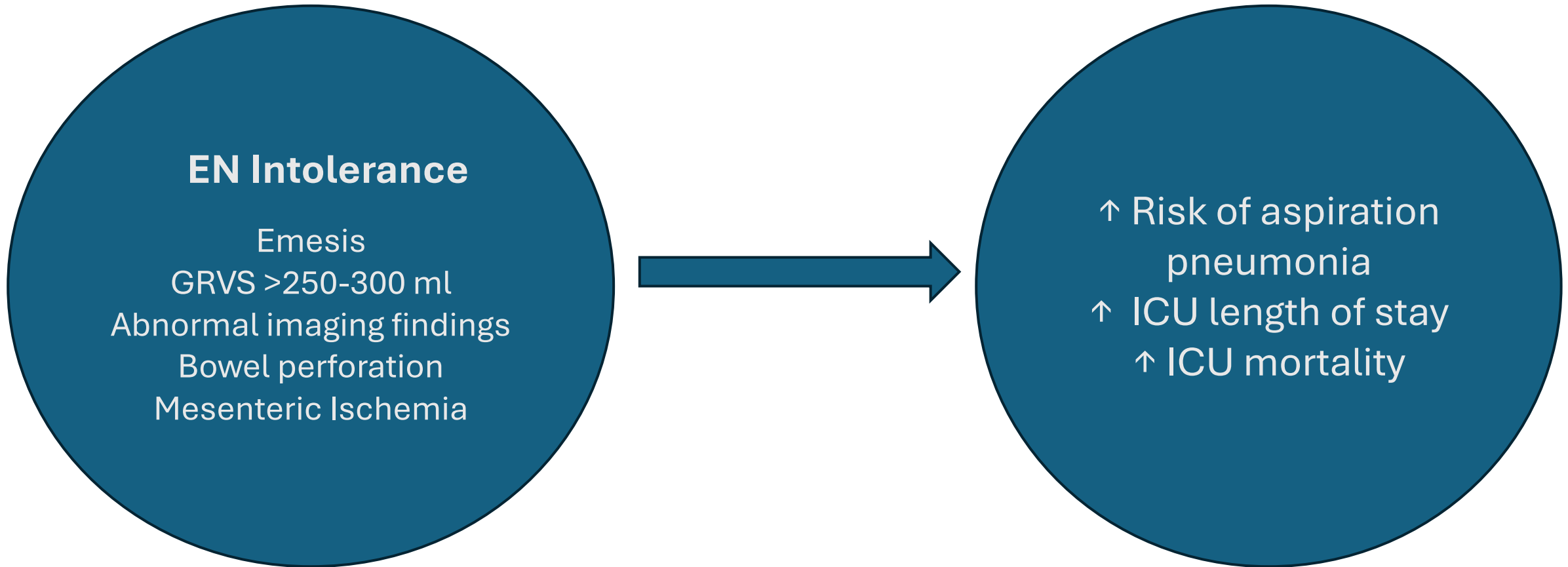
EN Tolerability and Vasopressor Dosage Impact



EN Tolerability and Vasopressor Dosage Impact



Vasopressor Dosages and EN Tolerance



Bowel Ischemia and Vasopressor

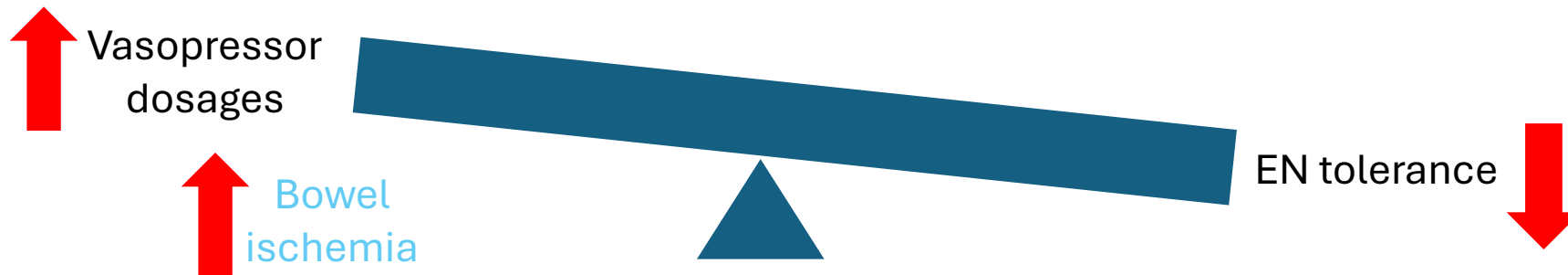
Trial	Outcome	EN (20-25 kcal/kg/day) (n = 1202)	PN (20-25 kcal/kg/day) (n = 1208)	P- value
NUTRIREA-2 (n = 2410)	Bowel ischemia	1.6%	0.4%	0.007

Trial	Outcome	Low Calorie (6 kcal/kg/day) (n = 1521)	Standard Calorie (25 kcal/kg/day) (n = 1515)	P- value
NUTRIREA-3 (n = 3036)	Bowel ischemia	0.9%	1.8%	0.030

- Potential factors leading to bowel ischemia:
 - High median vasopressor dose: ≥ 0.5 mcg/kg/min
 - Rapid EN rate titration
 - Lack of consistent safety monitoring

Vasopressors 101: Dosage and EN Summary

	Reported Dose (based on norepinephrine equivalent dose)
Safe and well-tolerated	≤ 12.5 mg/min
More likely tolerated	≤ 0.14 mcg/kg/min
↑ Bowel ischemia	≥ 0.5 mcg/kg/min



Merchan C, et al. *J Intensive Care Med*. 2017;32(9):540-546.

Mancl EE et al. *JPEN J Parenter Enteral Nutr*. 2013;37(5):641-651.

Patel JJ, et al. *Curr Opin Crit Care*. 2024;30:165-171.

Bechtold ML, et al. *JPEN J Parenter Enteral Nutr*. 2022;46(7):1470-1496

Back to DH – ICU Day 3



- DH's Norepinephrine Dose Equivalent: 0.47 mcg/kg/min
VS.
- **“Safe” Norepinephrine Equivalent Dosage ≤ 0.14 mcg/kg/min**

NOT likely to tolerate EN



When should we feed?

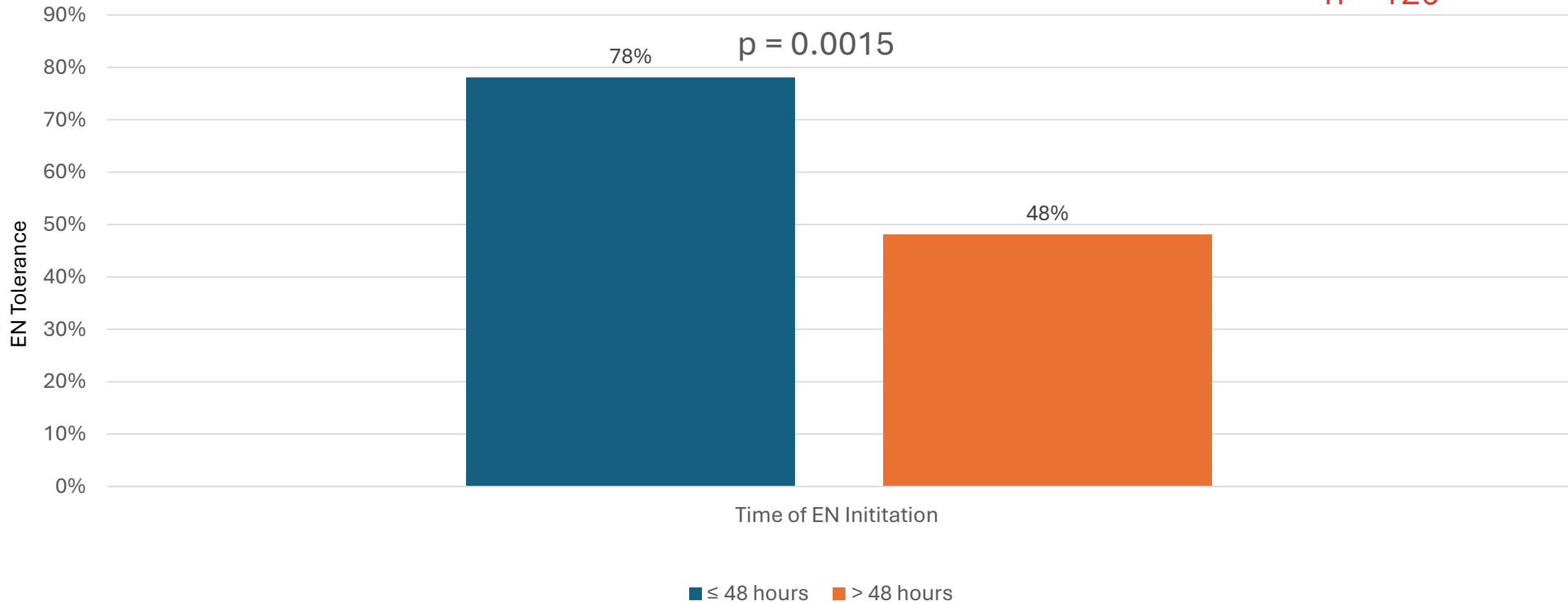
Safe EN Initiation and Vasopressors

- Factors to be considered:
 - Type of vasopressor agent(s)
 - Dosage of vasopressor agent(s)
 - **Time of EN initiation**
 - Feeding tube location
 - EN formula recommendation
 - Ongoing Monitoring

Timing of EN Initiation and Vasopressors

Norepinephrine-equivalent doses ≤ 0.14 mcg/kg/min

n = 120



Vasopressor Dose Equivalent Calculation

- VDE score is the sum of:

Agents	Dose	Multiplier
Norepinephrine	mcg/kg/min	x100
Epinephrine	mcg/kg/min	x100
Phenylephrine	mcg/kg/min	x10
Vasopressin	U/min	x250
Dopamine	mcg/kg/min	x1
Angiotensin II	mcg/kg/min	X1000

- If VDE score >12, consider:
 - *Trophic feed only (e.g., 10 ml/hr) **OR***
 - *Hold EN*

Timing of EN Initiation and Vasopressors

- Initiate EN within 48 hours of ICU admissions if patients are:
 - With controlled shock requiring small or moderate doses of vasopressor
 - $\text{MAP} \geq 60 \text{ mm Hg}$
 - Low-dose EN
- Within 48 hours of vasopressor initiation based on dosage
 - Vasopressor Dose Equivalent (VDE) score <12

$$\text{MAP} = 2/3(\text{DBP}) + 1/3 (\text{SBP})$$

Normal range: 80 to 100 mm Hg

Timing of EN Initiation and Vasopressors

- Delay or hold EN if patients are:
 - Actively being resuscitated or are unstable
 - VDE score >12:
 - Hold EN
 - MAP < 50 mm Hg
 - Hold EN

MAP = $\frac{2}{3}(\text{DBP}) + \frac{1}{3}(\text{SBP})$
Normal range: 80 to 100 mm Hg

Back to DH – ICU Day 3

- What is DH's VDE?
 - Epinephrine, 0.25 mcg/kg/min
 - Norepinephrine, 0.12 mcg/kg/min
 - Vasopressin, 0.04 Units/min



Back to DH – ICU Day 5 & 6



- DH's Vasopressor doses update
 - Epinephrine, **0.1** mcg/kg/min
 - Norepinephrine, **0.02** mcg/kg/min
 - Vasopressin, 0.04 Units/min
- Norepinephrine dose equivalents (or VDE): 0.22 mcg/kg/min (22)
- MAP: 65 mm Hg

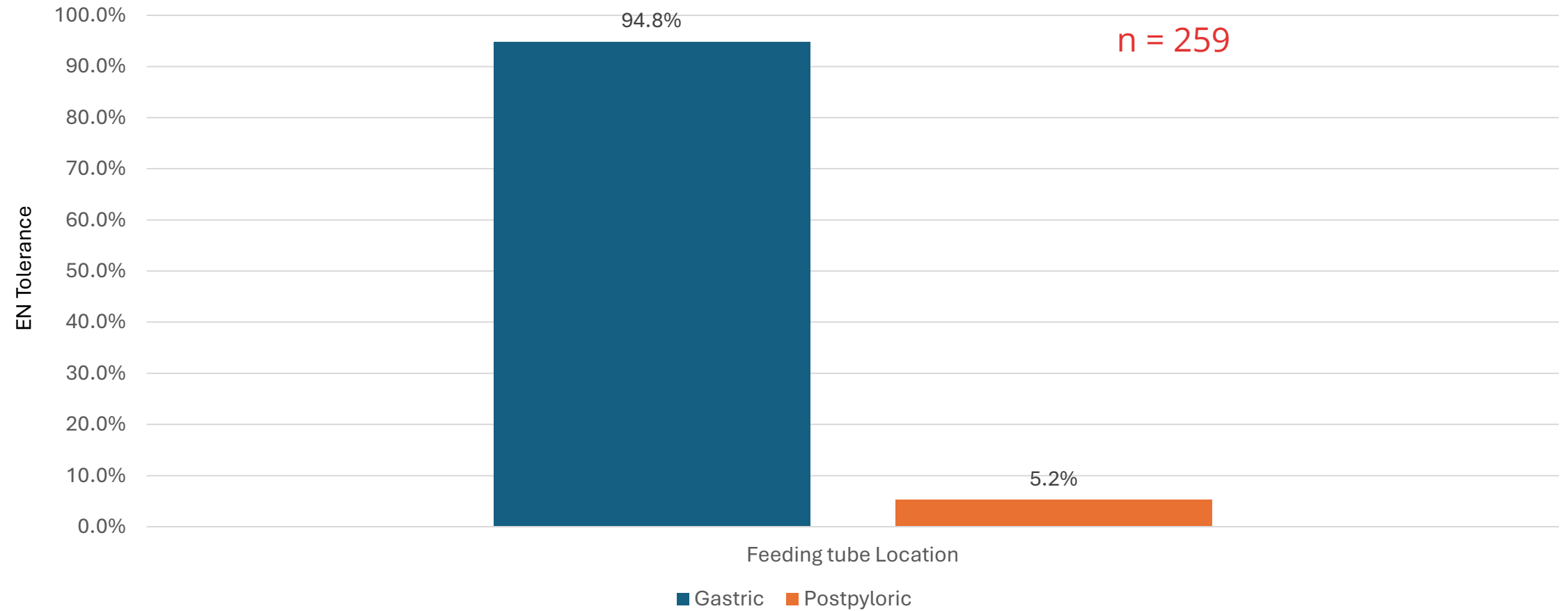
Which of the following is the most appropriate action regarding EN initiation for DH?



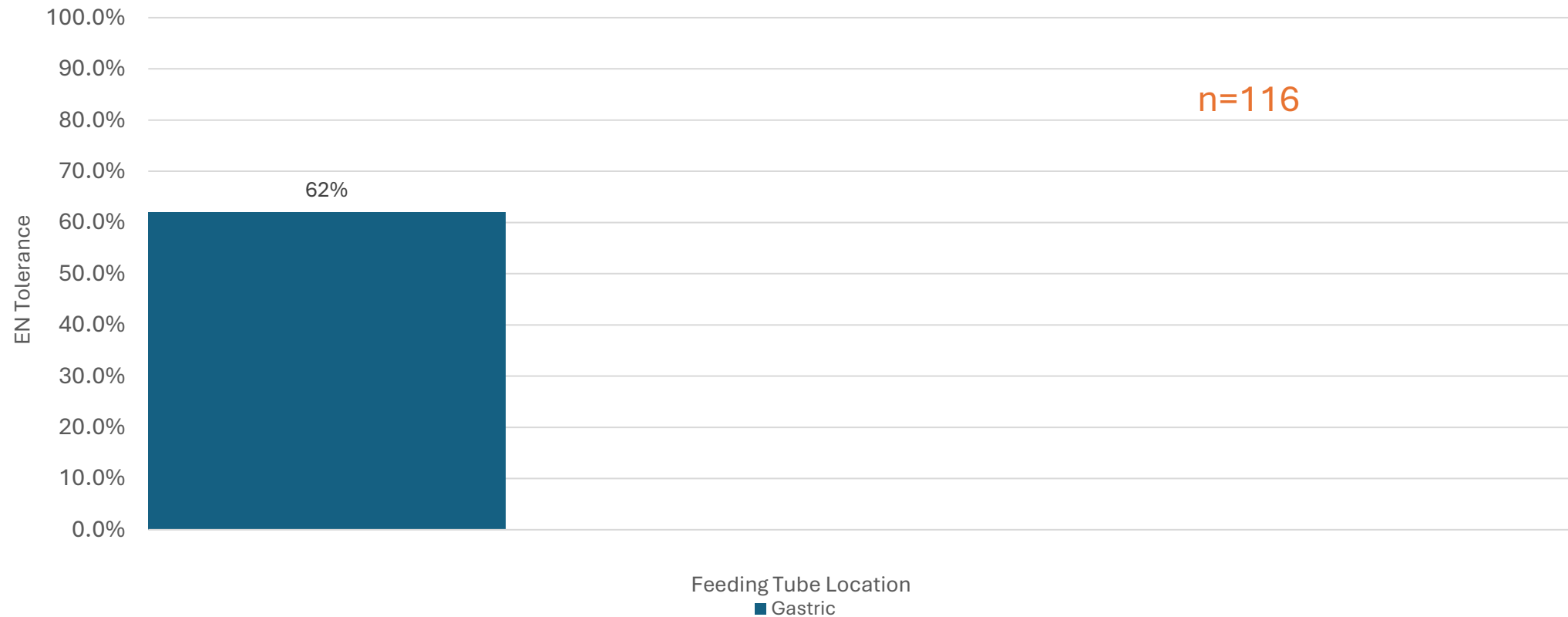
Safe EN Initiation and Vasopressors

- Factors to be considered:
 - Type of vasopressor agent(s)
 - Dosage of vasopressor agent(s)
 - Time of EN initiation
 - **Feeding tube location**
 - EN formula recommendation
 - Ongoing monitoring

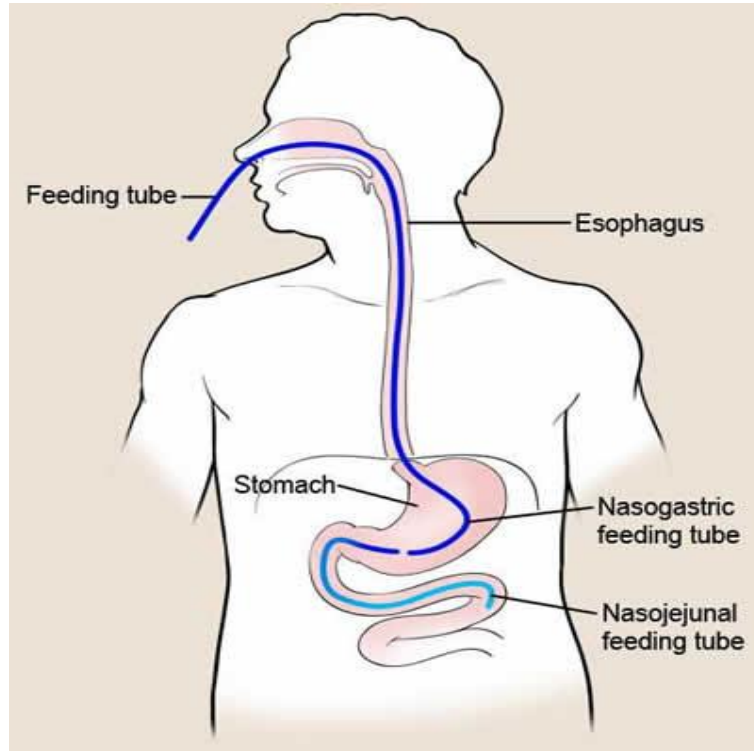
Feeding Tube Locations



Tolerance of Gastric Feeds in Patients with Sepsis



Feeding Tube Location and Mesenteric Ischemia



Incidence of GI ischemia is low but mortality is high

Difficult to say with certainty if gastric vs post-pyloric are associated with higher incidence of GI ischemia

Majority of reported cases associated with enteral nutrition in surgery, trauma, and burn patients occurred in those being fed into the jejunum (0.29-1.15%)

May be greater risk for decreased mesenteric flow to small bowel vs stomach in hemodynamic instability

Safe EN Initiation and Vasopressors

- Factors to be considered:
 - Type of vasopressor agent(s)
 - Dosage of vasopressor agent(s)
 - Time of EN initiation
 - Feeding tube location
 - **EN formula recommendation**
 - Ongoing monitoring

Formula Selection

- Considerations
 - Volume/caloric density
 - Renal function and protein content
 - Fiber content
 - Polymeric vs. Semi-elemental/peptide formulas

Formula Selection

Study	Formula Composition	Results
Revelly et al. 2001	Polymeric 1.0 kcal/ml with 22% protein (no data on fiber)	EN increased mesenteric GI blood flow with no evidence of gastric ischemia
Berger et al. 2005	Polymeric 1-1.2 kcal/ml, 20% protein, fiber free	No significant GI complications
Patel et al. 2016	1.2 kcal/ml low fiber formula (no data on composition of protein content)	No significant GI complications with trophic feeds
Mancl et al 2013	Median energy density 1.5 kcal/ml	3 ischemic bowel events (0.9%) when fed at 58% of energy goal
TARGET 2018	1.5 kcal/ml vs. 1.0 kcal/ml	Increased GI symptoms and hyperglycemia in 1.5 kcal/ml group
Ong et al. 2020	Semi-elemental, 1.2 kcal/ml, 25% protein, low-fiber	No increased incidence of ischemic bowel
NUTRIREA 2	Iso-osmotic, isocaloric, normal-protein, polymeric preparations	Higher incidence of GI complications in enteral group, 2% incidence of bowel ischemia

Protein Content of Enteral Formulas

- Higher protein formulas may generate a hyperemia effect to increase oxygen delivery to the gut
- ***Timing of protein dosing may be key***
 - A low protein intake (<0.8 g/kg) before day 3 and high protein intake after day 3 was associated with a lower 6-month mortality



Fiber Content of Enteral Formulas

Question: In adult critically ill patients, what are the indications, if any, for enteral formulations containing soluble fiber or small peptides?

“ **E4a. We suggest that a commercial mixed fiber formula not be used routinely in the adult critically ill patient prophylactically to promote bowel regularity or prevent diarrhea.**

[Quality of Evidence: Low]

E4b. Based on expert consensus, we suggest considering use of a commercial mixed fiber-containing formulation if there is evidence of persistent diarrhea. We suggest avoiding both soluble and insoluble fiber in patients at high risk for bowel ischemia or severe dysmotility. We suggest considering use of small peptide formulations in the patient with persistent diarrhea, with suspected malabsorption or lack of response to fiber.

Benefits

Normalization of bowel function

Improvement in diarrhea

Promotion of healthy gut bacteria growth

Risk

Increased stool bulk may put direct pressure on bowel wall mucosa leading to impaired mucosal blood flow

Polymeric vs. Semi-elemental/Peptide Formulas

The Theory

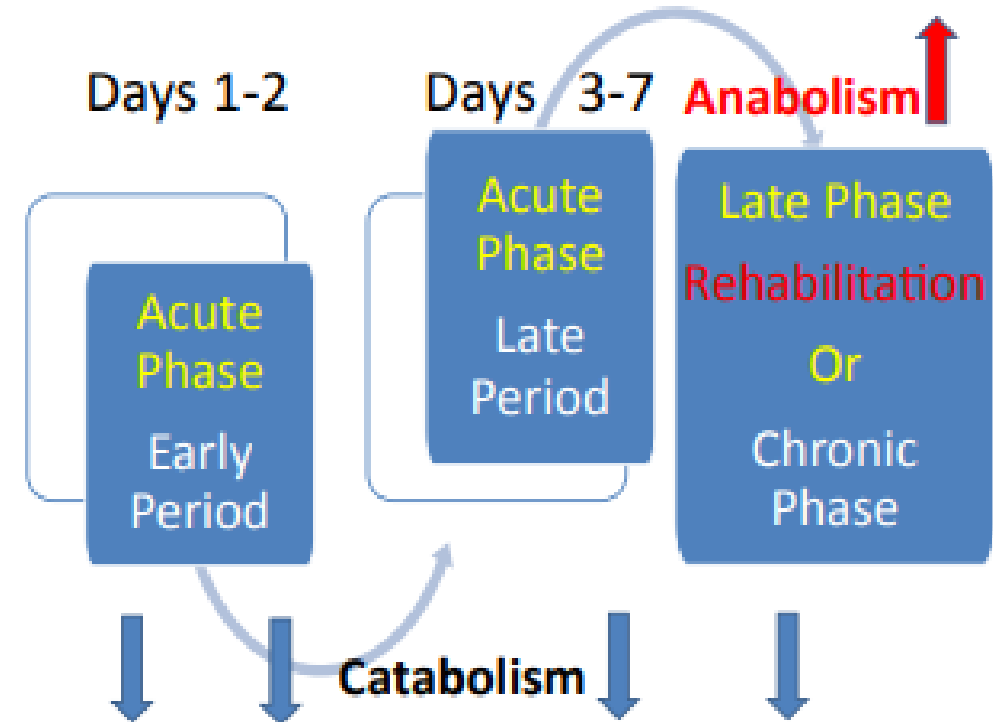
- Easier digestion and absorption resulting in improved GI tolerance
- Faster gastric emptying promoting better intestinal motility and nutrient delivery to the gut
- Reduced risk of intestinal ischemia due to less gut oxygen consumption

Recent studies haven't consistently demonstrated a direct protective benefit against gut ischemia or improved GI tolerance

How Much to Feed?

THE PHASES OF CRITICAL ILLNESS

- **Acute Phase Early Period** (*Days 1-2*)
 - Metabolic instability and severe increase in catabolism. Circulatory shock, respiratory distress, and GI dysfunction are all common.
- **Acute Phase Late Period** (*Days 3-7*)
 - Significant muscle wasting and a stabilization of various metabolic disturbances
- **Late Phase** (*Days 7+*)
 - Either improvement and rehabilitation with respect to disease state, physical activity, and nutrition status vs. persistent inflammation, immunosuppression, and catabolism with prolonged hospitalization



Caloric Delivery and Enteral Tolerance

Study Objective	Vasopressor and Dose Used	Results	Mesenteric Ischemia
To investigate if higher dose of protein provided to critically ill patients (fed at ~13 kcal/kg/d) would improve their clinical outcomes <i>Heyland et. Al 2023 EFFORT Protein</i>	Norepinephrine-equivalent, mean dose 0.2 mcg/kg/min	Higher protein dosing could be harmful in patients with greater severity of illness (as judged by baseline SOFA score and presence of acute kidney injury).	Not recorded
To test early EN prescribed at 17.6 kcal/kg/d (relative to early PN) in mechanically ventilated patients with shock <i>Reigner et. Al 2018 NUTRIREA-2</i>	Mean Norepinephrine dose 0.56 mcg/kg/min	Higher incidence of GI complications, worse glycemic control, and more daily insulin use in standard dose nutrition group. Early full-dose EN in mechanically ventilated patients with shock receiving high dose norepinephrine during the acute phase of critical illness might be harmful	Yes, 2% in early EN group vs. <1% in PN group
To compare low (6 kcal/kg/d and 0.2-0.4 g/kg/d protein) to standard (full) dose nutrition (25 kcal/kg/d and 1-1.3 g/kg/d protein) during the first 7 days of ICU stay in critically ill ventilated patients with shock <i>Reigner et. Al 2023 NUTRIREA-3</i>	Mean Norepinephrine dose 0.5 mcg/kg/min	In the low dose nutrition group, trend towards improved ICU mortality and time to weaning from vasopressors; significantly improved time to wean from invasive mechanical ventilation. More enteral feeding intolerance, instances of refeeding syndrome, insulin resistance, mitochondrial dysfunction, inhibition of autophagy, and fluid overload in high dose nutrition group	Yes, 1.8% in full nutrition group vs. 0.9% in low dose nutrition group

The **Sweet** Spot

The sweet spot for benefit of EN in patients requiring vasopressors may depend on disease severity and nutrition dose

Patel, JJ et al. *JPEN J Parenter Enteral Nutr.* 2023;47(7):859-865.

Table 2 Comparison of European and American nutrition guidelines, and considerations for future recommendations

From: Nutrition in the intensive care unit: from the acute phase to beyond

	European guidelines (2019; partially updated in 2023) [37]	American guidelines (2022) [46]	Considerations for future recommendations
Primary feeding route	Enteral (grade A recommendation)	Enteral or parenteral (strong recommendation)	Probably enteral
Feeding dose, time of initiation and mode of progression of nutrition	Early initiation of enteral nutrition (within 48 h) (grade B recommendation). Start with hypocaloric nutrition (grade B recommendation), progressive increase toward target within 3–7 days (grade A recommendation)	12–25 kcal/kg/day during the first 7–10 days; dose depending on clinical judgement (weak recommendation)	Avoid full feeding in the first days. The ideal time point of initiation and mode of progression of nutrition is unknown (to be studied). Suggestion to initiate medical nutrition support progressively and to accept below-target feeding for at least several days. Suggestion to alter nutritional intake depending on clinical evolution (higher doses and faster progression in recovering patients, temporary tapering in case of new severe insult), and to consider also non-nutritional calories when calculating the energy intake
Timing of supplemental parenteral nutrition (in case of insufficient enteral nutrition)	Case-by-case evaluation (grade GPP); suggestion to initiate supplemental parenteral nutrition between day 4 and 7	No supplemental parenteral nutrition prior to day 7 (strong recommendation)	Below-target feeding can be accepted for at least several days. The ideal time point to start supplemental parenteral nutrition is unclear and likely varies between patients, depending on the duration of anabolic resistance. Harm by too early initiation of supplemental parenteral nutrition is dose-related rather than route-related
Protein target	1.3 g/kg can be delivered progressively (grade O recommendation)	1.2–2 g/kg/day (weak recommendation)	Avoid high protein doses in the acute phase. Ideal dose in the post-acute phase unclear (to be studied)

Back to DH

- Vasopressor doses remained stable on ICU day 6
- Initiated EN via nasogastric tube
 - Started at 10 ml/hr (trophic feed)
 - Advanced by critical care team based on tolerance



Safe EN Initiation and Vasopressors

- Factors to be considered:
 - Type of vasopressor agent(s)
 - Dosage of vasopressor agent(s)
 - Time of EN initiation
 - Feeding tube location
 - EN formula recommendation
 - **Ongoing monitoring**

EN and Vasopressor – Ongoing Monitoring

- Adjust or withhold EN might be considered in the following situations:

Monitoring Parameters	Considerations
Vasopressor (type and dose)	New vasopressor initiation and/or escalation
Mean arterial pressure (MAP)	• ≥ 60 mm Hg: may administer EN • < 50 mm Hg: hold EN
Gastric residual volume (GRV)	• Routine monitoring is not recommended • Low quality evidence suggests to hold EN if GRVs > 300 mL
Lactate levels	• Not recommended to use to monitor EN tolerance (Insufficient data)

EN and Vasopressor – Ongoing Monitoring

- Signs and symptoms of EN intolerance
 - Abdominal distension
 - New abdominal pain
 - Nausea/vomiting
 - ↓ Passage of stool or flatus
 - ↑ Nasogastric tube output
 - Unexplained Metabolic acidosis
 - Radiographic signs

Summary

- EN is not contraindicated for patients requiring vasopressors
- Evaluate the type and the doses of vasopressor(s) or inotropic agent(s) being administered to determine the appropriateness of EN initiation
- Careful monitoring is essential when patients are receiving both EN and vasopressors to detect any EN intolerance

Summary

When to feed

- Initiate EN via gastric feeding within 48 hours of vasopressor initiation if VDE score < 12 (*Norepinephrine equivalent dose of 0.12 mcg/kg/min*)

Where to feed

- Gastric feeds likely most appropriate in majority of patients

What to feed

- A 1.0-1.2 kcal/ml, higher protein, low-fiber formula that is either semi-elemental or polymeric seems to be well tolerated

How much to feed

- Trophic feeds in first 24-48 hours; gradually increasing to goal in ~7 days

Question?!



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Thank you!



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