Current Topics in Critical Care Nutrition Support

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UTSW Medical Center, Dallas
Objectives

Pharmacist Objectives:
° Evaluate the impact of the stress response on metabolic demand
° Describe how to formulate an evidence-based nutritional strategy
° Evaluate the evidence and describe the role of the new IV lipid formulations in critically ill adult patients
° Describe the role of probiotics in critically ill patients
° Summarize the evidence for micronutrient supplementation in critically ill adult patients

Technician Objectives:
° Recognize the impact of the stress response on metabolic demand
° Review the evidence and describe the role of the new IV lipid formulations in critically ill adult patient
° Recognize the role of probiotics in critically ill patients
° Summarize the evidence for micronutrient supplementation in critically ill adult patients
Stress Response and the Impact on Metabolic Demand

ICU Nutrition Support Guidelines Timeline

- SCCM-ASPEN Guidelines 2016
- ESICM Guidelines 2017
- ESPEN Guidelines 2019
- DGEM Guidelines 2019
- SCCM-ASPEN Guidelines Update in process 2021
ICU Nutrition Support Questions

- When do we initiate nutrition support?
- What route do we use to administer nutrition support?
  - EN (enteral nutrition) vs PN (parenteral nutrition)
- What caloric goal do we target?
- When is EN safe for patients on vasopressors?
Benefits of Enteral Nutrition in Critically Ill

- Early enteral nutrition (EEN)
  - Enteral nutrition (EN) within 48 hr if ICU admission
  - Initiated after hemodynamic stabilization
- Preserves GI function and absorptive capacity
- Preserves GI mucosal integrity
- GI tract is an essential modulator of systemic inflammation
  - Preservation of mucosal immunology function

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESICM 2017</td>
<td>• Initiate EEN vs early PN or delayed EN (conditional recommendation, Grade 2C)</td>
</tr>
<tr>
<td></td>
<td>• Do not aim to cover full energy target with early NS. Hypocaloric EEN may be safe.</td>
</tr>
<tr>
<td>ESPEN 2019</td>
<td>• EEN should be initiated vs delaying EN (Grade A recommendation, strong consensus)</td>
</tr>
<tr>
<td></td>
<td>• If contraindication to EN or oral diet, initiate PN within 3-7 days (Grade B recommendation, consensus)</td>
</tr>
<tr>
<td></td>
<td>• Early full EN or PN should not be used in the ICU, but increased over 3-7 days (Grade A recommendation, strong consensus)</td>
</tr>
<tr>
<td>SCCM-ASPEN 2016</td>
<td>• Provide early feeding (within 24–48 h after ICU admission), via the enteral route when feasible (low quality of evidence)</td>
</tr>
</tbody>
</table>

When is Parenteral Nutrition Appropriate in Critically Ill Patients?

- More recent RCTs have shown no difference in mortality or nosocomial infections in ICU patients with EEN vs early PN (EPN)

- Increase in infection rates with PN may have been associated with increased caloric provision or different infection prevention practices with older trials

- ESPEN 2019 Guidelines
  - Implement PN within 3-7 days if EN contraindicated or not possible
  - Implement PN early (within 48 hr ICU admission) if severely malnourished

- SCCM-ASPEN 2016 Guidelines
  - Low nutritional risk, withhold PN first 7 days of ICU stay if EN not feasible
  - High nutritional risk or severely malnourished, initiate PN as soon as possible if EN not feasible
  - High or low nutritional risk, consider supplemental PN at 7-10 days if not meeting >60% energy and protein requirements

Infection Complications with EEN vs EPN

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>EEN Events</th>
<th>EEN Total</th>
<th>EPN Events</th>
<th>EPN Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1 ICU studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kompan 2004</td>
<td>9</td>
<td>27</td>
<td>16</td>
<td>25</td>
<td>9.5%</td>
<td>0.52 [0.28, 0.96]</td>
<td>2004</td>
</tr>
<tr>
<td>Lota 2008</td>
<td>10</td>
<td>41</td>
<td>25</td>
<td>41</td>
<td>9.8%</td>
<td>0.40 [0.22, 0.72]</td>
<td>2008</td>
</tr>
<tr>
<td>Atlintas 2011</td>
<td>7</td>
<td>30</td>
<td>13</td>
<td>41</td>
<td>7.0%</td>
<td>0.74 [0.33, 1.62]</td>
<td>2011</td>
</tr>
<tr>
<td>Justo Meirelles 2011</td>
<td>2</td>
<td>13</td>
<td>4</td>
<td>10</td>
<td>7.7%</td>
<td>0.42 [0.10, 1.82]</td>
<td>2011</td>
</tr>
<tr>
<td>Harvey 2014</td>
<td>194</td>
<td>1197</td>
<td>194</td>
<td>1191</td>
<td>18.3%</td>
<td>0.99 [0.83, 1.19]</td>
<td>2014</td>
</tr>
<tr>
<td>Reignier 2017</td>
<td>173</td>
<td>1202</td>
<td>194</td>
<td>1208</td>
<td>18.2%</td>
<td>0.90 [0.74, 1.08]</td>
<td>2017</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2509</td>
<td>2516</td>
<td>65.6%</td>
<td>446</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 395

Heterogeneity: Tau² = 0.06; Chi² = 12.66, df = 5 (P = 0.03); I² = 61%
Test for overall effect: Z = 2.14 (P = 0.03)

2.1.2 Studies with unclear proportion of ICU patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>EEN Events</th>
<th>EEN Total</th>
<th>EPN Events</th>
<th>EPN Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aiko 2001</td>
<td>0</td>
<td>13</td>
<td>1</td>
<td>1</td>
<td>1.1%</td>
<td>0.29 [0.01, 6.38]</td>
<td>2001</td>
</tr>
<tr>
<td>Bozzetti 2001</td>
<td>25</td>
<td>159</td>
<td>42</td>
<td>158</td>
<td>12.7%</td>
<td>0.59 [0.38, 0.92]</td>
<td>2001</td>
</tr>
<tr>
<td>Gupta 2003</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>9</td>
<td>1.3%</td>
<td>0.56 [0.06, 5.09]</td>
<td>2003</td>
</tr>
<tr>
<td>Eckerwall 2006</td>
<td>3</td>
<td>23</td>
<td>0</td>
<td>25</td>
<td>0.8%</td>
<td>7.58 [0.41, 139.32]</td>
<td>2006</td>
</tr>
<tr>
<td>Petrov 2006</td>
<td>11</td>
<td>35</td>
<td>27</td>
<td>34</td>
<td>11.1%</td>
<td>0.40 [0.24, 0.66]</td>
<td>2006</td>
</tr>
<tr>
<td>Sun 2013</td>
<td>3</td>
<td>30</td>
<td>10</td>
<td>30</td>
<td>3.8%</td>
<td>0.30 [0.09, 0.98]</td>
<td>2013</td>
</tr>
<tr>
<td>Boelens 2014</td>
<td>4</td>
<td>61</td>
<td>8</td>
<td>62</td>
<td>4.1%</td>
<td>0.51 [0.16, 1.60]</td>
<td>2014</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>329</td>
<td>446</td>
<td></td>
<td>34.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 47

Heterogeneity: Tau² = 0.00; Chi² = 5.66, df = 6 (P = 0.46); I² = 0%
Test for overall effect: Z = 4.49 (P < 0.00001)

Total events: 2838

Heterogeneity: Tau² = 0.09; Chi² = 29.81, df = 12 (P = 0.003); I² = 60%
Test for overall effect: Z = 3.50 (P = 0.0005)
Test for subgroup differences: Chi² = 3.92, df = 1 (P = 0.05), I² = 74.5%

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elke et al. Critical Care. 2020</td>
<td>Meta-analysis, ICU pt N=18 RCTs, n=3347</td>
<td>• No effect on overall mortality (RR 1.04, 95% CI: 0.82, 1.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EN vs PN reduced infection complications (RR 0.64, 95% CI: 0.48, 0.87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EN vs PN reduced infectious complications in subgroup where PN group received more calories (RR 0.55, 95% CI: 0.37, 0.82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No difference in infection EN vs PN with similar caloric intake (RR 0.94, 95% CI: 0.8, 1.1)</td>
</tr>
<tr>
<td>Reignier et al. NUTRIREA-2 Trial. Lancet. 2018</td>
<td>RCT, 44 French ICUs n= 2410 MV patient with shock EEN vs Early PN (within 24 hr of MV) target normocaloric goal Calorie intake similar in both groups ~17 kcal/lg/d (EN) vs 19 kcal/kg/d (PN)</td>
<td>• 28-day mortality was not different EEN (37%) vs early PN (35%) (absolute diff. 2%, 95% CI: -1.9%, 5.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No difference in ICU-acquired infections (HR 0.89, 95% CI: 0.72, 1.09)</td>
</tr>
</tbody>
</table>

General Recommended Caloric Provision in Critically Ill Patients

ESPEN 2019 Guidelines
- If predictive equations are used to estimate energy needs, hypocaloric nutrition (below 70% estimated needs) preferred over isocaloric the first week of ICU stay (Grade B recommendation, strong consensus).

ESICM 2017 Guidelines
- Start EN at a slow rate (10–20 ml/h) while carefully monitoring abdominal/gastrointestinal symptoms. Increase EN slowly once previous symptoms are resolving and no new symptoms occur.

SCCM-ASPEN 2016 Guidelines
- High nutritional risk or severely malnourished who cannot maintain volitional intake:
  - Advanced to goal as quickly as tolerated over 24-48 hr
  - Provide >80% estimated or calculated goal energy and protein within 48-72 hr
- Low nutritional risk or normal baseline nutritional status who cannot maintain volitional intake:
  - No need for specialized nutrition support first week of ICU stay

Hypocaloric vs Isocaloric EN in the ICU

**EDEN Randomized Trial. JAMA. 2012**
- Multicenter RCT, n=1000
- Initial trophic vs full EN in patients within 48 hr of acute lung injury on mechanical ventilation
- Trophic feed vs full EN first 6 days did not:
  - Increase number of ventilator-free days (difference -0.1 days, 95% CI: -1.4, 1.2 days)
  - Reduce 60-day mortality (difference 1%, 95% CI: -4.1, 6.3%)
- Full EN patients had more GI intolerance

Hypocaloric vs Isocaloric Impact on Mortality in Critically Ill

Hypocaloric vs Isocaloric Impact on Infection Complications in Critically Ill

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypocaloric Nutrition</th>
<th>Isocaloric Nutrition</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singer 2011</td>
<td>20</td>
<td>65</td>
<td>0.54 [0.35, 0.82]</td>
<td>2011</td>
</tr>
<tr>
<td>Heideggar 2013</td>
<td>85</td>
<td>152</td>
<td>1.11 [0.90, 1.37]</td>
<td>2013</td>
</tr>
<tr>
<td>Petros 2016</td>
<td>12</td>
<td>46</td>
<td>2.35 [0.96, 5.76]</td>
<td>2016</td>
</tr>
<tr>
<td>Allingstrup 2017</td>
<td>12</td>
<td>99</td>
<td>0.64 [0.33, 1.24]</td>
<td>2017</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>362</td>
<td>372</td>
<td>0.91 [0.54, 1.54]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 129
Heterogeneity Tau^2 = 0.20, Chi^2 = 14.29, df = 3 (P = 0.003); I^2 = 79%
Test for overall effect: Z = 5.35 (P < 0.001)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypocaloric Nutrition</th>
<th>Isocaloric Nutrition</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice 2011</td>
<td>30</td>
<td>98</td>
<td>0.95 [0.63, 1.42]</td>
<td>2011</td>
</tr>
<tr>
<td>Casser 2011</td>
<td>531</td>
<td>2328</td>
<td>0.87 [0.79, 0.96]</td>
<td>2011</td>
</tr>
<tr>
<td>Arabi 2011</td>
<td>53</td>
<td>120</td>
<td>0.95 [0.72, 1.25]</td>
<td>2011</td>
</tr>
<tr>
<td>Rice 2012</td>
<td>111</td>
<td>508</td>
<td>1.17 [0.91, 1.50]</td>
<td>2012</td>
</tr>
<tr>
<td>Charles 2014</td>
<td>29</td>
<td>41</td>
<td>0.93 [0.72, 1.20]</td>
<td>2014</td>
</tr>
<tr>
<td>Braunschweig 2015</td>
<td>8</td>
<td>38</td>
<td>1.68 [0.60, 4.70]</td>
<td>2015</td>
</tr>
<tr>
<td>Arabi 2015</td>
<td>161</td>
<td>448</td>
<td>0.90 [0.80, 1.13]</td>
<td>2015</td>
</tr>
<tr>
<td>Wischmann 2017</td>
<td>46</td>
<td>73</td>
<td>0.86 [0.68, 1.10]</td>
<td>2017</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>3654</td>
<td>3606</td>
<td>0.92 [0.86, 0.99]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 969
Heterogeneity Tau^2 = 0.00, Chi^2 = 6.50, df = 7 (P = 0.48); I^2 = 0%
Test for overall effect: Z = 2.33 (P < 0.02)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypocaloric Nutrition</th>
<th>Isocaloric Nutrition</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>4016</td>
<td>3978</td>
<td>0.94 [0.84, 1.05]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1098
Heterogeneity Tau^2 = 0.01, Chi^2 = 20.97, df = 11 (P = 0.03); I^2 = 48%
Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.98); I^2 = 0%

## Hypocaloric vs Isocaloric Nutrition Support in the ICU

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TARGET Investigators. NEJM. 2018</td>
<td>RCT, multi-center n=3957, MV ICU pt Standard EN 1 kcal/ml (Trial calories delivered 19.6±4 kcal/kg/d) vs Energy-dense EN 1.5 kcal/ml (Trial calories delivered 29.1±6.2 kcal/kg/d) Target goal= 1 ml/kg (IBW)/hr within 48 hr of trial initiation Protein intake similar in both groups</td>
<td>No SS difference in 90-day mortality standard vs energy-dense (RR 1.05, 95% CI: 0.94, 1.16) No SS difference in infectious complications or use and duration of organ support</td>
</tr>
</tbody>
</table>
# Hypocaloric vs Isocaloric Nutrition Support in the ICU

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
</table>
| Allingstrup et al. EAT-ICU. Intensive Care Med. 2017 | RCT, single-center n=203, MV ICU pt  
**Early goal-directed nutrition (EGDN)** (median caloric intake 1877 kcal/d & protein 1.47 g/kg/d) vs **Standard nutrition** (median intake 1061 kcal/d & protein 0.5 g/kg/d)  
EGDN- indirect calorimetry, protein calc. using 24 h UUN excretion  
Standard- predictive equation (25 kcal/kg/day) | Primary outcome: Physical component summary score (PCS) at 6 mos. no SS difference (adj. mean diff. -0.0, 95% CI: -5.9,5.8)  
**No SS difference in 28-day mortality, LOS, infections** |

## Hypocaloric vs Isocaloric Nutrition Support in the ICU

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arabi et al. PermiT. NEJM. 2015</td>
<td>RCT, multi-center n=894, ICU pt, 96.8% MV Permissive underfeeding (46±14% caloric requirement) vs Standard feeding (71±22% caloric requirement) Protein intake similar between groups Predictive equations used for energy calculations</td>
<td>Primary outcome: 90-day mortality similar with permissive underfeeding (RR 0.94, 95% CI:0.76,1.16) No SS difference in ICU infections, LOS, or duration of MV</td>
</tr>
</tbody>
</table>

Caloric Provision Bottom Line

- Overfeeding should be avoided
  - Endogenous energy production (~500 kcal/day) in acute phase of illness
  - Hyperglycemia
- Hypocaloric vs isocaloric feeding when using predictive equations does not provide significant difference in outcome with similar protein intake
- Accept limited caloric deficit 20-30% first week in ICU
  - Avoid prolonged deficits

General Approach to ICU NS

Enteral Nutrition Challenges in the ICU
# EEN with Vasopressors

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohbe H et al. <em>Clin Nutr.</em> 2019</td>
<td>Health outcome study, Japan n= 52,563, <strong>MV patients with shock</strong></td>
<td><strong>28-day mortality lower in EEN group on low- &amp; mod-dose NE vs LEN:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>EEN (EN within 48 hr MV) vs LEN</strong> with Low-dose NE (&lt;0.1 mcg/kg/min) vs. Mod-dose NE (0.1-0.3 mcg/kg/min) vs. High-dose NE (&gt;0.3 mcg/kg/min)</td>
<td>Low-dose NE (risk difference -2.9%, 95% CI: -4.5%, -1.3%) Mod-dose NE (risk difference -6.8%, 95% CI: -9.6%, -4%) <strong>High-dose NE</strong> (risk difference 1.4%, 95% CI: -7.4%, 4.7%) <em>(No SS difference)</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No difference in bowel ischemia EEN vs LEN among groups</td>
</tr>
</tbody>
</table>

## EEN with Vasopressors

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
</table>
| **Reignier et al. NUTRIREA-2 Trial. Lancet. 2018** | **RCT, 44 French ICUs n= 2410, MV patient with shock**  
**EEN vs EPN** (within 24 hr of MV) target normal caloric goal  
**Mean NE dose:**  
EEN group-0.56 mcg/kg/min (0.3-1.2 mcg/kg/min)  
vs.  
PN group-0.5 mcg/kg/min (0.25-1.03 mcg/kg/min) | **28-day mortality was not different EEN (37%) vs EPN (35%)**  
(absolute diff. 2%, 95% CI: -1.9%, 5.8%)  
No difference in ICU-acquired infections HR 0.89, 95% CI: 0.72, 1.09)  
**Higher incidence of bowel ischemia with EEN vs EPN**  
(HR 3.84, 95% CI: 1.43, 10.3)  
& **acute colonic pseudo-obstruction**  
(HR 3.7, 95% CI: 1.03, 13.2) |
## Enteral Nutrition with Vasopressors

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| SCCM-ASPEN 2016 | • With hemodynamic instability, EN should be withheld until the patient is fully resuscitated and/or stable. (expert consensus)  
• Hold EN if MAP < 50 or escalating doses vasopressors                                      |
| ESICM 2017      | • Delay EN if shock uncontrolled, hemodynamic goals not met. Start low-dose EN as soon as shock controlled with fluids/vasopressors/inotropes (conditional recommendation, expert opinion)  
• Concern with EN and very high dose vasopressors (i.e. NE dose >1 mcg/kg/min), persistent high lactate, or hypoperfusions signs |
| ESPEN 2019      | • Low-dose EN can be started as soon as shock controlled with fluids and vasopressors/inotropes (strong consensus) |

## EEN with Vasopressors Summary

<table>
<thead>
<tr>
<th>Vasopressor Choice</th>
<th>Vasopressor Dose</th>
<th>Resuscitation Markers</th>
<th>Feeding Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine/dobutamine/phenylephrine &gt; epinephrine &gt; vasopressin/dopamine</td>
<td>NE dose (equivalent)</td>
<td>- lactate decreasing, normalized</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 0.1 mcg/kg/min- most optimal 0.1-0.3 mcg/kg/min-may be acceptable &gt;0.3-0.5 mcg/kg/min-may have significant risk</td>
<td>- Vasopressor dose decreasing or stable --Fluid requirements stabilized</td>
<td>1. Start with trophic feeds 2. Advance slowly</td>
</tr>
</tbody>
</table>

- **EDEN trial**: Excluded patients on NE or EPI doses > 30 mcg/min
- **PermiT trial**: Excluded patients on NE or EPI doses > 0.4 mcg/kg/min or ½ this dose if on 2 vasopressors
- **NUTRIREA-2 Trial**: higher incidence of bowel ischemia & acute colonic pseudo-obstruction with EEN (NE mean dose 0.56 mcg/kg/min (0.3-1.2 mcg/kg/min)

Enteral Nutrition with Sustained Neuromuscular Blockade

- Neuromuscular blocking agents (NMBAs) relax skeletal muscle, not smooth muscle found in GI tract
  - Non-depolarizing NMBAs-competitive antagonist at nicotinic receptor in skeletal muscle
  - Smooth muscle controlled by acetylcholine acting on muscarinic receptor
- EN can be provided safely to patients on NMBA infusions
### Enteral Nutrition with Sustained Neuromuscular Blockade

<table>
<thead>
<tr>
<th>Study</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohbe H et al. <em>Crit Care Med.</em> 2019</td>
<td>Retrospective cohort, admin database, Japan n= 2340 MV and NMBA (rocuronium ≥ 250 mg/d or vecuronium ≥ 50 mg/d) x 2 consecutive days EEN (EN started within 48 hr of NMBA) vs LEN</td>
<td>In-hospital mortality lower EEN vs LEN (risk diff. -6.3%, 95% CI: -11.7%, -0.9%) No difference in rate of pneumonia (risk diff. 2.8%, 95%CI: -2.7%, 8.3%)</td>
</tr>
</tbody>
</table>

Enteral Nutrition with Sustained Neuromuscular Blockade

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESICM 2017</td>
<td>EN should not be delayed for concomitant use of NMBA (expert opinion, Grade 2D recommendation)</td>
</tr>
<tr>
<td>ESPEN 2019</td>
<td>EEN should be provided in patients receiving NMBAs (strong consensus)</td>
</tr>
</tbody>
</table>

Enteral Nutrition in Patients in Prone Position

- Prone position used in acute respiratory distress syndrome (ARDS)
- Studies supporting EN in prone position are mainly small, observational studies
- EN is safe in prone position in the absence of hemodynamic instability or severe GI dysfunction
Enteral Nutrition in Patients in Prone Position

  - Systematic review
  - 6 small, single-center, observational studies
  - n=241 patients
  - 5 studies reported no difference in gastric residual volume in supine vs prone position
  - Vomiting and EN interruption more frequent in prone position
  - Lengths of stay, mortality, and incidence of VAP similar in prone vs supine groups
# Enteral Nutrition in Patients in Prone Position

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Gastric tube placement, post-pyloric if intolerance</td>
</tr>
<tr>
<td></td>
<td>• Head of bed elevated (reverse Trendelenburg) at least 10-25 degrees to decrease aspiration risk, facial edema, and intra-abdominal hypertension.</td>
</tr>
<tr>
<td>Barazzoni R et al. ESPEN expert consensus and clinical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr. 2020</td>
<td>• “The prone position per se does not represent a limitation or contraindication for EN.”</td>
</tr>
</tbody>
</table>

IV Lipid Emulsions
IV Lipid Emulsion (ILE) Review

- Energy-dense source of calories and essential fatty acids
- Modulate inflammatory and immune responses and cell signaling
- Biological effects are dependent on fatty-acid (FA) composition
- Soybean oil has high concentration of omega-6 FA
  - Linoleic acid \rightarrow Arachidonic acid that promotes inflammation & suppresses cell-mediated immunity
- Fish oil has high concentration of omega-3 FA
  - Docosahexaenoic acid (DHA) & eicosapentaenoic acid (EPA)
    - Anti-inflammatory, immunomodulatory, antioxidative effects

High phytosterol content has been associated with hepatobiliary complications and intestinal failure associated liver disease (IFALD)

α-tocopherol is an antioxidant that is capable of scavenging free radicals
  • Oxidative stress associated with low amount of α-tocopherol in soybean oil

Pro-inflammatory
  • High omega-6 to omega-3 ratio (7:1) vs Smoflipid (2.5:1)
Beneficial Effects of ILE

° Fish oil
  • Specialized pro-resolution mediators (SPMs)
    • Synthesized directly from DHA and EPA
    • Mediators of inflammation
      • Beneficial in hypermetabolic or hyperinflammatory state
    • Higher α-tocopherol
      • Reduces oxidative stress
    • Minimal phytosterol content

° Medium Chain Triglyceride (MCT) oil
  • Easily metabolized
  • Not pro-inflammatory
# IV Lipid Emulsions

<table>
<thead>
<tr>
<th>Product</th>
<th>US Approval Date</th>
<th>Composition</th>
<th>Omega 6 to Omega-3 Fatty Acid Ratio</th>
<th>Phytosterols (mg/L)</th>
<th>α-Tocopherol (mg/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralipid®, Nutrilipid®, SO-ILE</td>
<td>1970s</td>
<td>100% Soy oil</td>
<td>7:1</td>
<td>422±130</td>
<td>0</td>
</tr>
<tr>
<td>Clinolipid® OO, SO-ILE</td>
<td>Approved 2013</td>
<td>80% Olive oil, 20% Soy oil</td>
<td>9:1</td>
<td>208±39</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Available 2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoflipid® SO, MCT, OO, FO-ILE</td>
<td>2016</td>
<td>30% Soy oil, 30% MCT oil, 25% Olive oil, 15% Fish oil</td>
<td>2.5:1</td>
<td>142±15</td>
<td>16.3-22.5</td>
</tr>
<tr>
<td>Omegaven® OO-ILE</td>
<td>2018</td>
<td>100% Fish oil</td>
<td>1.8:1</td>
<td>0</td>
<td>15-30</td>
</tr>
</tbody>
</table>

# IV Lipid Emulsions

<table>
<thead>
<tr>
<th>Product</th>
<th>Composition</th>
<th>Adult Dose</th>
<th>Potential Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intralipid®, Nutrilipid® SO-ILE</strong></td>
<td>100% Soy oil</td>
<td>Critically ill &lt;1 g/kg/d</td>
<td>Treatment of essential fatty acid deficiency (EFAD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stable 1 g/kg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max 2.5 g/kg/d, 0.11 g/kg/h</td>
<td></td>
</tr>
<tr>
<td><strong>Clinolipid® OO, SO-ILE</strong></td>
<td>80% Olive oil 20% Soy oil</td>
<td>1-1.5 g/kg/d</td>
<td>Elevated LFTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max 2.5 g/kg/d</td>
<td>Elevated triglycerides</td>
</tr>
<tr>
<td><strong>Smoflipid® SO, MCT, OO, FO-ILE</strong></td>
<td>30% Soy oil 30% MCT oil 25% Olive oil 15% Fish oil</td>
<td>1-2 g/kg/d Max 2.5 g/kg/d</td>
<td>Elevated LFTs Elevated triglycerides Inflammatory state</td>
</tr>
<tr>
<td><strong>Omegaven® OO-ILE</strong></td>
<td>100% Fish oil</td>
<td>n/a</td>
<td>Pediatric patient with PN-associated cholestasis (PNAC)</td>
</tr>
</tbody>
</table>

# IV Lipid Emulsions Meta-Analyses
## FO-based ILE vs Standard ILE

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results of FO-containing ILE vs Standard ILE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pradelli et al. J PEN. 2020</strong></td>
<td>ICU and non-ICU (surgical) pt 49 RCTs, n=3641</td>
<td>Fewer infections (RR 0.6, 95% CI: 0.49, 0.72) Reduced hospital LOS (mean diff. -2.14 d, 95% CI: -1.36, -2.93) Reduced ICU LOS (mean diff. -1.95 d, 95% CI: -0.42, -3.49) Reduction in sepsis (RR 0.44, 95% CI: 0.28, 0.7)</td>
</tr>
<tr>
<td><strong>Bae et al. AJHP. 2017</strong></td>
<td>Surgery pt 19 RCTs, n=1167</td>
<td>Fewer infections (OR 0.44, 95% CI: 0.3, 0.65) Reduced hospital LOS (weighted mean diff. -2.7 d, 95% CI: -3.6, -1.79)</td>
</tr>
<tr>
<td><strong>Manzanares et al. Crit Care Med. 2015</strong></td>
<td>ICU pt 10 RCTs, n=733</td>
<td>Fewer infections (RR 0.64, 95% CI: 0.44, 0.92) Reduced hospital LOS (4 trials) weighted mean diff. -7.42 d (95% CI: -11.89, -2.94)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESPEN 2019</strong></td>
<td>• ILEs enriched with EPA + DHA (Fish oil dose 0.1-0.2 g/kg/d) can be provided in patients receiving PN. <em>Grade of recommendation: 0 - strong consensus (100% agreement)</em></td>
</tr>
</tbody>
</table>
| **SCCM-ASPEN 2016**        | • Alternative ILEs may provide outcome benefit over soy-based IVFES; however, we cannot make a recommendation at this time due to lack of availability of these products in the United States.  
• When available, consider use in the critically ill pt on PN (expert opinion) |

November 2018

Expert consensus statements

- Sufficient scientific evidence to justify the indication of FO containing ILE as part of PN in:
  - Critically ill adult surgical patients (100% agreement)
  - Critically ill adult, non-surgical patients (sepsis) (94% agreement)
- Recommend use of FO containing ILE as part of PN in:
  - High-risk, critically ill, adult patients (i.e. sepsis, ARDS) (82% agreement)
  - High-risk, critically ill, adult patients (i.e. sepsis, ARDS) in the first week of PN (94% agreement)
  - Adult, surgical patients (94% agreement)
- FO containing ILE preferred over SO containing ILE
  - Home PN, & pt at risk for liver complications (100% agreement)

Probiotics
Probiotics in Critical Illness

- Disruption of microbiota → Dysbiosis

- Probiotics
  - Living microorganisms
  - Benefit the host when given in sufficient quantities
  - Modify gut microbiome
    - Induce cellular antimicrobial peptides
  - Suppress immune cell proliferation
  - Stimulate mucus and IgA production

Prebiotics and Synbiotics

° Prebiotics
  • Non-digestible sugars
  • Stimulate growth of certain bacterial colonies
  • Promote proliferation of commensal gut microbiota
  • Oligosaccharides, fiber, inulin
  • Metabolized to short chain fatty acids (SCFAs)
  • Little available data to support impact on clinical outcomes in the ICU

° Synbiotics
  • Contain both prebiotics and probiotics

## Probiotics

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCM-ASPEN 2016</td>
<td>We cannot make a recommendation at this time for the routine use of probiotics across the general population of ICU patients. Quality of Evidence: Low. May be beneficial in certain ICU pt (i.e. trauma, liver transplant, pancreatectomy, prevention of VAP)</td>
</tr>
<tr>
<td>DGEM 2019</td>
<td><em>Lactobacillus plantarum</em> and <em>Lactobacillus rhamnosus</em> GG may be used in patients after a severe trauma injury or liver transplantation requiring critical care. Strong consensus (90%)</td>
</tr>
</tbody>
</table>

# Probiotics in the ICU

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weng et al. Front Pharmacol. 2017</strong></td>
<td>Meta-analysis 13 RCTs, n=1969, <strong>MV patients</strong> probiotics vs PLB or other medication 11/13 trials included <em>Lactobacillus</em> spp.</td>
<td>• SS decrease in incidence of <strong>VAP</strong> (RR=0.73, 95% CI: 0.6,0.89) with probiotics</td>
</tr>
<tr>
<td><strong>Manzanares et al. Critical Care. 2016</strong></td>
<td>Meta-analysis 30 RCTs, n=2972, <strong>ICU patients</strong> Probiotics or probiotics + prebiotics vs PLB</td>
<td>• SS decrease in <strong>infections</strong> (RR 0.8, 95% CI: 0.68, 0.95) with probiotics &lt;br&gt; • SS decrease in <strong>VAP</strong> (RR 0.74, 95% CI: 0.61,0.9) with probiotics &lt;br&gt; • Studies with <em>L. plantarum</em> showed dec. infections vs trials without <em>L. plantarum</em></td>
</tr>
<tr>
<td><strong>Zhao et al. ERJ Open Res. 2021</strong></td>
<td>Meta-analysis 15 RCTs, n=2039, <strong>MV patients</strong></td>
<td>• SS decrease in <strong>VAP</strong> (RR 0.68, 95% CI: 0.60, 0.7) with probiotics</td>
</tr>
</tbody>
</table>

Effect of Probiotics on Infection in the ICU

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
<td>M-H, Random, 95%CI</td>
</tr>
<tr>
<td>Keckes 2003</td>
<td>1</td>
<td>22</td>
<td>0.15 [0.02, 1.12]</td>
<td>2003</td>
</tr>
<tr>
<td>Jain 2004</td>
<td>33</td>
<td>45</td>
<td>0.27 [0.93, 1.72]</td>
<td>2004</td>
</tr>
<tr>
<td>Lu 2004</td>
<td>8</td>
<td>20</td>
<td>0.73 [0.37, 1.42]</td>
<td>2004</td>
</tr>
<tr>
<td>McNaught 2005</td>
<td>21</td>
<td>52</td>
<td>0.34 [0.59, 1.48]</td>
<td>2005</td>
</tr>
<tr>
<td>Kotzamani 2006</td>
<td>22</td>
<td>35</td>
<td>0.70 [0.53, 1.93]</td>
<td>2006</td>
</tr>
<tr>
<td>Li 2007</td>
<td>8</td>
<td>14</td>
<td>0.33 [0.38, 1.03]</td>
<td>2007</td>
</tr>
<tr>
<td>Olah 2007</td>
<td>9</td>
<td>33</td>
<td>0.53 [0.27, 1.02]</td>
<td>2007</td>
</tr>
<tr>
<td>Basselink 2008</td>
<td>16</td>
<td>152</td>
<td>1.06 [0.75, 1.51]</td>
<td>2008</td>
</tr>
<tr>
<td>Barraud 2010</td>
<td>26</td>
<td>87</td>
<td>0.32 [0.53, 1.27]</td>
<td>2010</td>
</tr>
<tr>
<td>Ferrie 2011</td>
<td>14</td>
<td>18</td>
<td>0.38 [0.65, 1.18]</td>
<td>2011</td>
</tr>
<tr>
<td>Tan 2011</td>
<td>9</td>
<td>28</td>
<td>0.30 [0.32, 1.12]</td>
<td>2011</td>
</tr>
<tr>
<td>Lopez de Toro 2014</td>
<td>9</td>
<td>46</td>
<td>0.35 [0.31, 1.36]</td>
<td>2014</td>
</tr>
</tbody>
</table>

Total (95% CI): 550 (99.90%)

Total events: 206

Heterogeneity: $I^2 = 41\%$

Test for overall effect: $Z = 2.31 (P = 0.02)$

## Probiotics in prevention of VAP

### Additional RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mahmoodpoor et al. Nutr Clin Pract. 2019</strong></td>
<td>RCT, 2 SICUs in Iran n=120, <strong>MV patients</strong> Probiotic vs control x 14 d <em>Lactobacillus</em>, <em>Bifidobacterium</em>, and <em>Streptococcus</em> spp.</td>
<td>No SS difference in time to first episode of VAP (log-rank test 1.89, p=0.17)</td>
</tr>
<tr>
<td><strong>Johnstone et al. PROSPECT. BMJ Open. 2019</strong></td>
<td>RCT, multi-center, <strong>ongoing</strong> Planned n=2650 Probiotic vs placebo $1 \times 10^{10}$ colony forming units of <em>L rhamnosus</em> GG BID</td>
<td>Primary endpoint: Adjudicated VAP Safety: report sterile site cultures with <em>L rhamnosus</em> GG strain genotyping to evaluate consistency with the administered <em>L rhamnosus</em> GG strain.</td>
</tr>
</tbody>
</table>

Probiotics for Antibiotic-Associated Diarrhea (AAD) and Primary Prevention of *C. difficile* Infection (CDI)

- **American Gastroenterological Association (AGA) 2020 Practice Guidelines**
  - In patients with CDI, probiotic use only in clinical trial setting (no recommendation)
  - Suggest use of probiotics for those on antibiotic therapy for **prevention of CDI** (conditional, low quality of evidence)
    - Specifically recommend:
      - *S. boulardii*
      - 2-strain combination of *L. acidophilus* and *Lactobacillus casei*
      - 3-strain combination of *L. acidophilus, L. delbrueckii subsp. bulgaricus, B. bifidum*
      - 4-strain combination of *L. acidophilus, L. delbrueckii subsp. bulgaricus, B. bifidum, and S. salivarius subsp. thermophilus*
  - Based on 2017 Cochrane review including 39 studies, n=9955 patients
    - Probiotics reduced overall risk of CDI (RR, 0.4, 95% CI, 0.3-0.52)

Probiotics for AAD and Primary CDI Prevention

- 2017 Infectious Disease Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) *Clostridium difficile* Infection Guidelines
  - Insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials (no recommendation)

- 2017 IDSA Guidelines for Infectious Diarrhea
  - Probiotic preparations may be offered to reduce the symptom severity and duration in immunocompetent adults and children with infectious or antimicrobial-associated diarrhea (weak, moderate)

## Probiotics for AAD and Primary CDI Prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
</table>
| **Hempel et al. JAMA. 2012**   | Meta-analysis 63 RCTs, n=11,811, mainly outpatients on antibiotics  
Probiotics or synbiotic vs control  
Most trials included *Lactobacillus*-based probiotic/symbiotic (57/82) | Probiotics reduced AAD (RR=0.58, 95% CI: 0.5, 0.68)                     |
| **Allen et al. (PLACIDE). Lancet.2013** | RCT, multi-center  
n=2941, inpatient age ≥65 yr on IV antibiotics, excluded ICU pt  
*Lactobacillus* + *bifidobacteria* vs placebo x 21 d  
Probiotics could be started up 7d after antibiotics started | No SS difference with probiotic in AAD or C difficile diarrhea (RR=1.04, 95% CI: 0.84, 1.28) |
| **Shen et al. Gastroenterology. 2017** | Meta-regression analysis  
19 RCTs, n=6261, hospitalized pt on antibiotics  
ICU pt commonly excluded  
Probiotics vs control  
7 trials included *Lactobacillus* | Probiotics started within 48 hr antibiotic management had greater risk reduction of CDI (RR=0.32, 95% CI: 0.22,0.48) vs later administration (RR=0.7, 95% CI: 0.4, 1.23) |

Probiotic Safety Concerns

- PROPATRIA trial (2008) raised concerns in severe acute pancreatitis (SAP)
  - Probiotics given with fiber post-pyloric associated with higher mortality and small bowel necrosis
- Guo et al. (2014)- meta-analysis of 6 RCTs and 536 patients with SAP
  - No difference in pancreatic infection rate, infection rate, mortality
- Case reports of fungemia with *S. boulardii*
- Cases of bacteremia with *Lactobacillus* in immunocompromised patients and critically ill children
  - Whole genome sequencing identified strain-level relatedness with probiotic & isolate

Probiotics in the ICU: The Bottom Line

- Significant heterogeneity among trials of type, dose and treatment duration of probiotic, low quality of evidence
- Safety concerns in critically ill patients
- More studies used *Lactobacillus plantarum* and *Lactobacillus rhamnosus* GG
- Most evidence for probiotics in critically ill patients is for the prevention of VAP
  - Studies for other indications (AAD, CDI prevention) not in ICU population
- Most efficacy for primary prevention of CDI likely when started within 48 hr of antimicrobial therapy

Micronutrient Provision
Vitamin C

- Antioxidant, anti-inflammatory, and antithrombotic effects
- Cofactor for catecholamine synthesis
- Prevent sepsis-induced cytokine surge that activates/sequesters neutrophils in lung
- Recovery of glucocorticoid receptor function
- Thiamine promotes oxalate decomposition
  - Given with Vitamin C to reduce metabolite oxalate deposition, crystallization in the kidneys
- HAT
  - Hydrocortisone (HCT) 50 mg IV q6h
  - Ascorbic acid 1.5 g IV q6h
  - Thiamine 200 mg IV q6h
- Single-center observational study in 2017 showed 32% absolute reduction in mortality with HAT therapy in sepsis (n=94)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al. HYVCTSSSS. CHEST. 2020</td>
<td>RCT, single-center in China n=80, <em>sepsis or septic shock</em> &amp; procalcitonin ≥2</td>
<td>• Primary outcome: <strong>No SS in 28-day all cause mortality</strong> (27.5% vs. 35%, p=0.47)</td>
</tr>
<tr>
<td></td>
<td><strong>HAT vs placebo</strong> Duration: HCT x 7d, Vit C/thiamine x4d</td>
<td>• Sepsis subgroup showed improvement in mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No SS difference in other endpoints: Duration vasopressor use, MV, incidence of AKI</td>
</tr>
<tr>
<td>Fujii et al. VITAMINS. JAMA. 2020</td>
<td>RCT, multi-center n=211, <em>septic shock</em></td>
<td>• Primary outcome: <strong>No SS diff. in time alive &amp; vasopressor free up to day 7</strong> (median of all paired differences -0.6 h, 95% CI: -8.3, 7.2)</td>
</tr>
<tr>
<td></td>
<td><strong>HAT vs HCT 50 mg IV q6h</strong> Duration: Until shock resolution or up to 10 d</td>
<td>• No SS in other endpoints: 28-day mortality, AKI</td>
</tr>
<tr>
<td>Mohamed et al. ViCTOR. Indian J Crit Care Med. 2020</td>
<td>RCT, single-center, India n=90, <em>septic shock</em></td>
<td>• Primary outcome: <strong>No SS diff. in all-cause mortality in HAT vs routine care</strong> (57% vs 53%, p=0.4)</td>
</tr>
<tr>
<td></td>
<td><strong>HAT vs routine care</strong> Duration: x 4d</td>
<td>• Mean time to shock reversal SS lower in the HAT group (mean difference -10.84 h, 95% CI -20.8 to -0.87).</td>
</tr>
</tbody>
</table>

# Vitamin C Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient/Methods</th>
<th>Results</th>
</tr>
</thead>
</table>
| Fowler et al. CITRIS-ALI. JAMA. 2019 | RCT, multi-center, US n=167, sepsis and ARDS  
Vitamin C 50 mg/kg IV q6h vs placebo  
Duration: 96 h | • Primary outcomes:  
  • No SS diff. in mean modified SOFA score at 96 h  
    (diff. -0.10, 95% CI: -1.23,1.03)  
  • 43 of 46 secondary endpoints, no SS difference  
    • 28-day mortality improved with Vit C vs PLB  
      (29.8% vs 46.3%, p=0.03)  
    • Greater number of ICU and hospital-free days Vit C vs placebo |
| Iglesias et al. ORANGES. CHEST. 2020  | RCT, 2 ICUs, US n=137, sepsis and septic shock  
HAT vs placebo  
Duration: 96 h | • Primary outcomes:  
  • SS difference in time to resolution of shock (off vasopressors) with HAT vs PLB  
    (27±22 h vs 53±38 h, p<0.001)  
  • No SS in change in SOFA score at 96 h  
  • No SS diff in ICU mortality |

# Vitamin C Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moskowitz et al. ACTS. JAMA. 2020</td>
<td>RCT, multi-center, US n=206, septic shock&lt;br&gt;HAT vs placebo&lt;br&gt;Duration: 96 h&lt;br&gt;Open label corticosteroids in 6.9% HAT vs 14.1% placebo group.</td>
<td>• Primary outcome: <strong>No SS difference in change in Sequential Organ Failure Assessment (SOFA) score at 72 h</strong> (adj. mean diff. -0.8, 95% CI: -1.7, 0.2)&lt;br&gt;• No SS difference in incidence kidney failure or 30-day mortality</td>
</tr>
<tr>
<td>Sevransky et al. VICTAS. JAMA. 2021</td>
<td>RCT, multi-center, US n=501, sepsis-induced CV &amp;/or respiratory dysfunction d/t infection&lt;br&gt;HAT vs control&lt;br&gt;Duration: 96 h or until d/c or death&lt;br&gt;Open-label corticosteroids used in 33% HAT group and 32% controls</td>
<td>Primary outcome: <strong>No SS difference in number of consecutive ventilator-and vasopressor-free days in first 30 d</strong> (median diff. -1 d, 95% CI: -4, 2)&lt;br&gt;No difference in 30-day mortality (22% HAT vs 24% control) or RRT-free days</td>
</tr>
</tbody>
</table>

Vitamin C in the ICU: The Bottom Line

- Randomized trials since 2019 have failed to show a mortality benefit for HAT or vitamin C in sepsis
- ESPEN 2019 ICU Guidelines
  - Antioxidants as high dose monotherapy should not be administered without proven deficiency
    *(Grade B recommendation, strong consensus)*
- Argument for HAT
  - Some trials may be negative due to late timing of HAT (VITAMINS) or trial design (VICTAS stopped early, CITRIS-ALI survivorship bias)
  - No trials demonstrated safety concerns (AKI, RRT)
- Argument against HAT
  - 7 randomized trials with primary outcomes that do not support HAT in sepsis

Questions
Assessment Questions

1. Which probiotic is recommended for the primary prevention of *C. difficile* infection for adults on antibiotic therapy by the American Gastroenterological Association?
   a. *Lactobacillus rhamnosus GG*
   b. *Saccharomyces boulardii*
   c. *Lactobacillus acidophilus*
   d. *Bifidobacterium bifidum*
Saccharomyces boulardii

The AGA recommends the use of S boulardii, 2-strain combination of L acidophilus and Lactobacillus casei, or the 3-strain combination of L acidophilus, Lactobacillus delbrueckii subsp bulgaricus, and Bifidobacterium bifidum, or the 4-strain combination of L acidophilus, L delbrueckii subsp bulgaricus, B bifidum, and Streptococcus salivarius subsp thermophilus over other probiotics for prevention of C difficile infection in adults on antibiotic therapy. This is a conditional recommendation based on low quality of evidence.

What was the primary outcome result of the VICTAS trial?

a. Vitamin C decreased 28-day all-cause mortality in patients with acute lung injury in the setting of sepsis compared to placebo.

b. Vitamin C in combination with thiamine and hydrocortisone increased the number of ventilator and vasopressor-free days in the first 30 days in sepsis-induced respiratory dysfunction and/or cardiovascular dysfunction compared to placebo.

c. Vitamin C in combination with thiamine and hydrocortisone showed no significant difference in the number of ventilator and vasopressor-free days within 30 days in sepsis-induced respiratory dysfunction and/or cardiovascular dysfunction compared to placebo.

d. Vitamin C, thiamin, and hydrocortisone did not significantly improve duration of time alive or free of vasopressors over 7 days compared to hydrocortisone alone in patients with septic shock.
Assessment Questions

° Vitamin C in combination with thiamine and hydrocortisone showed no significant difference in the number of ventilator and vasopressor-free days within 30 days in sepsis-induced respiratory dysfunction and/or cardiovascular dysfunction compared to placebo.

° In the VICTAS trial, Vitamin C 1500 mg IV q6h in combination with thiamine 100 mg IV q6h and hydrocortisone 50 mg IV q6h showed no statistically significant difference in the primary outcome of the number of ventilator- and vasopressor-free days, compared to placebo (median, 25 [IQR, 0-29] days vs 26 [IQR, 0-28] days, respectively; difference, −1 (95% CI, −4 to 2) days; $P = .85$).

° Answer a and b are false, and answer d is the primary outcome for the VITAMINS trial.

° Reference:
Assessment Questions

Which of the statements below is true regarding IV lipid emulsions?

a. Omega-3 fatty acid enriched parenteral nutrition is associated with an increase in ICU length of stay.

b. Omega-3 fatty acid enriched parenteral nutrition is associated with an increase in infections in hospitalized patients compared to standard (non-omega-3 fatty acid enriched parenteral nutrition).

c. The ASPEN consensus statement from the Lipids in Parenteral Nutrition International Summit is that 0.1 to 0.2 g fish oil/kg/day should be provided as part of IV lipid emulsion in critically ill patients.

d. Omega-3 fatty acid enriched parenteral nutrition has not been shown to provide a clinical benefit in hospitalized surgical patients.
Assessment Questions

- The ASPEN consensus statement from the Lipids in Parenteral Nutrition International Summit is that 0.1 to 0.2 g fish oil/kg/day should be provided as part of IV lipid emulsion in critically ill patients.

- C is the correct answer, as ASPEN expert consensus statements from the Lipids in Parenteral Nutrition International Summit recommend that 0.1 to 0.2 g fish oil/kg/day should be provided as part of IV lipid emulsion in critically ill patients. Answers a and b are false, omega-3 fatty acid enriched parenteral nutrition is associated with a decrease in ICU length of stay and infections in hospitalized patients. Answer d is false, omega-3 containing IV lipid emulsions have been associated with a decrease in the risk of infectious complications in surgical patients.

- References:
Assessment Questions

Which of the following is the correct composition of Smoflipid®?

a. 20% soybean oil, 80% olive oil
b. 30% soybean oil, 30% medium chain triglyceride oil, 25% olive oil, 15% fish oil
c. 100% fish oil
d. 100% soybean oil
Assessment Questions

- **30% soybean oil, 30% medium chain triglyceride oil, 25% olive oil, 15% fish oil**

- Answer b is correct. Answer a is Clinolipid®, assert c is Omegaven®, answer d is standard IV lipid emulsion such as Intralipid® or Nutrilipid®.

AG is a 43 yr old male (50 kg, 69 inches) with a past medical history of renal cell carcinoma, NASH, diabetes, and severe malnutrition. He is on invasive mechanical ventilation for acute respiratory distress syndrome (ARDS), continuous renal replacement therapy, with an open abdomen. He is in the ICU currently day 5 s/p open right nephrectomy c/b IVC injury, hemoperitoneum, hemorrhagic shock and abdominal compartment syndrome. A parenteral nutrition (PN) consult is ordered as he cannot receive EN due to his small bowel being in discontinuity until he is stable to return to the OR. Which of the following is the best option for Day 1 PN macronutrient provision to be administered through his PICC line?

a. Amino acid 50 g, 120 g dextrose, 20 g Smoflipid®
b. Amino acid 20 g, 250 g dextrose, 50 g IV Intralipid®
c. Amino acid 50 g, 120 g dextrose, 100 g IV Smoflipid®
d. Amino acid 50 g, 120 g dextrose, 20 g IV Intralipid®
Amino acid 50 g, 120 g dextrose, 20 g Smoflipid®

Answer a is the best option, as this provides 1 g/kg/day amino acids, 120 g dextrose (glucose infusion rate 1.7 mg/kg/min) and 24% of calories as lipid injectable emulsion. This is appropriate for day 1 PN in a critically ill patient. Additionally, given his recent abdominal surgical history and current ARDS, the utilization of omega-3 fatty acid enriched parenteral nutrition may reduce his ICU length of stay and risk of infection compared to standard soybean oil-based lipid injectable emulsions (Intralipid®). Answer b is incorrect, 20 g of amino acid is too low, and the balance of calories is not appropriate. Answer c is incorrect, as lipid injectable emulsion accounts for 62.5% of total calories, which is high and not the best answer. Answer d has an appropriate caloric balance, but is not the best option for him given the evidence with omega-3 fatty acid enriched parenteral nutrition compared to standard soybean oil-based lipid injectable emulsion.

References:


References

- Mundi MS, Klek S, Martindale RG. Use of lipids in adult patients requiring parenteral nutrition in the home parenteral nutrition setting. JPEN. 2020;44:S39-S44.


