Managing Nutrition Support for Critically Ill COVID-19 Patients: Top 12 Key Recommendations

Welcome to the Webcast!

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Disclosure: Baxter advisory panel and educational development
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Today’s Speakers

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Disclosure: Advisory board – Nestle, Fresenius Kabi, and Baxter

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Disclosure: Baxter advisory panel

COVID-19 Resources
Objectives

• Discuss the role of delivering and monitoring nutrition support in COVID-19 ICU patients
• Describe best practices experienced in treating COVID-19 patients
• Identify characteristics and nutritional requirements of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
• Outline recommendations for SARS-CoV-2 patients to meet nutritional requirements using enteral and or parenteral nutrition
• Identify instances when managing SARS-CoV-2 deviates from current nutrition guidelines for enteral and parenteral nutrition in ICU patients
• Discuss potential novel nutrient recommendations for SARS-CoV-2 patients

Consider This Case

• A 62-year-old man with T2 esophageal cancer undergoing neo-adjuvant chemo/radiation preoperatively presents with 2-days of progressively worsening shortness of breath, fever, and malaise.
• In the clinic → tachypneic, hypoxemic, and oxygen saturation 80% despite 6 liters high-flow nasal cannula
• Transferred to the ED and intubated
• Hypotensive → 2 liters IV crystalloid and norepinephrine infusion
• Chest CT demonstrates dense bilateral lower lobe opacities.
• Transferred to the ICU:
  • Strict isolation
  • Febrile to 38.3°C (101°F)
  • Norepinephrine gtt 0.04 µg/kg/min.
Nutrition Is an Integral Component of Any Supportive Care in the ICU

- Critical illness exists in phases: early acute → late acute → post-acute.
- During the acute phase, hypercatabolism is the general rule, which leads to energy debt and loss of lean body mass.
- Amino acids are mobilized predominantly from muscle, which leads to negative nitrogen balance and acquired sarcopenia.
- Critical illness induces gut dysfunction and dysbiosis, which propagates and accentuates the inflammatory response, leading to cellular dysfunction, with end result being multiple organ failure.

Consider This Case...Now

- A 62-year-old man with T2 esophageal cancer undergoing neo-adjuvant chemo/radiation preoperatively presents with 2-days of progressively worsening shortness of breath, fever, and malaise.
- In the clinic → tachypneic and hypoxemic with oxygen saturation 80% despite 6 liters high-flow nasal cannula.
- Transferred to the ED and intubated.
- Hypotensive and receives 2 liters crystalloid and norepinephrine infusion initiated.
- Chest CT shows dense bilateral lower lobe opacities.
- Transferred to the ICU:
  - Strict isolation
  - Febrile to 38.3°C (101°F)
  - Norepinephrine 0.04 µg/kg/min.

TESTING FOR COVID-19 RETURNS POSITIVE
What Is It About This Virus That Is Different From Hundreds of Other Viruses Our Bodies Deal With Daily?

- Coronaviruses are a large family of viruses, including those that cause common cold.
  - Found throughout the world and account for up to 30% of upper respiratory tract infections in adults.
  - Found in many species of animals, including camels, cattle, and bats
    - Rarely jumps species
  - Several recent of virus outbreaks include SARS-CoV 2002 and MERS-CoV 2012
- Longer latency (incubation) period: up to 2 weeks
- Shedding virus without symptoms, estimated 20% asymptomatic
- Aerosolized droplet transmission, fecal/oral
- SARS-CoV-2 is good at taking over host cells’ metabolic machinery
  - SARS Co-2 is single-stranded positive-sense RNA
    - Only 30,000 bases vs. human genome with over 3 billion bases
    - Has 29 proteins encoded on its gene
- Encouraging news:
  - Many cities are flattening the curve
  - Promising target protein for vaccine found by multiple investigators
    - Spike protein: good target for vaccine development.
    - Spike protein allows entry into host cells.
Characteristics of and Important Lessons From the COVID-19 Outbreak in China

Summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention

Age distribution (N = 44,672)
- ≥ 80 years: 3% (1408)
- 30-79 years: 87% (38,680)
- 20-29 years: 8% (3619)
- 10-19 years: 1% (549)
- < 10 years: 1% (416)

Spectrum of disease (N = 44,415)
- Mild: 81% (36,160)
- Severe: 14% (6168)
- Critical: 5% (2087)

Case-fatality rates
- 2.3% (1023 of 44,672 confirmed cases)
- 14.8% in patients aged ≥ 80 years (208 of 1408)
- 8.0% in patients aged 70-79 years (312 of 3918)
- 49.0% in critical cases (1023 of 2087)

Healthcare personnel infected
- 3.8% (1716 of 44,672)
- 63% in Wuhan (1080 of 1716)
- 14.8% cases classified as severe or critical
- (247 of 1668)
- 5 deaths

Clinical Predictors of Mortality due to COVID-19 Based on an Analysis of Data of 150 Patients from Wuhan, China

Intensive Care Medicine 2020

Cause of Death

Age (Years)

Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized with COVID-19 in the New York Area

- 5700 sequential admission between 3/1/20-4/4/20
  - Mean age 63 (39% female)
  - Comorbidities
    - HTN 56.6%, Obesity 41.7%, Diabetes 33.8%
  - Presenting signs/symptoms
    - 30.7% febrile, 17% RR > 24 breaths/min, 28% received O2
  - Outcomes for 2634
    - 14% treated in ICU, 12% received mechanical ventilation
    - 3.2% required RRT
    - 21% Mortality
      - Mortality in MV patients 88%
    - 2.2% readmission rate

General Characteristics of COVID-19 Patients Being Admitted: Global Observations

**Most patients:**
- Severe inflammation
  - elevated C-reactive protein
- Increased work of breathing
- Hypoxemia
- Fever
- Anorexia
- Fatigue

**Many patients:**
- Normal or low WBCs
- Decreased lymphocytes
- Elevated liver function tests
- HTN
- Obesity
- Diabetes
- Acute kidney injury
- Gastrointestinal intolerance
- Alteration of taste and smell
Basic Principles to Consider With COVID-19 in the ICU

- Infection control
- Duration of disease
- Support and resources required
  - Space
  - Staff
  - Supplies

Guiding Principles Relevant to COVID-19

- Practice “cluster care,” meaning to make all attempts to bundle care to limit exposure.
- Adhere to CDC and WHO recommendations to minimize exposures with COVID-19-positive patients.
- Preserve use of PPE.
What Nutritional Inferences Can We Draw About Critically Ill Patients With COVID-19?

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Potential implications for nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older patients</td>
<td>Preexisting malnutrition, sarcopenia</td>
</tr>
<tr>
<td>More comorbidities</td>
<td>Preexisting malnutrition, refeeding</td>
</tr>
<tr>
<td>Severe acute respiratory distress syndrome</td>
<td>Safety of feeding in prone positioning and ECMO</td>
</tr>
<tr>
<td>Circulatory failure</td>
<td>Safety and tolerance of feeding</td>
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<tr>
<td>Multiple organ failure</td>
<td>Role of enteral nutrition in mitigating gut-derived inflammation</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>Monitoring triglycerides in parenteral nutrition and propofol</td>
</tr>
</tbody>
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Recommendation 1

Utilize a weight-based energy estimation for EN and PN:  
• 15-20 kcal/kg actual body weight (ABW)/day (70%-80% of needs)  
• 1.2-2.0 g protein/kg ABW/day

Rationale:  
• Indirect calorimetry, while the gold-standard for estimating energy needs, increases patient exposure to clinicians and risk for aerosolization.

Recommendaion 1a

Assess for refeeding syndrome risk, and if present, start 25% of caloric goal with slow increase while closely monitoring serum phosphate, magnesium, and potassium levels

Refeeding Syndrome Risk factor include:
• Anorexia or limited calorie intake 5 to 7 days
• 58% COVID-19 patients have anorexia on admission

Rationale:
• If extremely limited or no energy/caloric intake for at least 5-7 days, patients are often at risk of refeeding syndrome.

Recommendation 2

Start early EN, within 24-36 hours of ICU admission or within 12 hours of intubation

Rationale:
• Provision of early EN in ICU patients has shown improved mortality and reduced infections when compared to delayed EN or withholding EN.1,2 Meta-analysis from 2000-2013 still demonstrated less infectious risk with EN when compared to PN use in ICU patients.1
• EN shown safe with shock with stable dose vasopressor.3

**Recommendation 3**

Start early EN, delivered into stomach, over PN

- If unable to feed into stomach have low threshold to convert to PN

**Rationale:**

- Early EN may maintain gut barrier and immune functions
- Placing nasojejunal tubes in COVID-19 patients in most cases increases patient exposure to clinicians.
  - Limiting number of people and equipment in rooms (e.g., radiograph to confirm placement).
  - Large-bore NGTs do not normally require radiographic confirmation.
  - If attempting to place nasojejunal tubes, recommend N95 mask, PAPR suit, and PPE consistent with upper airway management PPE.

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**Recommendation 4**

Start low dose (10-20 mL/hour) of a standard EN isotonic (1.5 kcal/mL) high-protein formula and advance to 80% goal by end of the first week with medical stability.¹

- Maintain trophic rate with unstable hemodynamics.²
- If unable to progress by 5 to 7 days with EN, consider supplemental PN.
- If patient was malnourished before ICU admission and unsuccessful at EN, start PN earlier.

**Rationale:**

- The early acute phase of critical illness represents the period of greatest risk for enteral feeding intolerance, including vomiting, ileus, and mesenteric ischemia.
- Meta-analyses of RCTs comparing low to full dose EN in the first week of critical illness favor low-dose EN.³

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Recommendation 5

Do not check gastric residual volume (GRV).\(^2\)

**Rationale:**
- GRV is *not* a reliable indicator of enteral feeding intolerance in ICU patients and may lead to undernutrition
- Checking GRV several times per day will significantly increase risk of virus exposure and transmission.

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**Recommendation 6**

Deliver EN continuously into the stomach
- With gastric feeding, minimal expertise if placement needed
- Allows use of existing NGT/OGT placed at time of intubation

**Rationale:**
- Less staff time is required for NGT/OGT placement compared to post-pyloric tube, limiting virus exposure.
- Less risk of tube occlusion with larger-bore tubes
- Continuous over bolus feeding: less diarrhea, optimizes blood glucose control, less staff interaction needed and limiting exposure
- Newer studies confirm little metabolic difference in conserving muscle mass between bolus and continuous feeding in ICU patients.

*McNelly AS et al Chest 2020 (Epub ahead of print)*
**Recommendation 7**

Switch to PN when EN via gastric feeding is not an option.1,2

- Consider promotility agents and semi-elemental diet to improve tolerance.
- If signs of ileus persists, switch to PN.1
- If escalating vasopressor requirement, switch to PN.

**Rationale:**
- The threshold for switching to PN or supplementing with PN for COVID-19 patient may need to be lower, especially when EN is not safe or not tolerated.
- Intubated COVID patients require a prolonged ICU stay, and without adequate feeding, will actualize large calorie and protein deficits.
- As the patient’s condition improves, gastric EN should be reattempted.

**Note:** This is different from statements made in the 2016 guidelines.

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**What Do Guidelines Say About Exclusive PN?**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year</th>
<th>Recommendation for Exclusive PN</th>
</tr>
</thead>
</table>
| SCCM/ASPIN | 2016 | 1. We suggest that, in the patient at low nutrition risk (eg, NRS 2002 ≤ 3 or NUTRIC score ≤ 5), exclusive PN be withheld over the first 7 days following ICU admission if the patient cannot maintain volitional intake and if early EN is not feasible.  
2. Based on expert consensus, in the patient determined to be at high nutrition risk (eg, NRS 2002 ≥ 5 or NUTRIC score ≥ 5) or severely malnourished, when EN is not feasible, we suggest initiating exclusive PN as soon as possible following ICU admission. |
| ESPEN | 2018 | In patients who do not tolerate EN during the first week of critical illness, the safety and benefits of initiating PN should be weighted on a case-by-case basis. |
Safety of Exclusive PN Informed by RCTs

Trial of the Route of Early Nutritional Support in Critically Ill Adults


Enteral Versus Parenteral Early Nutrition in Ventilated Adults With Shock: A Randomised, Controlled, Multicentre, Open-Label, Parallel-Group Study (NUTRIREA-2)


<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>ENTERAL (n=1202)</th>
<th>PARENTERAL (n=1208)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 28 mortality, n (%)</td>
<td>443 (37)</td>
<td>422 (35)</td>
<td>0.33</td>
</tr>
<tr>
<td>Median days with EN (IQR)</td>
<td>6 (3-8)</td>
<td>1 (0-3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Daily caloric intake, kcal/kg/d (±SD)</td>
<td>17.8 (5.5)</td>
<td>19.6 (5.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Daily protein intake, g/kg/d (±SD)</td>
<td>0.7 (0.2)</td>
<td>0.8 (0.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICU LOS, median days (IQR)</td>
<td>9 (5-16)</td>
<td>10 (5-17)</td>
<td>0.08</td>
</tr>
<tr>
<td>ICU acquired infections, n (%)</td>
<td>173 (14)</td>
<td>194 (16)</td>
<td>0.25</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>406 (34)</td>
<td>246 (24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>432 (36)</td>
<td>393 (33)</td>
<td>0.009</td>
</tr>
<tr>
<td>Bowel ischemia, n (%)</td>
<td>19 (2)</td>
<td>5 (&lt;1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Colonic pseudo-obstruction, n (%)</td>
<td>11 (1)</td>
<td>3 (&lt;1)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Recommendation 8
Provide 2.0–2.5 g/kg ABW/day in critically ill patients with renal failure undergoing renal replacement therapy (RRT) and monitor micronutrients.

Rationale:
• Patients with renal failure requiring dialysis lose as much as 10 grams amino acids in the dialysate. Observational data has demonstrated that up to 2.5 g/kg/day protein is tolerated and associated with conversion to positive nitrogen balance.
• Micronutrients in critically ill patients with severe acute kidney injury
  • > 30% of patients on CRRT and non-CRRT had plasma level lower than normal.

Recommendation 9
Limit pure soybean lipid emulsions the first week and monitor triglyceride levels early in the PN course.
• Use alternative lipids or limit/withhold soybean lipids the first week.
  • Alternate lipid emulsions available in United States:
    • Olive oil: soy oil (80% olive oil/20% soy)
    • Soy, medium-chain triglycerides (MCT), olive oil, fish oil (30% soy/30% MCT/25% olive oil/15% fish oil)

Rationale: There are early anecdotal reports of rapid elevations in serum lipids with emulsions in those who have rapid progression of disease (from New York City, New Orleans, and Milan, Italy)
• Remember: Propofol in the United States is in 10% soy solution.
Recommendation 10

Use EN over PN during prone-positioning
- Isotonic high-protein formula starting at 10-20 mL/hr
- Keep head of bed elevated (reverse Trendelenburg position) to at least 10 to 25 degrees with gastric feeding.

Rationale:
- No increased risk of gastrointestinal or pulmonary complications in prone position has been noted.\(^1,2\)
- Increasing head of bed elevation decreases risk of aspiration of gastric contents, facial edema, and intra-abdominal hypertension.\(^3\)

Recommendation 11

Attempt EN via gastric feeding during ECMO
- Start early, low-dose EN
- Slow advancement to goal over first week
- If increasing vasopressor requirements: hold and consider PN.

Rationale:
- In the largest observational study of EN during VA-ECMO, early EN, as compared to delayed EN, was associated with improvement in 28-day mortality and zero incidence of bowel ischemia.\(^1\)
- Increased EN calories/protein delivered were associated with decreased risk of 90-day mortality.\(^2\)
- Anecdotal discussions with ECMO centers find very poor outcome with SARS-CoV-2.


**Sequence of Events at the Organ Level**

- Decrease of oxygenation of splanchnic organs
- Hypoxemic pulmonary failure
- Gut hypoxia
- Mesenteric ischemia: loss of mucosal integrity
- Toxins and bacterial translocation
  - Altered immune response
  - Microbiome to virulent pathobiome
- Further hypoxia
- Endotoxins, TNF, IL-1, IL-6, pancreatic lipase, FFA enter circulation via PV and lymphatics
- MOF
- Further hypoxia

**Recommendation 12**

Manage feeding in shock as any other shock patient (i.e., resuscitation takes priority)
- If EN unsuccessful (e.g., intolerance), transition to early PN.
  - Use caution with both EN or PN in hemodynamically unstable patients.

**Rationale:**
- No reason to alter standard guideline recommendation for therapy with the exception of minimizing exposure of healthcare workers.\(^1\text{-}^3\)
- Overall, risk for NOBN is rare - 0.3\% across observational and contemporary RCT-level data.\(^4\)

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Potential Nutritional Interventions for COVID-19: Theory, Extrapolation, and Anecdotes

• Large amount of conflicting information is coming out for nutritional options in COVID-19
• Providing false hope with untested and unstudied nutritional agents will only be detrimental to our patients and their families.
• In illnesses caused by SARS-CoV-2, the key is knowing what we know and, more importantly, knowing what we don’t know.
• Care for our patients cannot be driven by fear and misinformation, which often supersedes scientific evidence.
• These concepts should be thought of as hypothesis generating.

Potential Nutritional Approaches: Theory, Extrapolation, and Anecdotes: No COVID-19-Specific Data...Yet

• Inflammation control
• Fish oil
  • Enhancing inflammation resolution
    • Specialized pro-resolving mediator (SPM) and viral clearance
• Probiotics
  • Data from other viral etiology URI infections
• Vitamin supplements
• Mineral supplements
Inflammation Has 2 Phases: Initiation and Resolution

Infection Regulates Pro-Resolving Mediators That Lower Antibiotic Requirements

SPMs accelerate resolution of infections and reduce inflammation. Treating the host with SPM lowers the required antibiotic doses.

Influenza: Time to Target the Host?

Clinical Implications of Basic Research

- Several SPMs lower mortality in viral illness.
- Protectin D1 inhibits viral replication.

Controlling Herpes Virus Simplex Virus-Induced Ocular Inflammatory Lesions with the Lipid-Derived Mediator Resolvin E1

Human Sepsis Eicosanoid and Pro-resolving Lipid Mediator Temporal Profiles: Correlations With Survival and Clinical Outcomes

- Associated outcome with resolution mediators
- N = 22 septic patients
  - Followed proinflammatory and pro-resolution mediators
    - Lipid mediator profiling: 30 bioactive mediators followed
      - AA, EPA, DHA metabolome
    - Serum lipid profiles within 48 hours of admission, then at 3 and 7 days

- Conclusion:
  - Resolution lipid mediators associated with **better survival and decrease ARDS.**

**Caution: Association does not indicate causation!**
Probiotics and Prevention of Upper Respiratory Viral Infections

- Rhinovirus, coronavirus, parainfluenza virus, respiratory syncytial virus, adenovirus

Probiotics for Preventing Acute Upper Respiratory Tract Infections (Review)

- To assess the effectiveness and safety of probiotics (any specified strain or dose), compared with placebo, in the prevention of acute upper respiratory tract infections (URIs) in people of all ages
- 12 studies included in the analysis (71 studies available)
  - 3720 participants (children and adults)
  - Placebo versus probiotics
- **Probiotics were better than placebo in number of acute URIs**
  - OR 0.53; 95% CI, 0.36-0.76; p < 0.001
- **Probiotics were better than placebo in reducing the mean duration of URI**
  - OR –1.89 days; 95% CI, –2.03 to –1.75, p < 0.001

Vitamin Supplementation

Animal data or theoretical concepts: no COVID-19-specific data

Vitamin B₁, B₂, B₃ (nicotinamide), B₆
• Multiple reports: results are quite variable¹
  • Suspected benefits from “enhancing” immune function

Vitamin D
• If deficient, helpful in viral infections (animal models)²
• Recent well done ICU trials in vitamin D-deficient patients: no benefit³,⁴

Vitamins: No COVID-19-Specific Data

Vitamin A
• Animal model (chickens) on low vitamin A diets show increased risk of coronavirus.¹

Vitamin C
• SARS coronavirus (increased resistance to avian coronavirus in broiler chickens)²
  • Vitamin C reported to decrease mechanical ventilation³
  • Vitamin C in critically ill meta-analysis inadequate data to support⁴
  • Vitamin C study in sepsis and ARDS. 96-hour infusion of vitamin C versus placebo:
    • no benefit⁵

Vitamin E
• Data in animals (murine, bovine)
• Coxsackie virus B₃ a RNA virus

References:
Trace Minerals

Selenium
- Oxidative stress associated with viral infections
  - Selenium associated with many antioxidant enzymes (selenoproteins)
    - GPX, SOD, thioredoxin reductase
  - Suspected to alter viral replication, protect cell from viral-induced oxidative stress
    - Speculation, many questions regarding dose, timing, +/- deficiency

Zinc
- Key to development and function of immune system, both innate and humoral
- Impairs viral replication (in vitro)
  - Works in a variety of RNA viruses
  - Shown in SARS-CoV with pyrithione inhibits replication
- Reported to be beneficial in some viral infections if deficient
  - Supplements given to zinc-deficient children with measles decreases mortality
  - Data is not consistent
- Zinc acetate lozenges?

Bottom Line

1. There are insufficient data to recommend any additional specific supplement over the standard ICU requirements unless vitamin or mineral deficiency is suspected on admission.
2. Caution: There are no COVID-19-specific data for antioxidant cocktails, megadoses of supplements, etc.

**Bottom Line**

- The delivery of nutritional therapy to the patient with SARS-CoV-2 should follow the basic principles of critical care nutrition as recommended by European and North American societal guidelines.
- Early use of continuous gastric feeds, not checking GRVs, early use of PN in patients intolerant to gastric feeds to avoid endoscopic/fluoroscopic-placed post-pyloric tube are strategies that:
  1. Promote clustered care
  2. Reduce the frequency with which healthcare providers interact with COVID-19 positive patients
  3. Minimize contamination of additional equipment while promoting optimal nutrition therapy for these patients

**Case Resolution**


**Does he have preexisting malnutrition or risk of refeeding?**

**Taking guiding principles into consideration:**

- Start trophic dose EN but preserve protein dose at 1.2 g/kg/day.
- Deliver EN into the stomach.
- Monitor for enteral feeding intolerance and refeeding.
- If intolerant despite prokinetic → low threshold to start PN.
- Slow ramp-up over the first week of critical illness.
- Special considerations (e.g., dialysis, triglyceride levels).
Question and Answer

Robert Martindale, MD, PhD
Jayshil Patel, MD
Beth Taylor, DCN, RDN-AP, CNSC, FAND, FASPEN, FCCM
Moderator

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