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April 3, 2020

Enteral Nutrition in the ICU: COVID-19 Challenges

Speakers:

Robert Martindale, MD, PhD

Jayshil Patel, MD

Moderator:

Cindy Lowen, RD, CNSC, CCRP

Sponsor Disclosure

Sponsor Disclosure: Financial support for this presentation was provided by Nestlé Health Science. The views expressed herein are those of the presenters and do not necessarily represent Nestlé's views. The material herein is accurate as of the date it was presented, and is for educational purposes only and is not intended as a substitute for medical advice.

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Speakers

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Professor of Surgery
Division of General Surgery
Oregon Health & Science University
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Associate Professor of Medicine
Division of Pulmonary Medicine
Medical College of Wisconsin
Milwaukee, Wisconsin

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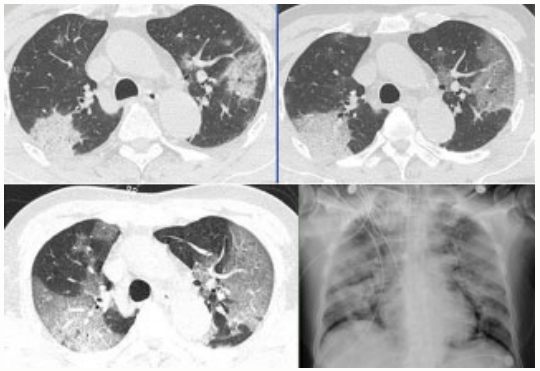
Objectives

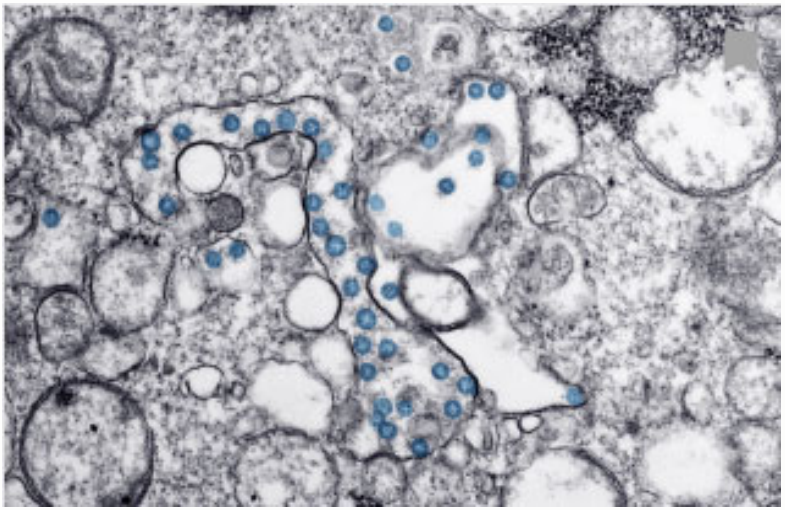
- Identify characteristics and nutritional requirements of the patient with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
- Describe the recommendations for enteral nutritional support of the patient with SARS-CoV-2 and applicability of current ICU EN protocols
- Discuss potential novel nutrient recommendations for the SARS-CoV-2 patient

Guidance and Recommendations for Nutritional Support for Critically ill Patients with COVID-19

- Robert Martindale MD, PhD
- Oregon Health and Science University

- Jayshil Patel MD
- Medical College of Wisconsin





Worldwide cases **Tuesday 3-31-20 12:00pm**

Location	Confirmed	Recovered	Deaths
Worldwide	**823,479**	**162,937**	**40,636**
United States	**177,320**	**5,995**	**3,447**
Italy	105,792	15,729	12,428
Spain	94,417	19,259	8,269
China	83,059	76,052	3,305

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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, hyper-catabolism is the general rule, which leads to energy debt and loss of lean body mass

Amino acids are mobilized from predominantly muscle, which leads to negative nitrogen balance and acquired sarcopenia

Critical illn*ess* induces gut dysfunction and dysbiosis, which propagates *and* accentuates the inflammatory response leading to cellular dysfunction with end result being multiple organ failure

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Characteristics of and Important Lessons from the Corona Virus Disease 2019 (COVID-19) Outbreak in China

› Summary of a Report of 72,314 Cases from the Chinese Center for Disease Control and Prevention

Wu, Z JAMA 2020

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

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

Case-fatality rate
- 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)

Health care 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

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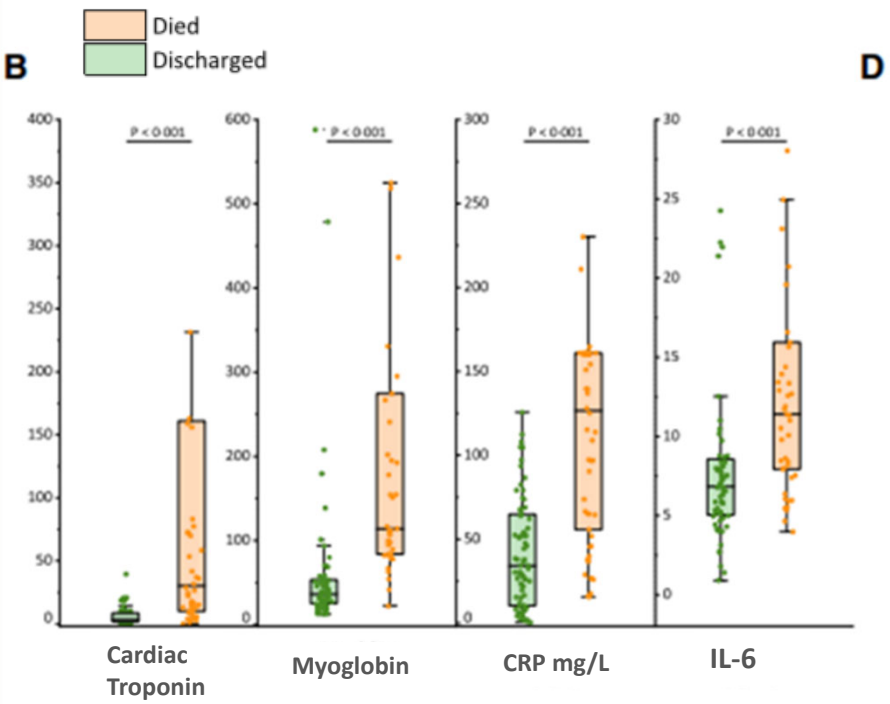
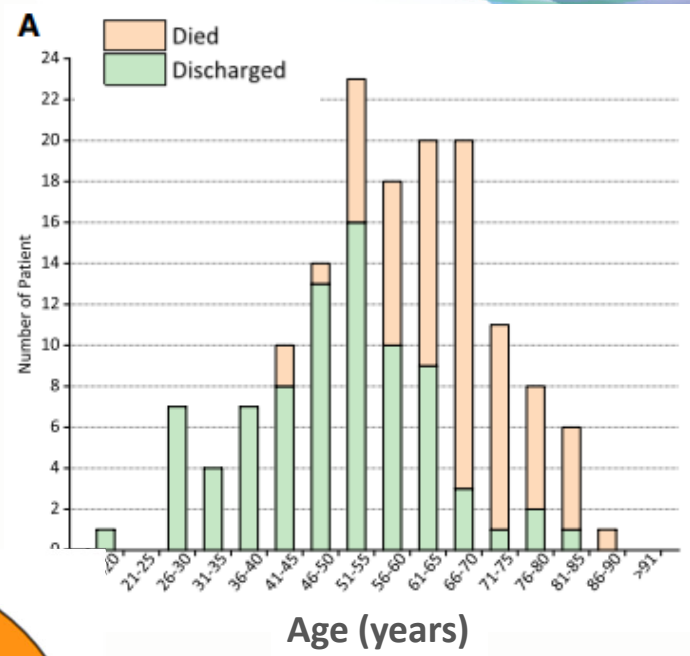
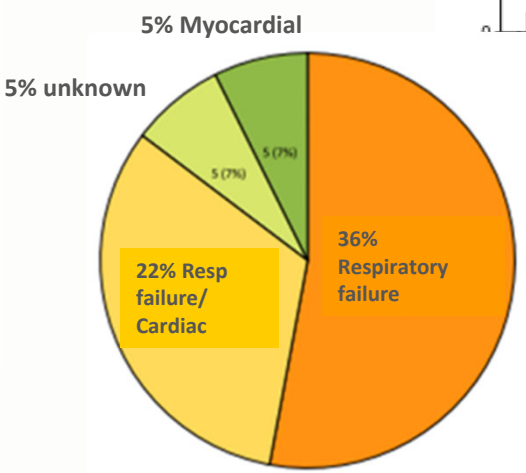
Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China

Qiurong Ruan, Kun Yang, Wenxia Wang, Lingyu Jiang, and Jianxin Song







Cause of death

Intensive Care Medicine 2020

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Covid-19 in Critically Ill Patients in the Seattle Region — Case Series

Pavan K. Bhatraju, M.D., Bijan J. Ghassemieh, M.D., Michelle Nichols, M.D., Richard Kim, M.D., Keith R. Jerome, M.D., Arun K. Nalla, Ph.D., Alexander L. Greninger, M.D., Sudhakar Pipavath, M.D., Mark M. Wurfel, M.D., Ph.D., Laura Evans, M.D., Patricia A. Kritek, M.D., T. Eoin West, M.D., M.P.H., Andrew Luks, M.D., Anthony Gerbino, M.D., Chris R. Dale, M.D., Jason D. Goldman, M.D., Shane O'Mahony, M.D., and Carmen Mikacenic, M.D.

NEJM March 30, 2020

Report of first 24 critically ill with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) from 9 hospitals in Seattle

- Mean age 64, 63%male
- Symptoms began 7 days before admission
  - Dry cough, SOB most common. 50% had fever. 58% DM
- Admitting diagnosis: hypoxemic respiratory failure 24/24
  - 18 needed mechanical ventilation (75%), 17/18 needed vasopressors for hypotension
- 12 patients (50%) died between day 1 and day 18
  - 4 patients had DNR on admission
- Of 12 surviving patients
  - 5 discharged, 4 still in hospital out of ICU, 3 still on mechanical ventilation

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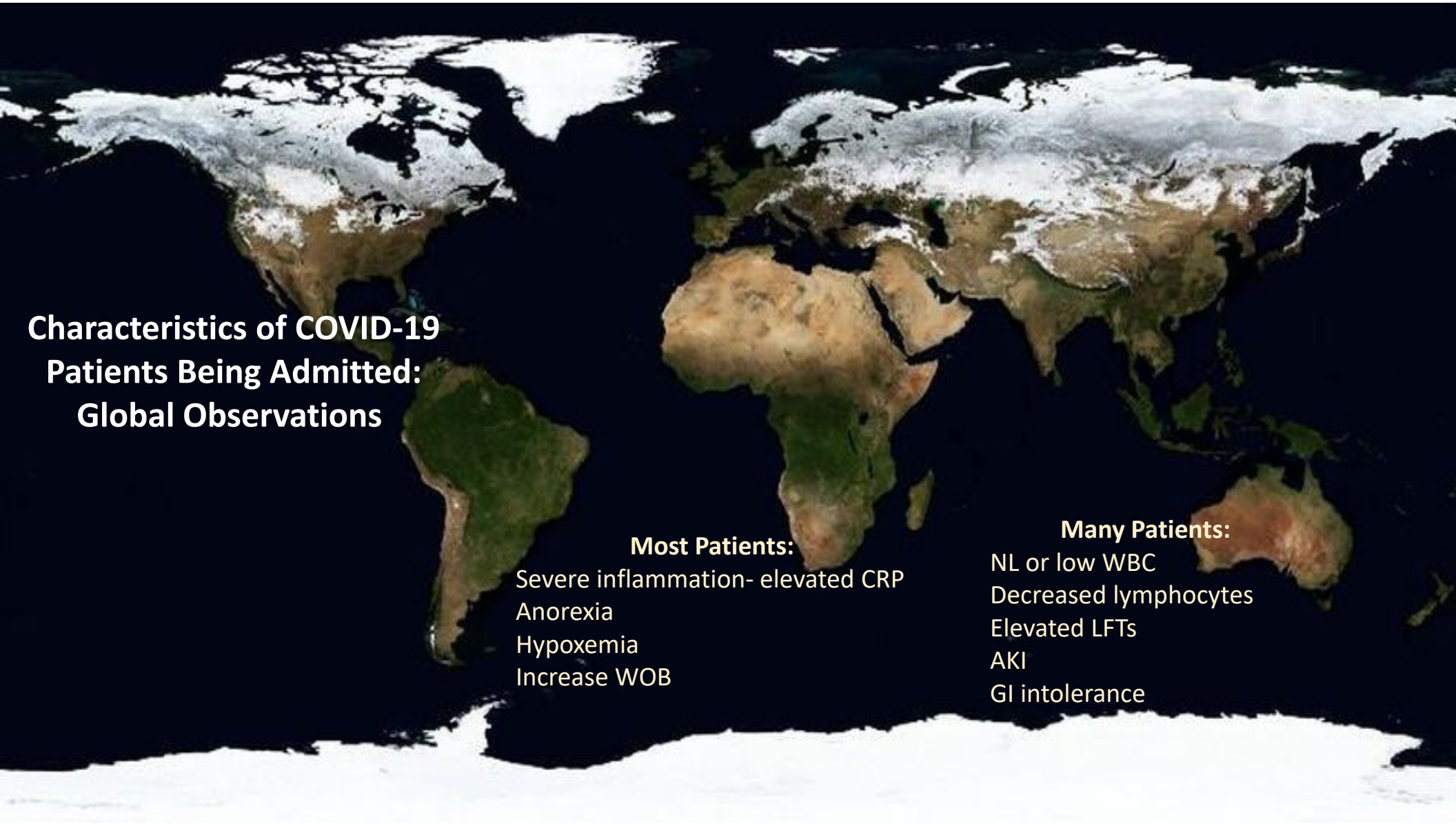

Characteristics of COVID-19 Patients Being Admitted: Global Observations

Most Patients:

Severe inflammation- elevated CRP
Anorexia
Hypoxemia
Increase WOB

Many Patients:

NL or low WBC
Decreased lymphocytes
Elevated LFTs
AKI
GI intolerance

What Inferences Can We Draw About The Critically ill Patient with COVID-19?

Covid-19 in Critically Ill Patients in the Seattle Region — Case Series

Pavan K. Bhatraju, M.D., Bijan J. Ghassemieh, M.D., Michelle Nichols, M.D., Richard Kim, M.D., Keith R. Jerome, M.D., Arun K. Nalla, Ph.D., Alexander L. Greninger, M.D., Sudhakar Pipavath, M.D., Mark M. Wurfel, M.D., Ph.D., Laura Evans, M.D., Patricia A. Kritek, M.D., T. Eoin West, M.D., M.P.H., Andrew Luks, M.D., Anthony Gerbino, M.D., Chris R. Dale, M.D., Jason D. Goldman, M.D., Shane O'Mahony, M.D., and Carmen Mikacenic, M.D.

Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China
Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention

- **Older patients** → **risk for pre-existing malnutrition and sarcopenia**
- **Comorbidities** → **risk for pre-existing malnutrition and refeeding**
- **Develop severe ARDS** → **refractory therapies like ECMO and prone**
- **Have circulatory failure** → **makes us think about EN quantity (PN?)**
- **Develop multiple organ failure** → **makes us think about early EN**

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Basic principles to consider with COVID-19 in the ICU

- Infection control
- Support required
- Duration of disease
- Resources

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Guiding Principles RELEVANT to COVID-19

1. "Cluster care," meaning all attempts are made to bundle care to ***limit exposure***

2. Adhere to Centers for Disease Control (CDC) recommendations to minimize exposures with COVID positive patients

3. Preserve use of personal protective equipment (PPE)

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Recommendation #1

- **Estimated Needs:**
  - **15-20 kcal/kg actual body weight (ABW)/day (70-80% of needs)**
  - **1.2-2.0 gm protein/kg ABW/day**

- **If refeeding syndrome risk is present[2]**
  - **Suspect if energy/calorie intake has been limited > 7 days**
  - **Start at 25% of caloric goal with slow increase**
  - **Frequent monitoring of serum phosphate, magnesium and potassium levels**

Rationale:

The above guidelines should be followed for patients receiving either enteral nutrition (EN) or parenteral nutrition (PN). Critically ill patients with severe COVID-19 disease tend to be older with multiple co-morbidities. If extremely limited or no energy/caloric intake for at least 5-7 days such patients are often at-risk of refeeding syndrome.

[1]Taylor B. McClave S et al. CCM 2016:44;390
[2]Doig G et al. Lancet Respir Med 2015;3:943-52
Arabi YM et al NEJM 2015;372:2398-2408

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Recommendation #2

Initiate enteral nutrition (EN) early

- **Within 24-36 h of ICU admission**
- **Within 12 h of intubation**

Rationale:

Provision of early EN in ICU pts 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 can be safely provided in patients with sepsis and shock in the absence of escalating vasopressors and symptoms of gastric ileus.[3]

[1]Taylor B, McClave S, et al. *CCM*. 2016:44;390.
[2]Singer P, et al. *Clin Nutr*. 2019:38;48.
[3]Patel J, et al. *JPEN*. Feb 2020.

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Recommendation #3

EN preferred over PN (parenteral nutrition)

- If patient can be successfully fed via gastric route through a nasogastric or orogastric tube placed at time of intubation
- If unable to feed into stomach have low threshold to convert to PN

Rationale:

Placing nasojejunal tubes in COVID 19 patients in most cases *dramatically increases the risk of exposure to the health care providers.*

Limiting # of people and equipment in rooms, i.e. x-ray to confirm placement. Large bore nasogastric tubes do not normally require radiographic confirmation

Considerations of “timing” on converting to PN

Distention, worsening hemodynamics, gastric contents noted in suctioning

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Recommendation #4

Start a standard EN isotonic (1 kcal/ml or 1.5 kcal/ml) high protein formula

- Start slowly 10-20 ml/h advancing to 80% of goal by the end of the first week with medical stability.[1]
- Maintain trophic rate with worsening hemodynamics[2]
- If unable to progress by 5 to 7 days with EN consider supplemental PN
- If patient was malnourished pre-ICU admission and unsuccessful at EN start PN earlier

Rationale:

Escalating vasopressors with a MAP < 65 mmHg, rising lactate levels or when high pressure respiratory support is required (NIV, CPAP or PEEP) pt is at increase risk of ischemic bowel and potential for aspiration.[1]

[1] McClave S, et al. *JPEN*. 2016;40:159-211 [2]Arabi YM, et al. *CCM.* 2020;40:119-121.

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Recommendation #5

- **Do not check gastric residual volumes (GRVs)[2]**

Rationale:

GRV's are not reliable in ICU patients[1] and checking several times per day will increase risk of virus exposure and transmission

1.Reignier J, et al. *JAMA*. 2013;309:249-56.
2.Taylor B, et al *CCM* 2016;44:390-438.

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Recommendation #6

EN – Gastric feeding preferred over Post-pyloric

- With gastric feeding- minimal expertise, allows use of existing NGT/OGT placed at time of intubation
- Continuous over bolus feeding – less diarrhea[1], optimizes BG control, less staff interaction needed

Rationale:

Less staff time is required for NGT/OGT placement as opposed to post pyloric tube, limiting virus exposure. There is less risk of tube occlusion with larger bore tubes. Continuous feeding requires less patient interactions and thus limits exposure.

[1]Singer P, et al. *Clin Nutr*. 2019:38;48.

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Recommendation #7

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

- Consider pro-motility agents and semi-elemental diet to improve tolerance
- If signs of ileus persists – change to PN[1]
- If escalating vasopressor requirement – change to PN

Rationale:

- The threshold for switching to PN or supplementing with PN for the patient with COVID-19 may need to be lower, especially in sepsis or shock and EN is not safe.
- These patients will likely require a prolonged ICU stay and without adequate feeding will realize a large calorie and protein deficit. As the patient's condition improves, gastric EN should be reattempted.
- 1) **NOTE**: This is different than statements in Guidelines 2016

[1] McClave S, et al. *JPEN*. 2016;40:159-211.
[2] Singer P, et al. *Clin Nutr*. 2019:38;48.

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Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2)

Jean Reignier, Julie Boisramé-Helms, Laurent Brisard, Jean-Baptiste Lascarrou, Ali Ait Hssain, Nadia Anguel, Laurent Argaud, Karim Asehnoune, Pierre Asfar, Frédéric Bellec, Vlad Botoc, Anne Bretagnol, Hoang-Nam Bui, Emmanuel Canet, Daniel Da Silva, Michael Darmon, Vincent Das, Jérôme Devaquet, Michel Djibre, Frédérique Ganster, Maité Garrouste-Orgeas, Stéphane Gaudry, Olivier Gontier, Claude Guérin, Bertrand Guidet, Christophe Guitton, Jean-Etienne Herbrecht, Jean-Claude Lacherade, Philippe Letocart, Frédéric Martino, Virginie Maxime, Emmanuelle Mercier, Jean-Paul Mira, Saad Nseir, Gael Piton, Jean-Pierre Quenot, Jack Richecoeur, Jean-Philippe Rigaud, René Robert, Nathalie Rolin, Carole Schwebel, Michel Sirodot, François Tinturier, Didier Thévenin, Bruno Giraudeau, Amélie Le Gouge, for the NUTRIREA-2 Trial Investigators and the Clinical Research in Intensive Care and Sepsis (CRICS) group

PRCT EN vs PN in ventilated patients with shock (n=2410)

- Mixed etiology of shock: 20% cardiac, 60% septic, 20% other
- Pts met strict criteria for shock, feeding 10kcal/kg/d w/in 15 h of intubation

Data collected:

- Similar calories to both groups
- Protein gm/kg/d 0.7 EN vs 0.8 PN

No difference in major outcomes

Enteral group:

- Ischemia 19 EN v 5 PN ($p < 0.007$)
- EN had increase in vomiting, diarrhea, colonic pseudo-obstruction (all significant)

Reignier J, et al. *The Lancet.* 2018;391:133-143.

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Recommendation #8

Limit pure soybean lipid emulsions the first week[1,2]

- **Use alternative lipids or limit/withhold soybean lipids the first week**
  - Alternate lipid emulsions available in USA:
    - Olive oil : Soy oil (80% Olive Oil : 20% soy)
    - Soy, MCT, Olive, Fish oil (30% soy: 30% MCT: 25% Olive oil: 15% Fish Oil)
- Monitor triglyceride levels early in the PN course
  - Early anecdotal reports are seeing rapid elevations in serum lipids with emulsions in those who have rapid progression of disease (from NYC, New Orleans and Milan, Italy)
  - Propofol in USA is in 10% soy solution

[1] McClave S, et al. *JPEN*. 2016;40:159-211.
[2] Singer P, et al. *Clin Nutr*. 2019:38;48.

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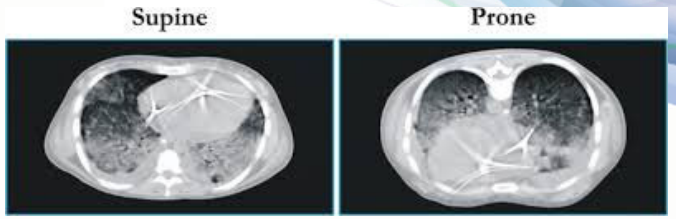
Recommendation #9



Prone Position – use EN over PN

- Isotonic high protein formula starting at 10-20 ml/hr
- Keep HOB elevated (reverse Trendelenburg) to at least 10 to 25 degrees w/ gastric feeding

Rationale:

No increased risk of GI or pulmonary complications in prone position has been noted.[1,3]

Increasing HOB will decrease the risk of aspiration of gastric contents, facial edema, and intra-abdominal hypertension.[2]

[1]Saez de la Fuente I, et al. *JPEN*. 2016 Feb;40(2):250-5.
[2]Kallett RH, et al. *Resp Care*. 2015:60;1660-1687.
[3]Reignier J, et al. *Clin Nutrition*. 2010;29:210-216.

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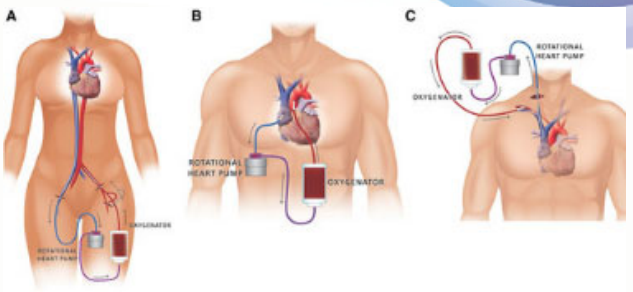
Recommendation #10

ECMO – attempt EN via gastric feeding



- Start early, low dose EN
- Slow advancement to goal over the first week
- If septic, increasing vasopressor requirements – hold and consider PN

Rationale:

In the largest observational study of EN during veno-arterial (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]

[1]Ohbe H, et al. *Intensive Care Med*. 2018;44:1258-1265.
[2]Park J, et al. *Clin Nutr*. 2019 Nov 30 ahead of print.

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Recommendation #11

Feeding patients in shock

- Manage as any other shock patient
- If unsuccessful (e.g., EN intolerance) transition to PN early
  - Caution with both EN or PN in hemodynamically unstable pts

Rationale:

No reason to alter standard Guideline recommendation for therapy with the exception of minimizing exposure of health care workers

[1] McClave S, et al. *JPEN*. 2016;40:159-211.
[2] Singer P, et al. *Clin Nutr*. 2019:38;48.
[3] Puthucheary ZA .*Thorax*. 2018;0:1-10,

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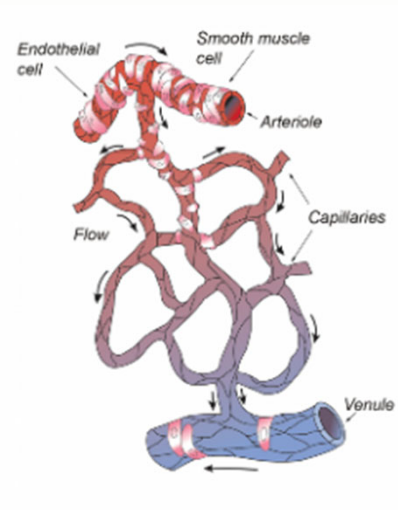
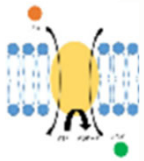
At the cellular level: O2 demand > O2 supply



Inadequate perfusion
↓
Cell hypoxia → HIF-1 activated (hypoxia inducible factor)
↓
Energy deficit
↓
Lactic acid accumulation and fall in pH → Anaerobic metabolism
↓
Metabolic acidosis → Vasoconstriction
↓
Failure of pre-capillary sphincters
↓
Peripheral pooling of blood

Metabolic acidosis
↓
Cell membrane dysfunction and failure of 'sodium pump'
↓
Intracellular lysosomes release digestive enzymes → Efflux of potassium; Influx of sodium and water
↓
Toxic substances enter circulation
↓
Capillary endothelium damaged
↓
Destruction, dysfunction, and cell death



Hypoxemic Pulmonary Failure

Decrease of oxygenation of splanchnic organs

Further hypoxia

Further hypoxia

Gut hypoxia

Mesenteric ischemia---
Loss of mucosal integrity

Toxins and Bacterial translocation
Altered Immune response
Microbiome to virulent pathobiome

Endotoxins, TNF
IL1, IL6, pancreatic lipase, FFA enter circulation via PV and Lymphatics

MOF

Feeding in Shock

Type of shock	Author	Journal	Year	Study	Outcome
Cardiogenic shock	Berger M	Clin Nutr	2005	Prospective descriptive	Cardiogenic shock pts can be fed with EN successfully
Hemorrhagic shock	McQuiggan M	JPEN	2008	Prospective (pilot)	Increase tolerance to enteral feeding
Septic shock	Elke G	Med Klin Inten Med	2013	Prospective Randomized (secondary analysis)	EN improves outcome
Septic shock	Patel JJ	J Int Care Med	2016	Retrospective early EN	Early trophic EN decrease LOS and need for MV
Septic shock	Patel JJ	JPEN	2016	Prospective EN vs No nutrition (pilot)	No differences between EN and no nutrition
Shock (mixed etiology)	Reignier J	Int Care Med	2018	Prospective EN vs PN	Early nutrition either EN or PN reduced mortality
Shock (mixed etiology)	Reignier J	Lancet	2018	Prospective EN vs PN	EN more ischemia ($p<0.007$) (EN 19/1202 2% vs PN 5/1208 <1%)
Septic shock	Ewy	NCP	2020	Retrospective observational	No worsening hemodynamics with vasopressors addition in EN

Disclaimer statement;

- Being fully transparent when delivering medical information is **always optimal**.
- The worst thing we can do as health care professionals is give false hope.
- If no studies are available, consistently give solid fact based science which are rooted in rationale hypothesis

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Potential nutritional approaches
Theory, extrapolations, anecdotes:
NO COVID specific data yet

- Fish oil
  →SPM and viral clearance
- Probiotics
  →Data from other Corona virus studies
- Vitamin Supplements
- Inflammation control
- Absorption dynamics
  - PEPT1 first mucosal transporter to return

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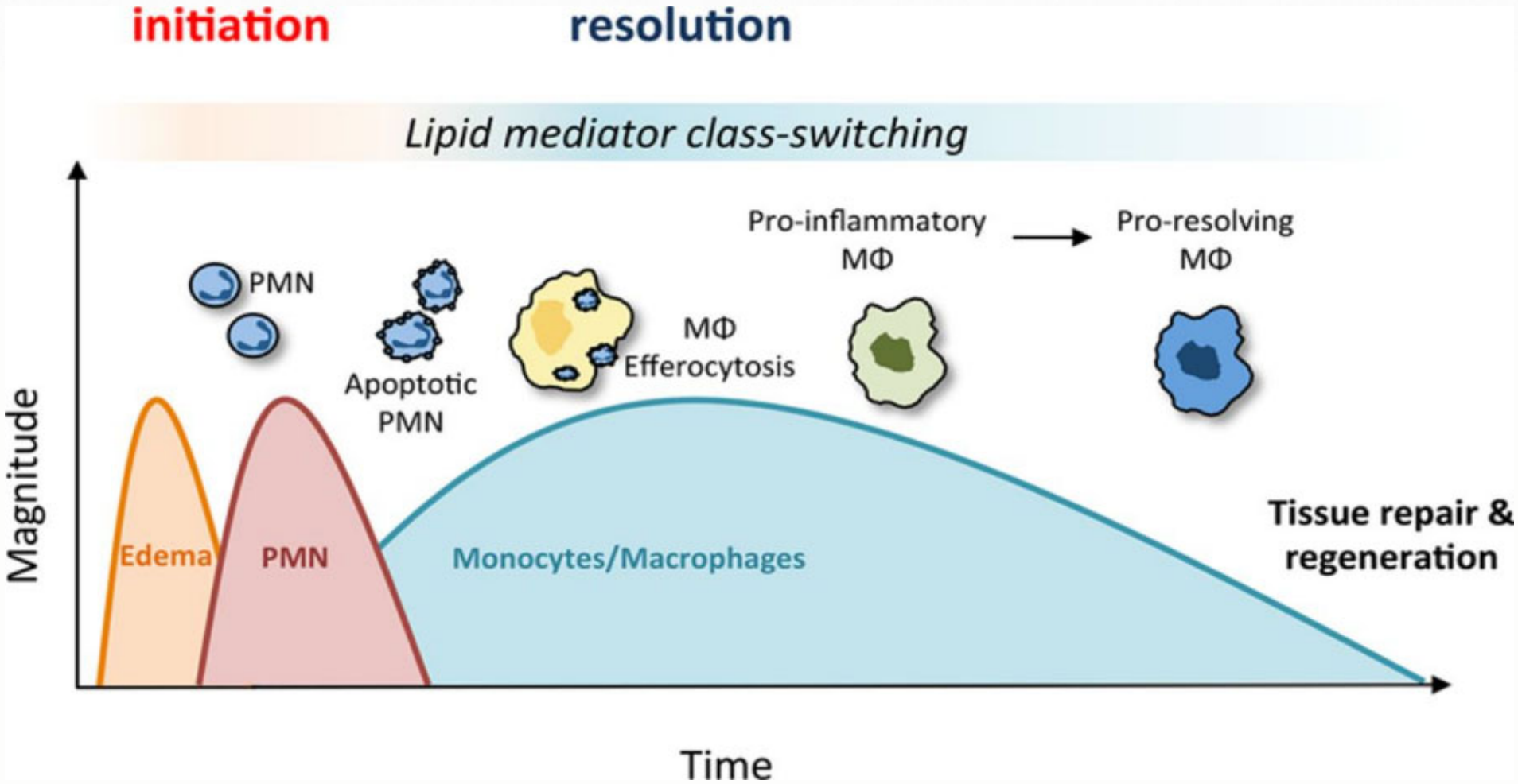

Serhan CN. *Nature*. 2015
Werz O, et al. *Nature Comm*. 2018

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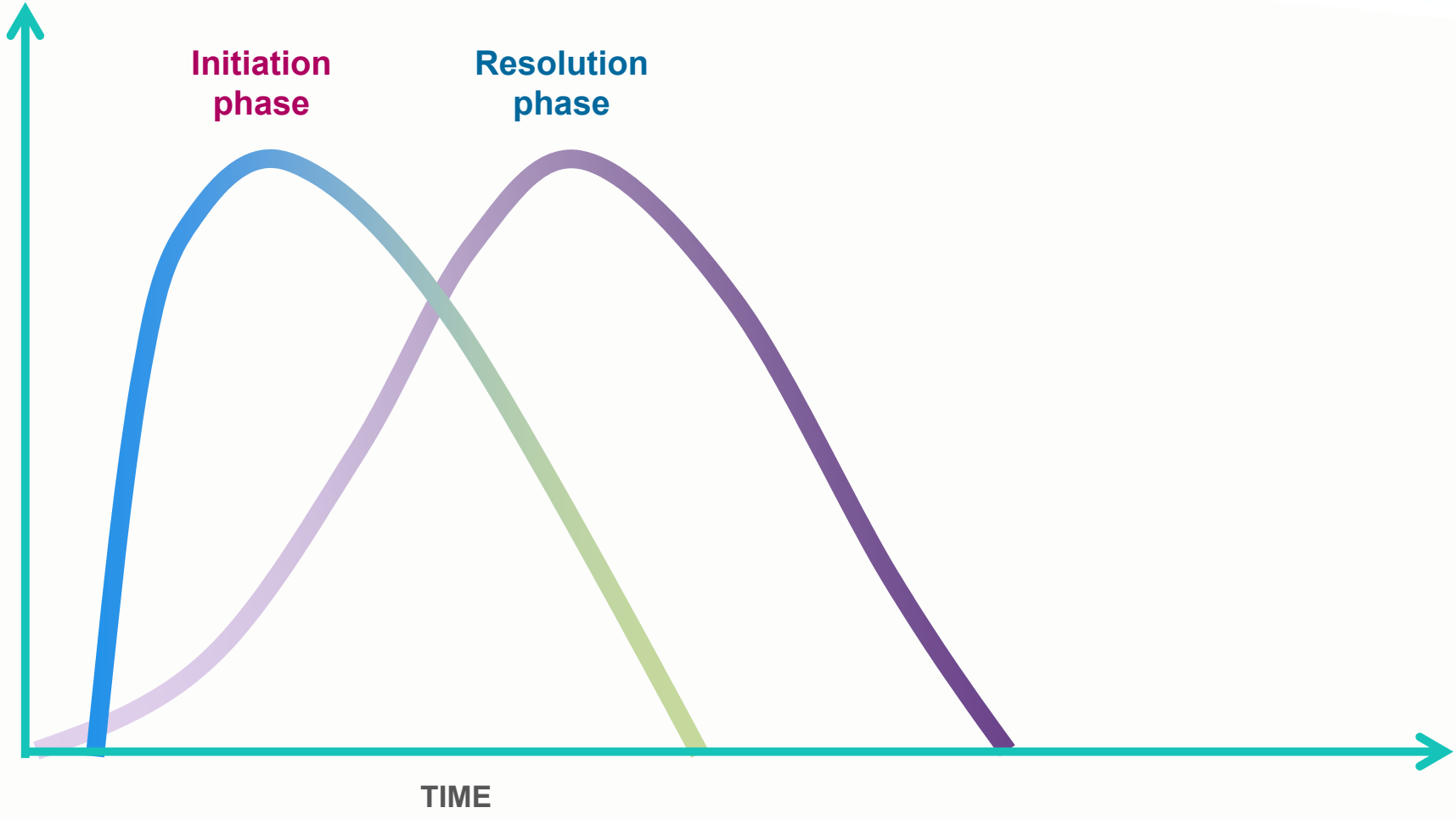
Inflammation has two phases: initiation and resolution



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CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., Editor

Influenza — Time to Target the Host?

J. Kenneth Baillie, M.D., Ph.D., and Paul Digard, Ph.D.

Several Resolvins lower mortality in viral illness

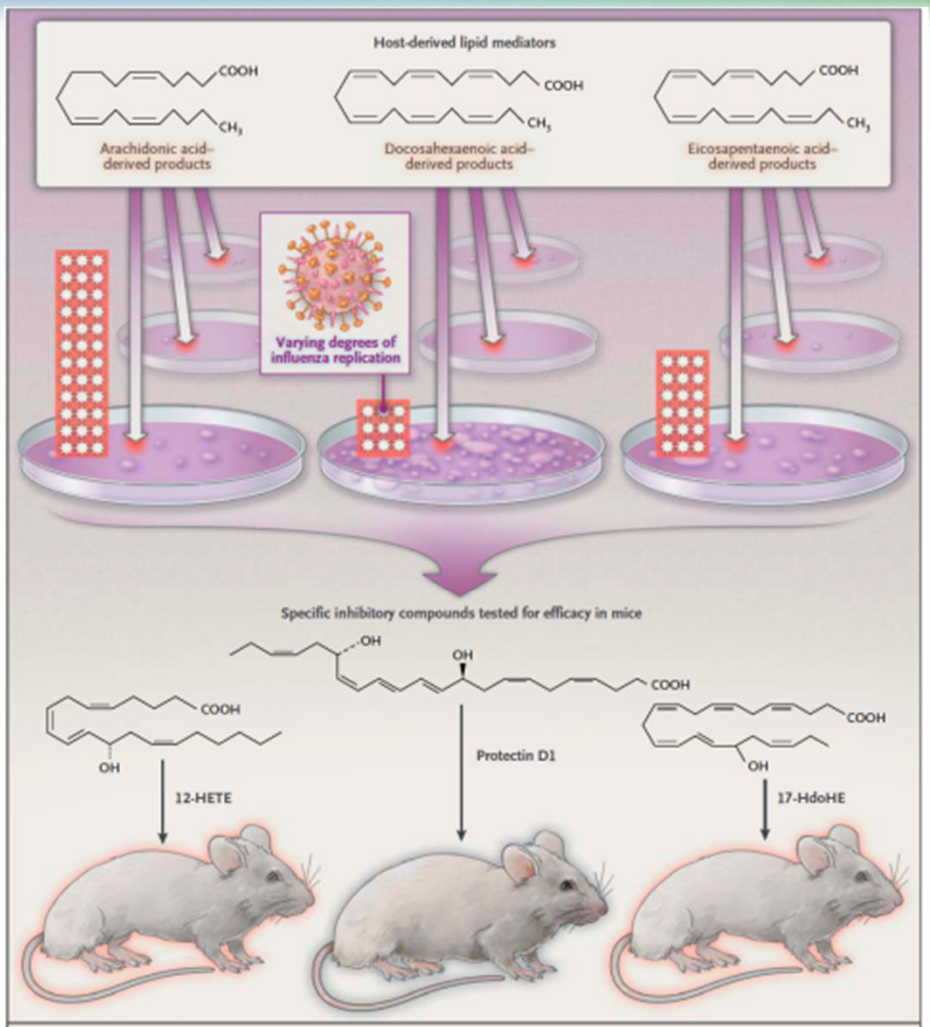

Figure 1. Identification of Protectin D1 as a Potential Therapeutic Agent.
In the discovery process used to identify protectin D1 as a potential therapeutic agent to modulate the host response in severe influenza infection, a wide range of different host lipid mediators were tested in cell-culture models of viral replication. Candidate mediators that restricted replication in vitro were then tested in mouse models of severe disease. With protectin D1, mice had significantly reduced mortality, whereas mice treated with 12-hydroxyeicosatetraenoic acid (12-HETE) or 17-hydroxydocosahexaenoic acid (17-HdoHE) had severe illness and high mortality, similar to infected animals left untreated.

Baillie JK, et al. *NEJM*. 2013.

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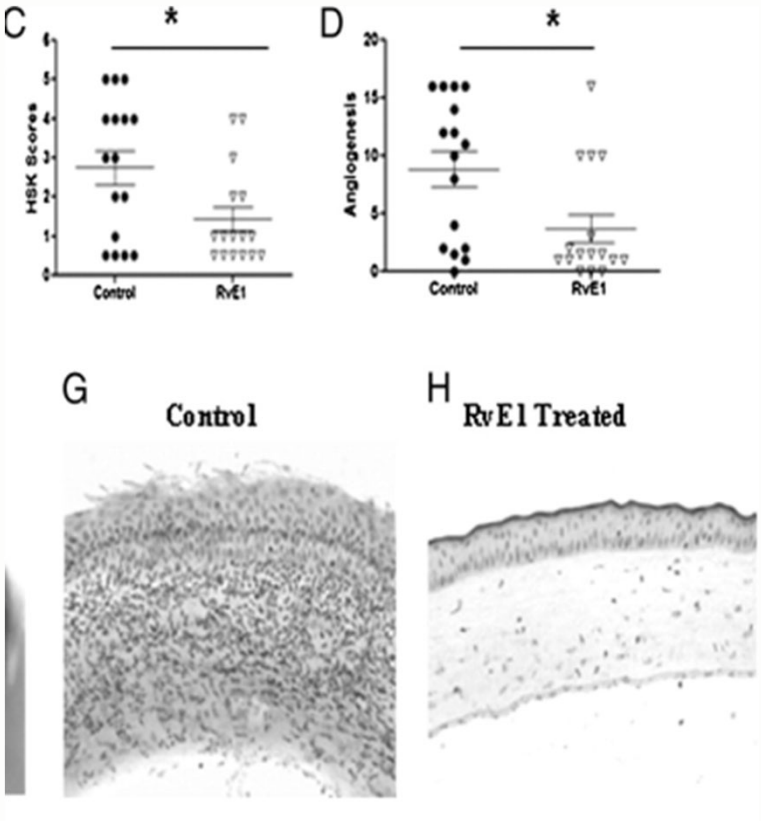
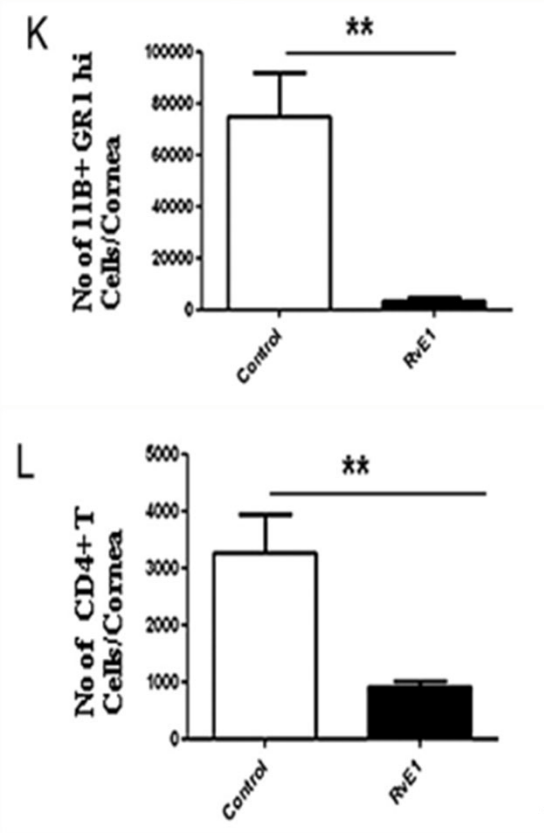
Controlling Herpes Virus Simplex Virus-Induced Ocular Inflammatory Lesions with the Lipid-Derived Mediator Resolvin E1





Rajasagi NK J. *Immunology.* (2011) 186, 1735

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Infection regulates pro-resolving mediators that lower antibiotic requirements

Nature 2012

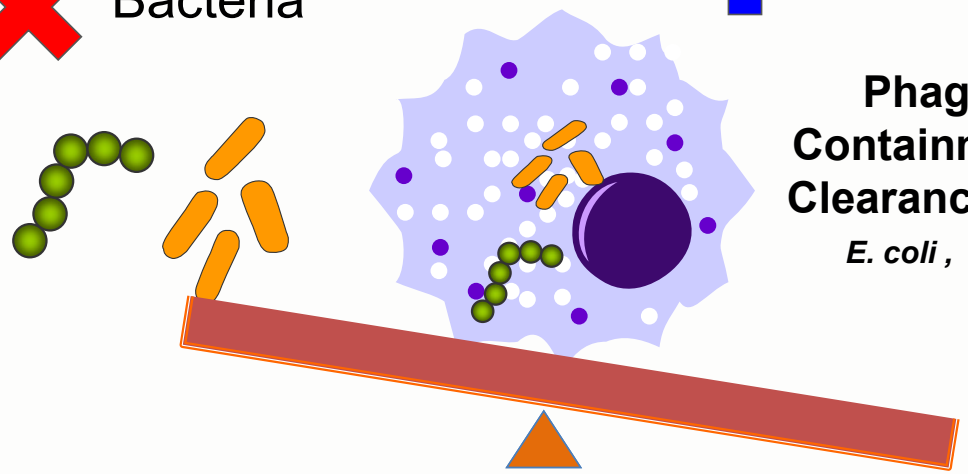
Nan Chiang[1], Gabrielle Fredman[1], Fredrik Bäckhed[2], Sungwhan F. Oh[1], Thad Vickery[1], Birgitta A. Schmidt[1] & Charles N. Serhan[1]

Antibiotics

SPM Resolvins

Bacteria

Host response



Phagocytosis, Containment, Killing, Clearance of Bacteria

E. coli* , *S. aureus skin

SPM's accelerate resolution of infections

Enhance bacterial killing , reduce inflammation

Treating the host with SPM *lowers* the required antibiotic doses

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Human sepsis eicosanoid and pro-resolving lipid mediator temporal profiles: correlations with survival and clinical outcomes

Jesmond Dalli, PhD[1], Romain A. Colas, PhD[1], Carolina Quintana, MD[2], Diana Barragan-Bradford, MD[2], Shelley Hurwitz, PhD[3], Bruce D. Levy, MD[2], Augustine M. Choi, MD[2,#], Charles N. Serhan, PhD[1,$], and Rebecca M. Baron, MD[2,$]

Critical Care Medicine 2017

- Associated outcome with resolution mediators
- N=22 septic patients
  - Followed pro-inflammatory and pro-resolution mediators
    - Lipid mediator profiling - >30 bioactive mediators followed
      - AA, EPA, DHA metabolome
    - Serum lipid profiles w/in 48h admission then at 3 and 7 days
- Conclusion:
  - Resolution Lipid mediators associated with better survival and decrease ARDS
- Caution: association does not indicate causation!

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Probiotics and Prevention of Upper Respiratory Viral Infections

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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 URTIs in people of all ages
- 12 Studies included in the analysis
  - 3720 Participants (Children+Adults)
  - Placebo versus Probiotics
- Probiotics were better than placebo in number of acute URI
  - 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

Hao Q, Dong BR, et al *Cochrane*. Feb 3, 2015

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Vitamin and Mineral Supplementation

- Animal data or theoretical – NO COVID-2 specific data -
  - Vit A- may help if deficient (Corona virus in chickens fed low Vit A diet)
  - Vit B_1,B_2,B_6- multiple reports ----- results all over the map
  - Vit C – J Antimicrobial Chemotherapy 2003 ----SARS Coronavirus
  - Vit D – if deficient may be helpful in viral infections (animal models)
  - Vit E – data in animals, Coxsackie virus B3
  - Selenium – speculation- lots of questions dose, timing
  - Zinc– beneficial if deficient

  - Bottom Line:
    - 1) insufficient data for any additional specific supplement over standard requirements UNLESS vitamin deficient upon arrival
    - 2) No data for "antioxidant" cocktails, megadoses of supplements etc

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Conclusions

- 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 pts intolerant to gastric feeds to avoid endoscopic/fluoroscopic placed post-pyloric tube are strategies which:

1. Promote clustered care
2. Reduce the frequency with which healthcare providers interact with COVID positive patients
3. Minimize contamination of additional equipment while promoting optimal nutrition therapy for these patients.

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Resources

Society of Critical Care Medicine (SCCM)

https://www.sccm.org/Disaster

American Society of Parenteral and Enteral Nutrition (ASPEN)

http://www.nutritioncare.org/COVID19/

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Questions?

The recording will be available on Nestlé Nutrition Institute the week of April 6, 2020.

nestlenutrition-institute.org/resources/videos

Use filter by keyword and enter title or speaker's last name "Martindale"

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