Let food be thy medicine ...

Prof.dr Arthur R.H. van Zanten, internist-intensivist

Inaugural lecture upon taking up the position of Special Professor of
Role of Nutrition in the Recovery from Metabolic Stress at
Wageningen University & Research on 9 June 2022

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Esteemed Rector Magnificus, dear colleagues, students, family, and friends,

Thank you very much for attending my inaugural lecture after two years of COVID-19 preventing this event from happening.

Misquotation of Hippocrates

In the 5th Century before Christ, Hippocrates of Cos, considered the father of Western medicine, recognised the importance of food in medicine.

Figure 1: Hippocrates of Cos

Over 70 texts have been bundled by his followers, known as the Hippocratic Corpus. For decades the phrase: "let food be thy medicine and medicine be thy food" was considered to originate from Hippocrates. However, it cannot be found in his work.[1] Therefore, it should be considered a misquotation of enormous magnitude. However, more importantly, it also may lead to fundamental misconceptions.

Food versus medicine in antiquity

In the Hippocratic era, food was considered material that could be assimilated after digestion and converted into the substance of the body, such as muscles and nerves. [1] The concept of medicines then was a product that was able to change the body's nature but not be converted into the body's substance. Food was not considered medicine. However, Hippocrates used medicines from Willow trees, called sallows (or Salix trees in Latin), to relieve pain and treat fever. The active extract of the bark, called salicin, is metabolised into salicylic acid in the human body and is a precursor of aspirin.[2]
In Antiquity, guidelines on the duty of physicians, were established in the Hippocratic

Oath, whose legacy persists until today. The imperative “primum non nocere” or “Do no harm” is implicit in the following statement concerning diet: “I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice”. Thus, with Hippocrates’ endorsement, diet became a moral value and responsibility in medical practice. [1]

Personal career

First, I will take you back to more recent times. After my training in medicine at the Erasmus University in Rotterdam and training in internal medicine and intensive care medicine in hospitals in Rotterdam and Amsterdam, I was appointed as the first formally trained intensivist at the Intensive Care department of Gelderse Vallei Hospital in Bennekom, in 1998. In 2000, we moved our patients from the ICU departments in Wageningen and Bennekom to our new hospital in Ede, the present location of Gelderse Vallei Hospital.

During my first decade as an intensivist, my research focused on infections, sepsis, and antibiotics. It resulted in a PhD in 2008 at the Free University in Amsterdam, reporting on infectious complications in critical illness and pharmacokinetics and pharmacodynamics of antibiotics.

Afterwards, I led several programmes on sepsis, and recently, we have developed the first guidelines on early sepsis recognition and treatment in the Netherlands. Over the last decade, I have dedicated most of my research to the metabolism of ICU patients and Critical Care Nutrition.

Intensive Care Medicine

Our ICU team, comprising really caring dedicated ICU nurses, junior residents, intensivists, and allied healthcare professionals, has treated thousands of critically ill patients, sometimes under difficult circumstances. ICU patients are severely ill and need continuous monitoring, high intensity 24/7 nursing and medical attention, and treatments to support failing organ systems.

Typically, patients need vasopressor infusions to treat circulatory shock, sedatives and analgetics to provide comfort and reduce pain, and organ support by mechanical ventilation for lung failure and renal replacement therapy for kidney failure.

ICU survival, functional outcomes, and quality of life

Before I continue to address nutrition therapy, I would like you to ask yourself about your assumptions on ICU survival. How many patients survive their hospital stay when they have been admitted to the ICU? Is it A 85% survivors, B 58% or C 26% survivors? Based on data from the National Intensive Care Evaluation (NICE), we know the in-hospital

Figure 2: ICU department Gelderse Vallei Hospital, Ede, The Netherlands

mortality was 15%. [3] So, 85% survival. ICU outcomes in the Netherlands are among the best in the world. Surviving ICU admission is a primary goal of Intensive Care medicine, but more and more, we realise that optimal functional outcomes and quality of life are as important as survival for patients.

While over several decades, mortality rates among ICU patients with sepsis have dropped, the number of patients that cannot be discharged home but must be transferred to rehabilitation centres or nursing homes has tripled. [4] My good friend, Professor Paul Wischmeyer, used the following rhetorical question to describe this dilemma: "Are we creating survivors or victims of Intensive Care?" [5] We must refocus our efforts on our patient's functional recovery and quality of life. Nutrition therapy plays a pivotal role in recovering from critical illness.

Feeding the critically ill

When we take in our food, our nutrients, we eat. This route is called oral nutrition or oral feeding. Most ICU patients cannot eat and are unable to achieve daily nutrition targets for essential macronutrients (carbohydrates, proteins, and fat) and micronutrients (vitamins and trace elements).

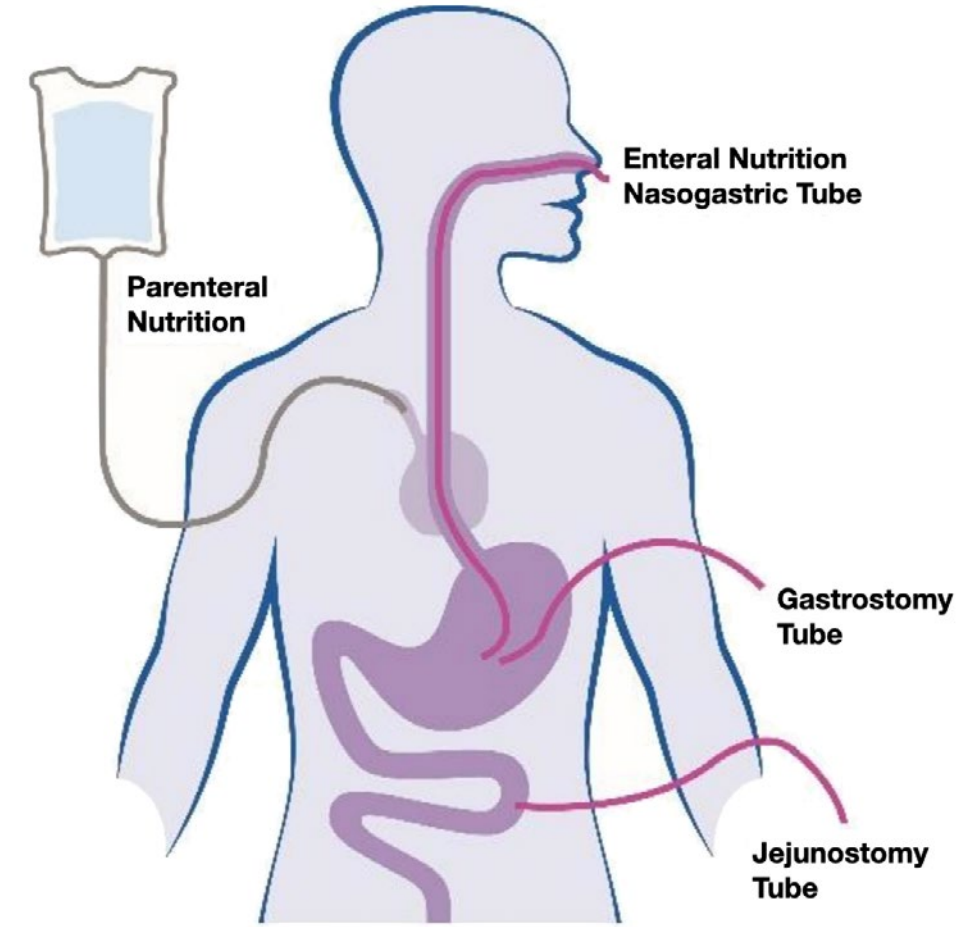

Figure 3: Feeding routes in critical illness

Medical nutrition then is essential to survive critical illness. Typically, we feed our patients via the enteral route using enteral nutrition or tube feeding after a feeding tube has been inserted. Sometimes, we consider surgical access to the gut to directly administer nutrition into the stomach or small intestine. When we cannot use the gastrointestinal tract or enteral feeding is not tolerated or contraindicated, we use parenteral nutrition administered via the bloodstream. [6] However, feeding ICU patients is not as simple as just changing the route of administration. Acute inflammatory and metabolic alterations interfere with digestion, absorption, metabolisation, and utilisation of nutrients.

Critical illness, metabolism, and nutrition

I will summarise some latest insights into the complex interactions between critical illness and metabolism and show you that the metabolic consequences of feeding during critical illness are different than during health. Therefore, we cannot simply extrapolate nutrition research from healthy persons to the critically ill.

Critical illness is characterised by a predominantly early enhanced inflammatory response, or hyperinflammation, and often in a later phase of illness immunoparalysis, a phase of insufficient immune response that may persist for weeks.[7] During this immunoparalysis phase, patients are vulnerable to new infections. Frequently, specific infections seen in patients with severe immune deficiency are encountered.

Acute metabolic stress

ICU patients suffer from acute metabolic stress. What is metabolic stress?
Metabolism is the sum of chemical reactions within each cell that provides energy for vital processes and for synthesising new organic material.

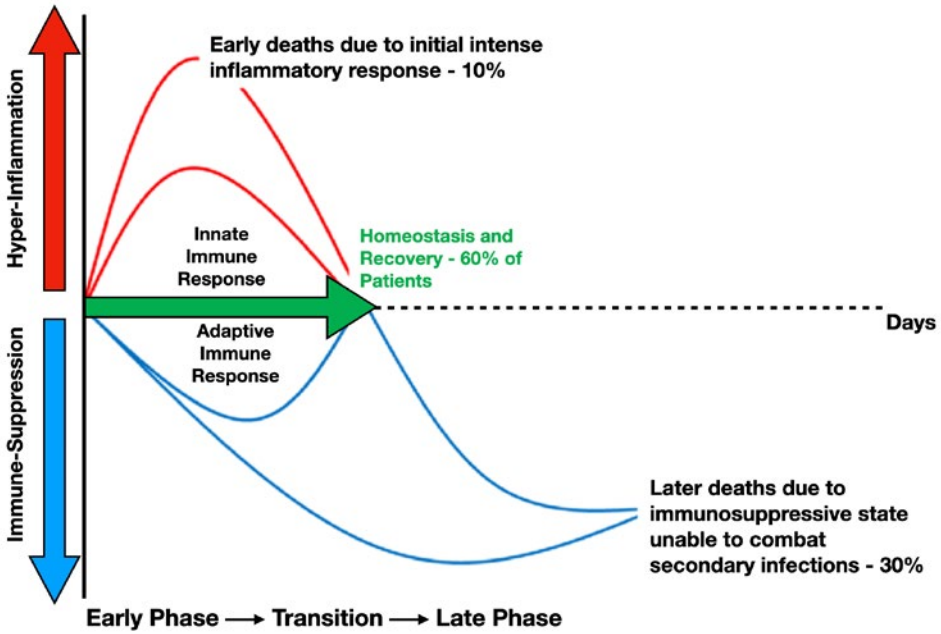

Figure 4: Inflammatory response during phases of critical illness and convalescence

Stress can be defined as any type of change that causes physical, emotional, or psychological strain. In critical illness, the physical stress response is essential and mediated by the neural, endocrine, bioenergetic, and immune systems.

No formal definition is available for metabolic stress in acute disease states. However, I suggest applying several descriptions that relate to acute metabolic stress, such as:

1 The physiological process in response to low energy or oxygen, leading to the accumulation of metabolites such as lactate and protons in muscle cells and other organs, and
2 The hypermetabolic, catabolic response to severe injury or disease.

The metabolic stress response is part of the adaptive response to survive critical illness. The problem lies in that we cannot survive most critical illness situations from a biological perspective. However, due to the progress of Intensive Care medicine, most ICU patients nowadays can survive disease states, trauma and extended surgical procedures, bringing them back to life when they otherwise would be characterised as being in conditions beyond repair. Consequently, we will encounter metabolic conditions that cannot be compared with short periods of metabolic or catabolic stress in health.

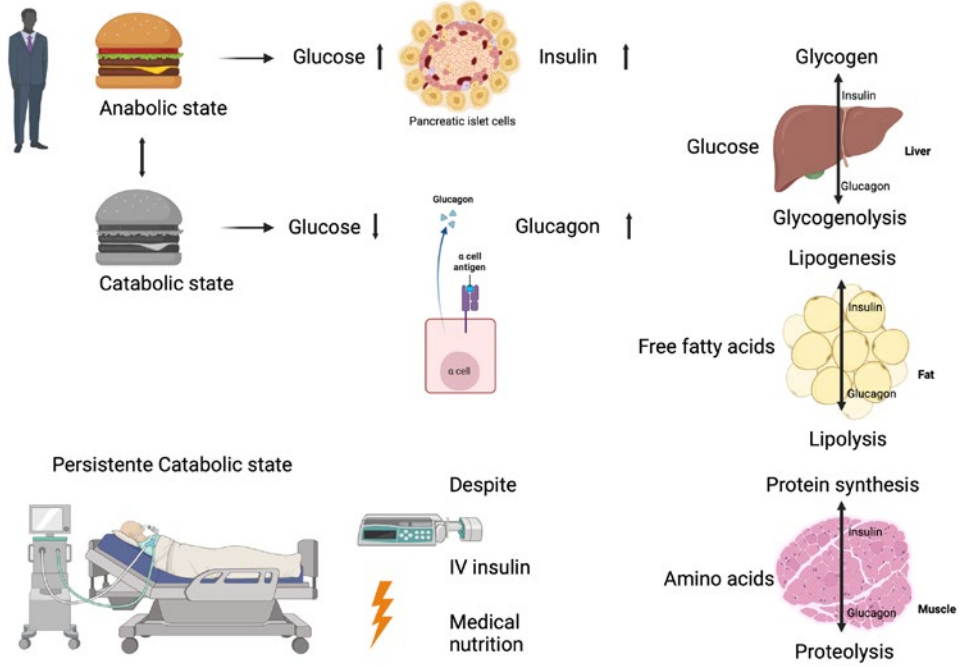

Figure 5: The anabolic-catabolic pendulum during health versus persistent catabolism in metabolic stress

You may question: so, what? In my view, this acute metabolic stress response has significant consequences for the way we should apply nutrition therapy as nutrition interacts with metabolic processes.

Catabolic response in critical illness

In health, we have periods characterised as an anabolic status, building up tissues, storing glucose in glycogen in the liver, triglycerides in fat, and amino acids in muscle proteins. When we do not eat, we have these endogenous stores that can be used during the catabolic phase after starvation. This anabolic-catabolic pendulum is always swinging. The hormone insulin is secreted in response to increased blood glucose levels to store glucose, and when levels drop, the counteracting hormone glucagon will facilitate the production of endogenous glucose by breaking down glycogen.

In contrast, there is a persistent catabolic response during critical illness and metabolic stress that cannot be inhibited by nutrition. [8] This implies that although nutrition is provided and insulin is administered, the catabolic response still will lead to the continuous breakdown of tissues.
Notably, this is a problem for the protein stores. It has been demonstrated that ICU patients with multiple organ failure can lose up to 25% of their muscle mass in the first ten days of ICU admission. [9] This translates into a muscle mass loss of 1 kilogram per day.

The obesity paradox in critical illness

Possibly counterintuitive, patients with a high Body Mass Index (or BMI) have better survival chances in the ICU. This phenomenon is called the obesity paradox. Obesity seems to reduce mortality risk among ICU patients. Excellent work by Dutch colleagues has shown that it is not the body weight, BMI, or fat mass but the muscle mass that is protective, suggesting that the more muscles patients can bring to the ICU, the better the survival chance. [10] Therefore, obese patients with an active lifestyle carrying all their weight can even have an increased muscle mass. These patients show better outcomes. However, the morbidly obese bedridden patients with a low muscle mass, called sarcopenic obesity, have poor outcomes.

How is metabolic stress characterised?

Insulin resistance is present in most if not all ICU patients. Endogenous and exogenous catecholamines such as adrenalin and noradrenalin and adrenal glucocorticoid hormones like cortisol increase blood glucose levels. Although most patients do not have a history of diabetes mellitus, many non-diabetic ICU patients need insulin therapy during their ICU stay.

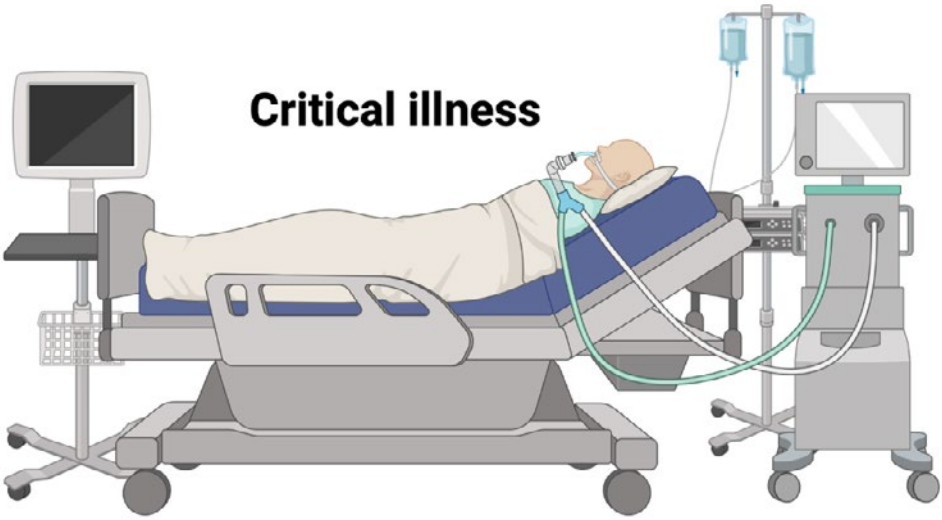

Figure 6: Metabolic alterations occur during critical illness

In patients with septic shock, we investigated glucose metabolism and demonstrated that after 40 hours, the risk of hypoglycaemia increases, especially when insulin therapy is continued, not well-controlled and insulin resistance vanishes. [11]
Also, other hormones in the endocrine system are markedly disrupted during ICU stay; for instance, downregulation of thyroid hormones leads to the low T3-syndrome. [12] However, probably this should not be treated as it seems an adaptive response.

Mitochondrial dysfunction

A crucial part of metabolism is the production of energy. All human cells, except for erythrocytes, have miniature energy plants named mitochondria that can produce energy. In a complex process, mitochondria continuously produce adenosine triphosphate or ATP. Our group and others investigate mitochondrial dysfunction in critical illness. Reduced ATP production in cells has been demonstrated, while more ATP can be produced when mitochondria are stimulated. [13]

Mitochondria seem to work slower, referred to as mitochondrial hibernation, as this phenomenon is also encountered among animals that slow down their metabolism during their winter sleep. Critical illness may therefore be seen as a situation of flat batteries. [14]
Whether this response in patients during metabolic stress is an adaptative protective process to survive critical illness or whether it contributes to worse outcomes still is

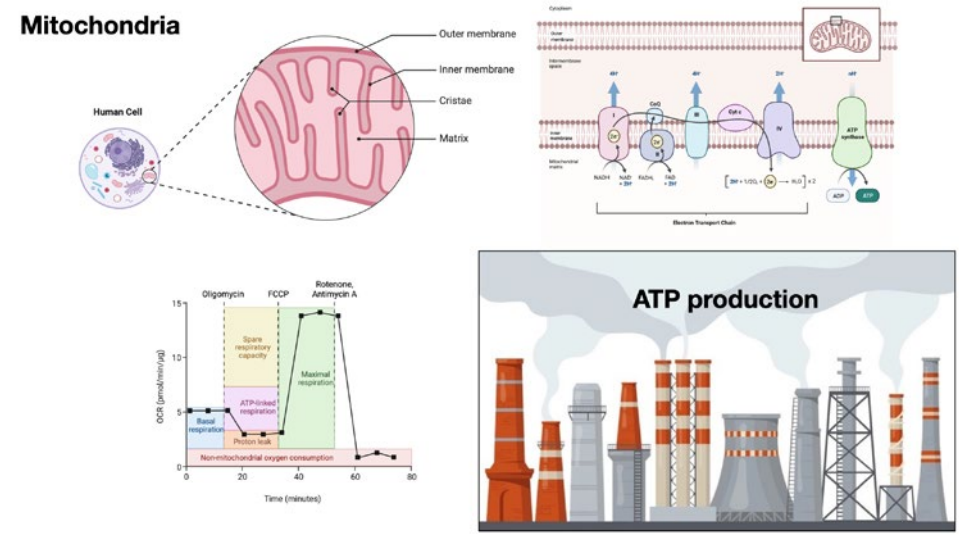

Figure 7: Mitochondria: the energy plants of cells producing ATP

unclear. However, after ICU discharge, persistent mitochondrial dysfunction has been demonstrated in patients with ICU acquired weakness. This may be an exciting target for interventions.

Early enteral nutrition

In the initial phase of ICU admission, it is recommended to start tube feeding early to preserve the morphological and immunological condition of the gut. [15] Over the last decade, newer insights led to less aggressive, slower build-up schemes for enteral nutrition. [16] There is a reason for that: During acute metabolic stress, endogenous energy production is markedly increased and can be more than 1000 kilocalories per day. Endogenous energy production will not be inhibited by administering exogenous feeding or insulin, as typically in health, and may increase overfeeding risk. [17]

Optimal energy targets in critical illness

A U-shaped relationship between energy and mortality has been found in early critical illness, suggesting that underfeeding and overfeeding increase mortality risk and slight hypocaloric feeding is optimal. [18]

Calories from glucose-rich infusion fluids, lipid-based propofol infusions for sedation, and citrate, an anticoagulant used during continuous renal replacement therapy, add to energy intake. Therefore, non-intentional calories should be considered to prevent overfeeding. [19]

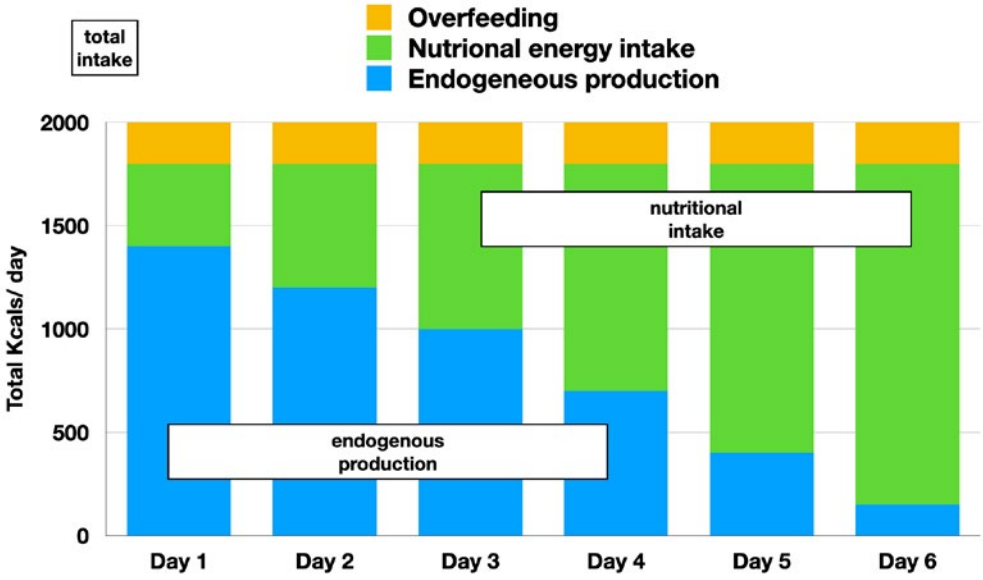

Figure 8: Non-inhibitable endogenous energy production in early critical illness

Furthermore, energy expenditure should be measured with an indirect calorimetry device that can estimate individual energy demands by measuring oxygen consumption and carbon dioxide production during mechanical ventilation or with a canopy. Our group has published numerous papers on indirect calorimetry. Recent meta-analyses show improved survival among ICU patients when nutrition therapy is guided by indirect calorimetry. [20]

Optimal protein timing in critical illness

Although proteins cannot reverse the catabolic response, they provide amino acids to serve as substrate for protein synthesis. The total body protein balance will become less negative by inducing more protein synthesis. Protein synthesis will slow down muscle mass loss and achieve some damage control. Observational studies have suggested the more proteins, the better. This may not always be true. [21]

Investigators from Leuven have shown that early parenteral nutrition with high protein content was associated with worse outcomes. [22] In the Protinvent study from our group, we have demonstrated that high protein intake during the first three days of ICU stay is associated with increased long-term mortality. [23] However, this association flips to lower mortality later in the first week.

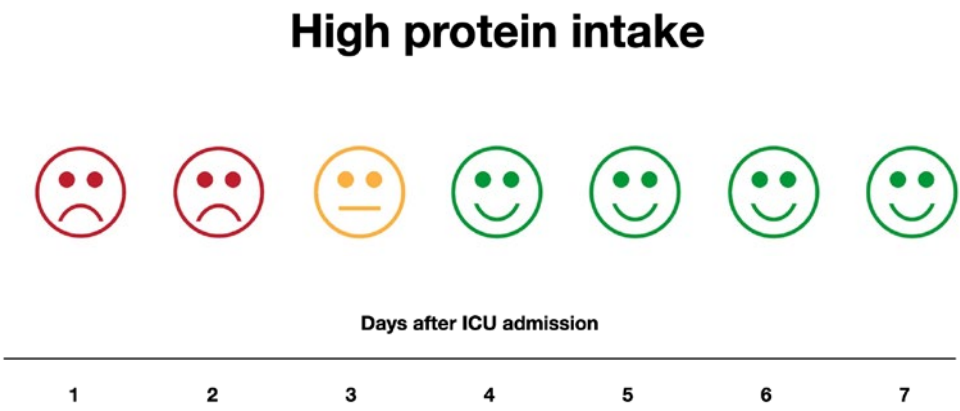

Figure 9: Importance of timing high protein intake in early critical illness

These studies suggest that the timing of macronutrient administration during metabolic stress is essential.
Why can early high protein administration lead to increased mortality? At least two mechanisms may be involved:

1 First, autophagy is a cleaning mechanism in cells. When proteins are too large to be discarded by the ubiquitin-proteasome pathway, lysosomes need to break down intracellular debris. [24] Accumulation of intracellular components impairs optimal cell functioning. Protein administration may induce autophagy suppression.
2 Second, during low ATP production, direct signalling from mitochondria to the cell's nucleus leads to downregulation of protein synthesis. In other words, a proteostatic response emerges during phases of low energy availability, potentially leading to a more significant negative protein balance. [25] Moreover, non-utilised proteins may induce unintended urea production. [26]

Refeeding Syndrome in critical illness

Another metabolic problem frequently encountered is Refeeding Syndrome, a poorly understood metabolic condition that arises after low nutritional intake. It is characterised by electrolyte abnormalities, vitamin B1 deficiency, insulin resistance, and fluid overload in response to the reintroduction of nutrients after starvation.[27]

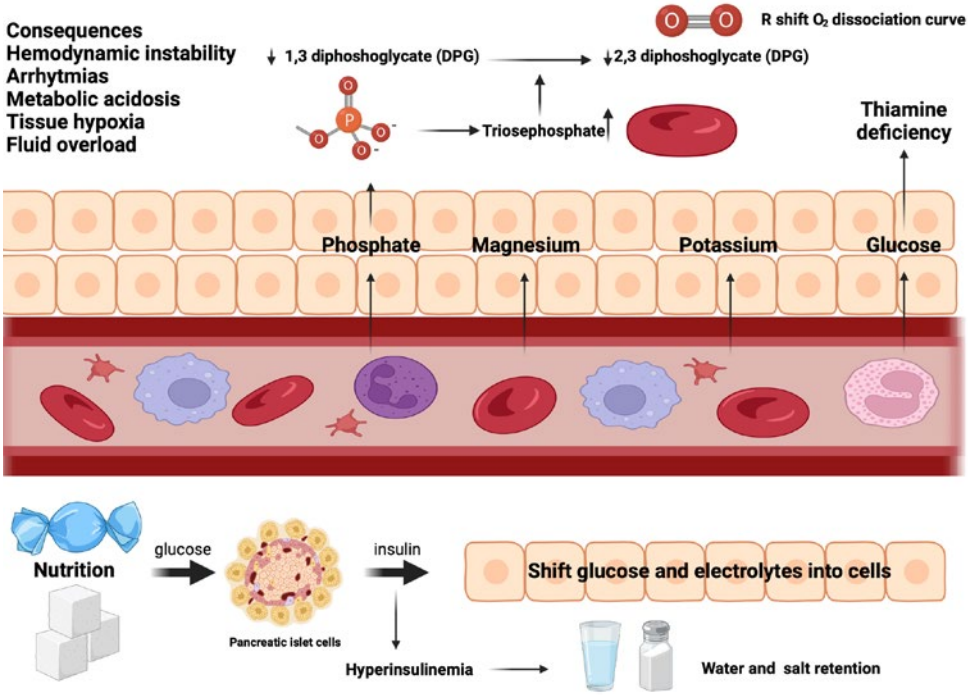

Figure 10: Pathophysiology and consequences of Refeeding Syndrome

We found that 1/3 of long-stay ICU patients show refeeding hypophosphatemia after the start of feeding. In contrast to non-ICU patients, risk scores do not predict Refeeding Syndrome during critical illness. Therefore, phosphate monitoring is warranted. Doig and coworkers and our group have demonstrated that caloric restriction is essential during refeeding syndrome to reduce mortality. [28],[29] I am proud to be a member of an international group of experts from the European Society for Clinical Nutrition and Metabolism (ESPEN). We published practice guidelines in 2019 for nutrition therapy in adult ICU patients to guide daily practice. [30] It is fascinating that our team's publications on protein timing and refeeding syndrome have been incorporated into international recommendations to treat ICU patients globally.

China and SARS-CoV-1

Over the last decade, I have visited many cities in China to give lectures.
The Chinese Society of Critical Care Medicine opening session, with more than 15,000 participants, was entirely dedicated to ICU healthcare professionals who lost their lives

during the SARS outbreak in 2002-2004, caused by severe acute respiratory syndrome coronavirus (also called SARS-CoV-1). This virus infected over 8,000 people from 29 countries and resulted in around 900 deaths worldwide. [31]
During scientific meetings and clinical rounds in Chinese University hospitals, I have disseminated the latest insights on critical care nutrition to healthcare professionals. I visited famous places between lectures, including the Huanan Seafood Wholesale market in Wuhan, not knowing what would occur years later.
I was on the way back from Shanghai in 2017. The purser sounded over the intercom of the KLM Boeing 747: "Is there a doctor on board this plane? Please make yourself known." Three passengers felt unwell. I checked them out, gave some medical advice and returned to my seat. Minutes later, the purser asked me to enter the plane's cockpit. I asked: "Is this allowed after 9-11?" She persisted as the captain of the flight wanted to have me there.
The captain followed strict rules after the SARS outbreak in China. When an infectious disease spreads among passengers, the plane must be quarantined in a particular location on the outskirts of Schiphol airport and the passengers and crew are not allowed to disembark the plane.

Figure 11: Healthcare authorities' consultation at 36.000 feet during flight from Shanghai to Amsterdam

After consultation with the KLM, Schiphol medical staff, and National Aviation authorities, I convinced everyone that no infectious disease was responsible for the passengers' symptoms. We were allowed to go to the gate and disembark.

SARS-CoV-2 and COVID-19

I could not wonder that visitors of the same Wuhan market would spread a new coronavirus by air travel three years later, initiating a pandemic with SARS-CoV2. This virus infected more than 550 million inhabitants of our planet. Over 6.3 million deaths were recorded. [32] This virus resulted in the disruption of global healthcare, destroyed economies, and led to enormous personal grief.
In the early phase of this pandemic, we mainly focused on Intensive Care capacity, treating as many patients as possible. Our ICU of 17 beds was temporarily expanded to 29 beds. Priority was preventing mortality from COVID-19.

Figure 12: Expanded ICU ward during COVID-19 pandemic, Ede, The Netherlands

I was part of a group of clinicians that were asked to provide information in the media on the pandemic, vaccinations, and future perspectives. However, at that time, we were unaware of the long-term consequences of COVID-19, called long COVID.

As soon as the first patients with long COVID or PACS were diagnosed, we realised that it resembled PICS or Post-Intensive Care Syndrome. [33]

Long-term consequences of acute metabolic stress

A recent study from Nijmegen has demonstrated that 74% of patients one year after ICU treatment for COVID-19 had physical symptoms. The most frequently reported new physical problems were weakened condition (39%), joint stiffness (26%), joint pain (26%), muscle weakness (25%) and muscle pain (21%). [34]
Why do some patients recover, and others do not? This refers to metabolic stress resilience. I would like to define this as the process of adapting well in the face of significant acute metabolic stress. Several issues play a role here:

- First, it takes a long time to regenerate muscle mass losses of 10-25% of the total muscle mass.

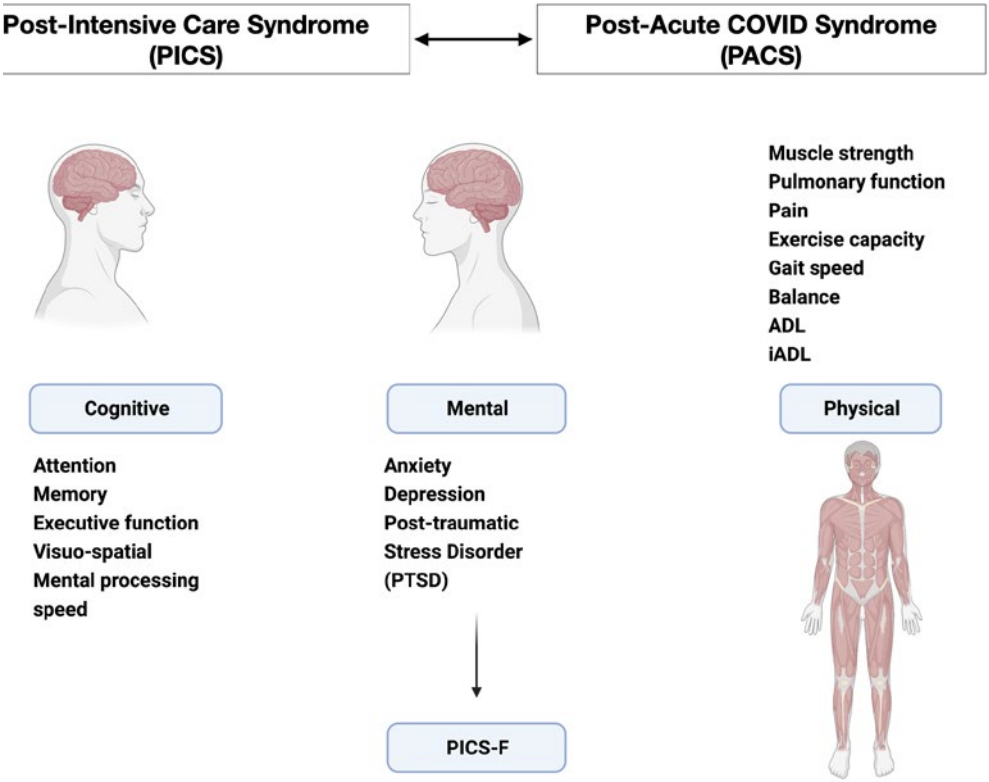

Figure 13: Domains of Post-Intensive Care Syndrome and Post-Acute COVID Syndrome

- Second, the exercise dose may be too low.
- Third, nutritional intake is not sufficient.
- Fourth, anabolic resistance in the elderly is a factor. This is the blunted stimulation of muscle protein synthesis to common anabolic stimuli in skeletal muscles, such as dietary protein and exercise. In other words, when you want to become a geriatric bodybuilder, you must eat more proteins and work out longer and harder than a young person.
- Fifth, persistent inflammation may hamper recovery.

These limitations suggest that the window of opportunity for muscle recovery is after ICU discharge when inflammation has resolved. Moreover, more proteins, energy and exercise are needed to improve outcomes.

Post-ICU nutrition

In the Prospect I study, we took photographs of the leftovers on the food trays of post-ICU patients delivered by our hospital's room service staff. [35] Cameras were connected with cables to the patients' beds because after the first week, we lost all cameras. Moreover, sometimes we could not find elements of the food ordered in the electronic system among the leftovers on the trays. Food was redistributed to home refrigerators by family members. Not the best way to improve food intake of our patients.

Figure 14: Prospect I study evaluating nutrition intake post-ICU

We have observed that nutritional intake is too low among post-ICU patients in general wards. There are several reasons for this: Patients may have a poor appetite, depression, post-traumatic stress disorder, loss of taste and smell, swallowing disorders, eat slower, and not all food ordered is eaten. Furthermore, prescriptions are too low, and still, nutrition therapy is not always considered essential. [36]
We have noticed marked drops in intake the day after nasogastric feeding tubes were removed. [35] Patients cannot compensate for the intake provided the previous day during the tube feeding administration. Insufficient intake may lead to further loss of muscle mass and delay recovery. However, exact nutrition targets for calories and proteins after ICU stay are unknown.

Historical refeeding programmes

Let us look back into history to find these targets.
In 1944, the Minnesota starvation experiment was conducted by Dr Ancel Keys using volunteers who had been inducted into public wartime service. Healthy young men

voluntarily lost weight to BMIs below 14 on an 1800 kilocalories restricted diet. Subsequently, they were put on refeeding regimens to gain weight. [37]

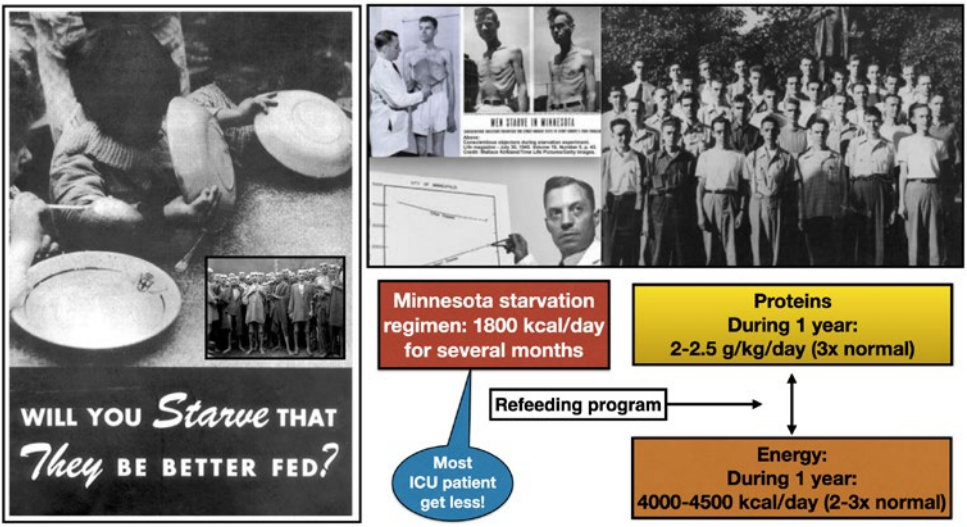

Figure 15: The Minnesota starvation study

This study is still relevant as many civilians die from starvation in war today. During recovery, the men ate more than 4000 kilocalories per day and had protein intakes three times normal. [37] These targets cannot be achieved by oral feeding alone in post-ICU patients. Drink feeds, or tube feeding should be added.
Interestingly, the average starvation diet's caloric intake in this experiment was similar to or even higher than what the average ICU patient receives. [38] We must conclude that most patients are starved in the ICU and after discharge. We must do a better job.

Food versus medicine

Hippocrates knew that food was not medicine, and medicine was not food. I strongly agree with that. Food and nutrition cannot easily be compared with pharmacotherapy. Food typically consists of proteins, carbohydrates, fat, and other nutrients to sustain growth and vital processes and furnish energy.
Pharmaceuticals are substances used to diagnose, treat, or prevent disease and restore, correct, or modify functions. The complexity is in the fact that nutrients may also have such properties.

Nowadays, we use the term "Food for Special Medical Purposes" (or FSMPs) in medical nutrition products to make things even more complex. FSMPs are evidence-based nutritional solutions for disease-related malnutrition and various other conditions. They can partially or wholly replace a regular diet. Claims made should be evidence-based, and high-quality standards apply. Oral Nutritional Supplements (ONS) are sterile liquids, semi-solids or powders which provide macronutrients and micronutrients and can be added to an oral diet. Tube feeding is a liquid form of nutrition delivered through a feeding tube. Parenteral nutrition is medication as it is infused intravenously.

Reductionism in nutrition research

In medicine, we are used to the reductionistic approach. Reductionism is centred on the belief that we can best explain something by breaking it down into its individual parts. Reductionism is indispensable in answering specific questions on ingredients. However, only thinking in terms of substances quickly becomes a dogma. It led to the introduction of the concept of Pharmaconutrition, referred to as medical food products with increased levels of specific ingredients. Immune-enhancing or immune-modulating nutrition products have been considered logical options for ICU patients. We have also studied these feeds.

Immune-modulating feeding: the MetaPlus trial

Based on existing knowledge, a new tube feed was designed. It was known from smaller studies that glutamine could reduce infectious complications. Reductions in infections were also reported with antioxidant vitamins and trace elements such as vitamin C, vitamin E, selenium, and zinc. Furthermore, fish oil could mitigate the pro-inflammatory response. Extrapolating all available data, we designed a study and expected to observe an infection reduction of 50%. The study was conducted in 12 hospitals in 14 ICUs in four countries, and we included around 300 patients. The two products tested in the MetaPlus trial are shown here. [39] Products were isonitrogenous and isocaloric, meaning that the protein and energy content was similar. However, the new feed contained more glutamine, fish oil, antioxidant vitamins and trace elements.

To our surprise, we did not find any effect on infections, the primary study endpoint. More seriously, we found increased mortality in the medical immune-modulating feed group. No benefit, but more harm.
Hippocrates's wrote in De Alimento: In food excellent medicine can be found, in food bad medicine can be found: Good and bad are relative. He further suggested: "do no harm". Therefore, this immune-modulating feed was not further developed and not introduced into the market.

Nutrients (per 1500 mL)	Immune-modulating feed	Standard Feed
Energy	1920 kcal	1920 kcal
Protein (g) ▪ Cas/ wheat hydr / Ala-Gln	112.5 g (23.4 En%) ▪ 41% / 39% / 20%	112.5 g (23.4 En%) ▪100 %/0/0
▪Glutamine	▪ 30 g	▪ 9 g
Carbohydrates ▪ Fructose	141 g - (29.3 En%) ▪ 0 g	231 g - (48 En%) ▪ 0 g
Fat ▪ MCT	96 g (45 En%) ▪ 19.5 g	55.5 g (26.3 En%) ▪ 0 g
▪EPA – DHA (Fish oil)	▪ 7.5 g	▪ 0 g
Anti-oxidants ▪ vitamin C ▪ vitamin E (alpha toco) ▪ Selenium ▪ Zinc	Above normal values ▪ 690 mg ▪ 266 mg (400 IU) ▪ 285 mcg ▪ 30 mg	Normal values ▪ 195 mg ▪ 22.5 mg ▪ 112.5 mcg ▪ 22.5 mg
Other Vit / Min./ trace el.	Normal values	Normal values
Fiber	22.5 g (2.3 En%)	22.5 g (2.3 En%)

Figure 16: MetaPlus trial product compositions

In a post-hoc analysis, we found strong effect associations between fish oil and increased mortality. Patients with the most significant increase in plasma fish oil levels showed the highest mortality. [40]

What can we learn from the MetaPlus trial?

First, large randomised controlled trials do not always confirm observations from smaller studies.

Second, and counterintuitive, in critical illness, immune-modulating lipids, such as fish oil, suggested to reduce the hyperinflammatory response, may aggravate a state of immunoparalysis. However, this does not imply that fish oil may not benefit other patients. We must study nutritional interventions in the right population, using rigorous designs and the highest scientific standards.

Third, we performed this study, although we did not know the exact immune status of our patients. When a patient already has an immunoparalysed immune system, providing anti-inflammatory nutrients such as fish oil may not be a good idea.

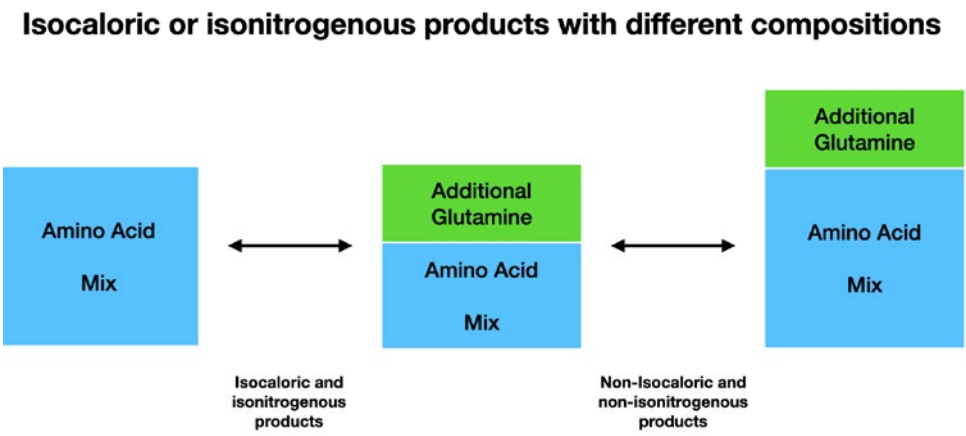

Figure 17: The problem of changing product compositions concerning energy and protein dose

Fourth, using isocaloric or isonitrogenous products with different compositions results in two interventions. Let me explain. When glutamine levels should be higher, but the total content of amino acids should be equal, other amino acid concentrations must be lower. Is the effect observed then due to higher glutamine levels or the lower levels of other amino acids? When nutrients are added and protein and energy levels are different between study arms, we cannot know whether effects are induced by the specific ingredients or a higher total nutrition dose. These conundrums cannot be solved in nutrition research.

Finally, the intervention itself may change metabolic processes. When glutamine is infused, glutamine plasma levels will increase. However, plasma levels of other amino acids also increase by conversions, such as citrulline and arginine. [41]

This is relevant as in sepsis patients, these two amino acids have been associated with

nitric oxide production, potentially enhancing vasodilation and shock in patients with sepsis and organ failure.

Monotherapy versus combination therapy

Another complex issue of nutritional research is monotherapy versus combination therapy. Our typical reductionistic approach would study individual vitamins and trace elements in placebo-controlled randomised trials. All such trials in critically ill patients have failed to improve outcomes. Why? Maybe, because we must combine micronutrients. I will illustrate this with two examples:

1 During inflammation, increased reactive oxygen species or ROS are produced, interfering with intracellular processes and damaging organelles and DNA. The antioxidant network is designed to counteract ROS production. Several micronutrients are cofactors in this antioxidant network. We cannot observe marked effects in monotherapy interventions when other micronutrients are still deficient. This system will only work optimally when replenishing all limiting cofactors. [42]

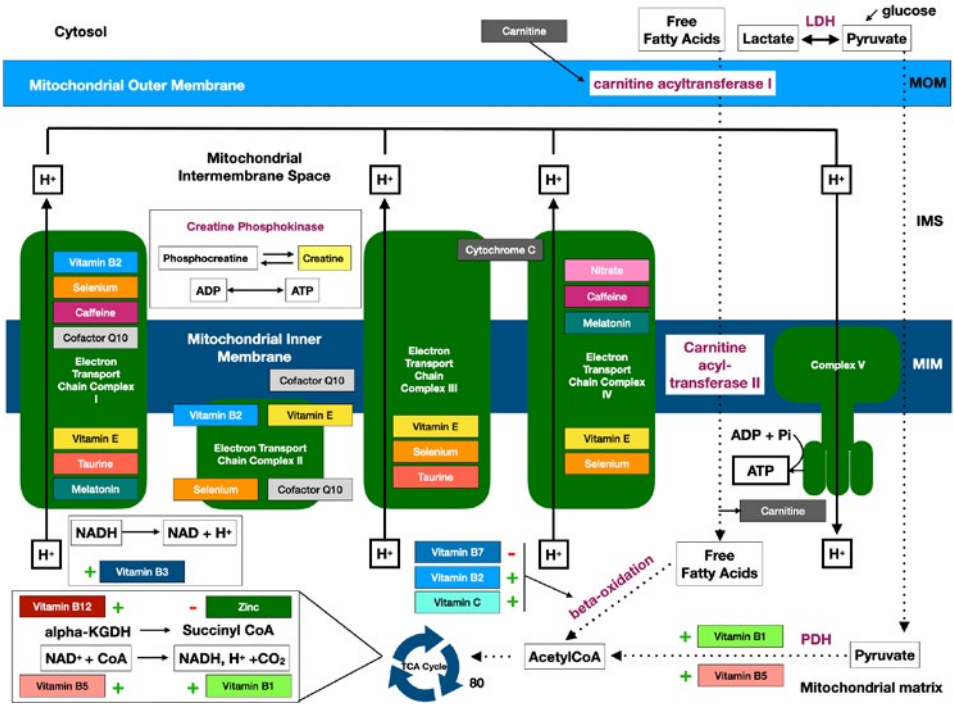

Figure 18: Essential nutrients for optimal mitochondrial functioning

2 Similar reasoning could be applied to the resuscitation of hibernating mitochondria. How can we wake up the mitochondria? Insufficient micronutrient intake may prevent mitochondrial recovery.

In a recent paper, we have summarised all relevant cofactors. [43] When looking at some of these essential nutrients, such as vitamin C, resveratrol, and caffeine, it appears attractive to recommend combinations of eating oranges and drinking a glass of red wine and a cup of coffee to improve recovery. Of course, first, we must prove effects of these interventions in human research.

Future research areas of interest

The focus of our future research is based on the question: Why do some patients show excellent functional, cognitive, and mental recovery, and why some patients do not? This relates to resilience after acute metabolic stress.

Post ICU intake optimisation

Several studies are ongoing or will start soon to optimise the post-ICU intake. The Confucius trial will evaluate differences in muscle function and quality of life by comparing patients taking daily protein versus carbohydrate supplements. In the Prospect II- study, we will address the effects of a new protocol to taper tube feeding and progress oral nutrition to close the gap between target and intake achieved. The Valifood studies will investigate electronic food charts used by ward nurses, patients, and families to score post-ICU food intake.

Mechanistic studies

Several mechanistic studies are ongoing: the MIC study addresses mitochondrial dysfunction during early septic shock.
The HYPPOCRATES study will answer why phosphate levels drop during refeeding syndrome. Other studies focus on energy metabolism and body composition. We collaborate with Karolinska University in Stockholm on autophagy research and Maastricht University on muscle protein synthesis.
In collaboration with Human and Animal Physiology at WUR, we will further study mitochondrial dysfunction using extracorporeal filters and micronutrient cocktails to resuscitate mitochondria during and after metabolic stress.

High-protein intake in ICU

We study high protein intake in 800 ICU patients in the ongoing Precise RCT led by the Maastricht ICU team. Our group leads five sub-studies of this multicentre binational RCT.

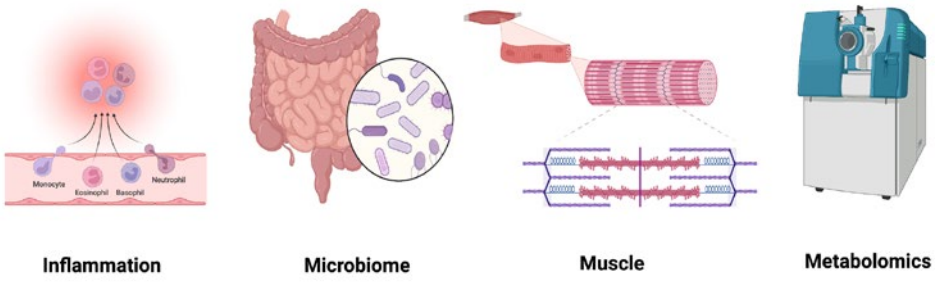

Figure 19: Future study domains

New studies will be designed on longitudinal research during and after ICU discharge addressing inflammation, the microbiome, muscle resilience, and metabolomics, with academic consortia and private-public collaborations.

Sports medicine and metabolic stress
We can also learn from top sports medicine, one of the centres of excellence in our hospital, on how to best design nutrition schemes and exercise programmes. Similar efforts are undertaken there to optimise muscle mitochondrial performance, strive for gold, and enhance recovery from extreme exercise or injuries.

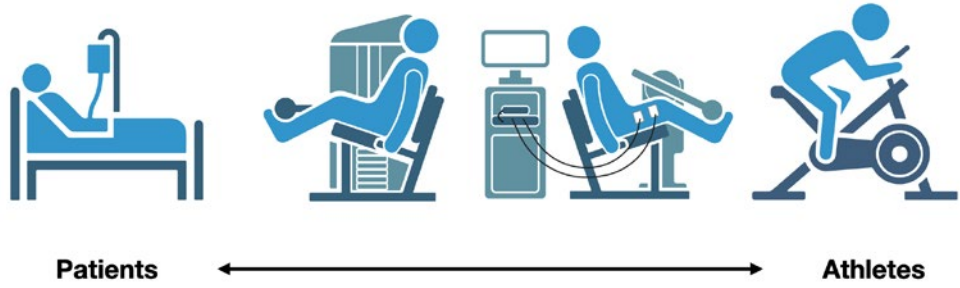

Figure 20: Combining knowledge from sports medicine and intensive care medicine

It is exciting to combine knowledge. It may be a two-edged sword benefiting both future patients and athletes.

Dissemination of knowledge of nutrition and metabolism

To improve functional outcomes and patients' quality of life, disseminating knowledge of nutrition and metabolism is paramount. Two strategies should be considered:

First, in academic institutions, such as Wageningen University & Research, we must expand our activities and give students opportunities to learn more about medical nutrition such as tube feeding, ONS, and parenteral nutrition. Furthermore, more medical physiology, dietetics, and nutrition therapy during disease and recovery should be taught. Many students will find jobs in medical nutrition research or industry developing specific products for patients. Providing clinical internships, master thesis projects and PhD positions may facilitate their careers in this challenging field.
Second, although there is a paucity of nutrition programmes in medical schools, interest among medical students in nutrition is high. In contrast, knowledge of metabolism and nutrition therapy is minimal. Nutrition may be less fancy than other medical procedures. However, as was recently stated in The Lancet: "you must consider that a poorly trained medical workforce can be viewed in and of itself as one structural contributor to diet-related disease". [44]

Figure 21: Educational strategies to enhance nutrition and metabolism knowledge

Most effective strategies to incorporate nutrition curricula into medical training include integrating nutrition-related topics in lectures on disease pathogenesis and treatment, self-paced online curricula, and greater utilisation of interprofessional education. Also, postgraduate training is essential as many doctors and nurses do not have sufficient exposure to training in nutrition. Therefore, I will continue training healthcare

professionals globally, providing in-depth knowledge on the latest insights and practical tools to improve feeding performance.
I am proud to state that Gelderse Vallei Hospital is recognised as the Nutrition hospital in the Netherlands. However, it can further develop into an internationally recognised field lab for nutrition strategy implementation based on the latest scientific insights, following the dictum: "Practice what you preach!"

How can we change future perspectives for patients?

In the future, I hope we can better understand metabolic and functional resilience after metabolic stress. Improved knowledge will lead to targeted, personalised precision multimodal therapies tailored to achieve the best results for individual patients. A healthy lifestyle and preserving muscle mass during ageing is the best way to survive critical illness from the patient perspective. Additionally, rapid and high-quality critical care medicine should be provided when critical illness emerges. However, ICU treatments should not only focus on lower mortality but also on strategies to confer better functional outcomes and quality of life.
This imperative implies that nutrition therapy's potentially harmful effects should be avoided in the early phase. Conversely, progressive nutrition therapy, preferably combined with exercise rehabilitation, is essential during recovery. Most likely, this combined intervention should last for 6-12 months. Ultimately, the difference will be made by the execution. Not only advocate what should be done but achieve what should be done. Therefore, we need more awareness concerning the importance of nutrition therapy and exercise for the recovery of patients with Post Intensive Care Syndrome, long COVID and sepsis.
I call to action from the government, funding bodies and health insurance companies to facilitate research funding and quality projects for this crucial field of interest.
Moreover, educational organisations, such as Universities, should increase efforts to include nutrition and metabolism in educational programmes. The knowledge gap is still wide. Let us start closing the gap and guarantee optimal nutritional support for our patients with acute metabolic stress during all phases of the patient journey, to provide them with a better future.

Closing statements

I have commenced this inaugural lecture with the dictum: "let food be thy medicine and medicine be thy food". In the end, I want to rephrase this imperative: "Let food and nutrition therapy be a personalised, targeted, and integral part of any medical treatment strategy in all phases of metabolic stress and recovery to contribute to the maximum functional recovery and quality of life for those we take care of and dedicate our research to:
Our patients."

Dankwoord

Tenslotte wil ik enkele voor mij dierbare en belangrijke mensen bedanken.

De Raad van Bestuur van Wageningen University & Research, het college voor promoties, en de leden van de benoemingsadviescommissie dank voor het instellen van mijn buitengewone leerstoel en het in mij gestelde vertrouwen.

Ik ben trots een van de ambassadeurs van Ziekenhuis Gelderse Vallei te zijn en mag optreden namens een van de speerpunten voeding, bewegen en slaap. De Raad van Bestuur (Miriam in 't Veld, Marjolein de Jong en Arjen Hakbijl), en de de medisch staf van Ziekenhuis Gelderse Vallei (Frans Timmer en André Jansen, voorzitters): Heel veel dank dat het ziekenhuis mijn leerstoel mogelijk maakt.

Ik denk terug aan de inspirerende tijd van mijn proefschrift en de stimulerende discussies met mijn Promotor professor Armand Girbes, en copromotor Kees Polderman. Zonder hen was ik nooit zo diep in de research gedoken.

Dank ook aan de Alliantie Voeding in de Zorg (Tom van Loenhout, voorzitter en Menrike Menkveldt, manager), voor de steun die ik steeds ervaar bij het versterken van de samenwerking tussen de WUR en de aangesloten zorgorganisaties.

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Professors Olav Rooijackers, Luc van Loon, Elisabeth de Waele, Pierre Singer, Paul Wischmeyer, Marian de van der Schueren, Hans Zwerver, Ben Witteman, dank voor de plezierige samenwerking.

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Dank ook aan het NIV-bestuur, het Concilium, de Sectie IC en de GIC waar ik met vele collega's een bijdrage lever aan het versterken van onze mooie vak Inwendige geneeskunde, Intensive Care geneeskunde en de opleiding tot intensivist.

Dave Tjan, Roel Schellaars, Mark van Iperen, Barbara Festen, Fiona van Gelder, Sjoerd van Bree, en Ruben van der Wekken, mijn naaste collega intensivisten. Dank om zoveel ruimte te krijgen om mijn research plannen te kunnen verwezenlijken. Zonder inzet van alle IC-verpleegkundigen, arts-assistenten, en overige ondersteunende staf hadden we nooit zoveel bereikt. Martin Smink, afdelingshoofd IC, dank voor het partnership waarin we de afdeling mogen leiden. Dora, Sureya, en Hester, zonder jullie zou mijn agenda een chaos zijn.

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Research kan niet zonder funding. Dank aan ZonMw, KCE, Nutricia-Danone, Mermaid, Cardinal Health, Rousselot, Wetenschapsfonds Ziekenhuis Gelderse Vallei en allen die financieel hebben bijgedragen aan verschillende studies. Ook dank voor alle donaties in het kader van deze oratie.

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Promovendi Feike Loots, Kristine Vonhoff-Koekkoek, Rianne Slingerland-Boot, Hanneke Moonen, Max Melchers, Anoek Hermans en Yente Boelens en alle WUR

studenten en medische wetenschapscoassistenten, jullie enthousiasme, ontwapenende vragen en inzet inspireren mij iedere dag. Dank dat ik met jullie mag werken. Ook veel dank aan alle betrokken docenten, promotoren en copromotoren.

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Mijn hele carrière ben ik geïnspireerd door mijn patiënten, voor hen wil ik die extra inspanning graag leveren. Twee ex-Intensive Care patiënten wil ik in het bijzonder noemen: Idelette Nutma, die met Sepsis en daarna veel goed werk doet om de uitkomsten van sepsispatiënten te verbeteren. En Suze Korver, met haar man Siem en hun gezin, die op mij een enorme indruk hebben gemaakt tijdens en na de behandeling op onze IC. Hoe geweldig is het, dat jullie hier zijn, en dat we samen kunnen bouwen aan een betere toekomst voor IC-patiënten.

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Graag wil ik nog jaren door met mijn collega's van de programmacommissies van het Nationale Voedingscongres, de Mythen, Missers en Maatwerk congressen, Optimale Antibiotica toepassing, en het International Sepsis Symposium Netherlands, Begrenzingen aan Intensive Care en de MasterclassIC Schiermonnikoog.

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Hoe bijzonder is het dat ik vandaag publiekelijk het hoogleraarschap, het hoogste academische ambt aanvaard met deze lezing. Helaas zonder mijn moeder, die aan de gevolgen van de ziekte van Alzheimer overleed midden in de coronacrisis. Ze was vast heel trots geweest op haar oudste zoon.

Gelukkig is mijn vader hier wel aanwezig. Toch zag dat er even niet naar uit toen hij 3 weken met een Corona-infectie in ons ziekenhuis was opgenomen. Maar zoals hij zelf altijd zegt: "Doorzettingsvermogen begint waar het leuk zijn ophoudt." Daar heb ik vast iets van meegekregen.

Mijn jongere broers, met jullie lieve vrouwen Marion en Marinel en prachtige gezinnen Nathalie, Laura, Julian en Floris. Frank en Robert, ik ben ongelooflijk trots dat jullie mijn broers zijn en het als ondernemers helemaal gemaakt hebben. We hebben gedrieën best wat bereikt. Ik geniet van onze heerlijke tijd in Portugal samen, waar ik menig artikel schreef. We delen ook bijzondere muzikale interesses, als 3 trombonisten, in onze app 4 brothers minus one, verwijzend naar een jazz compositie voor 4 trombonisten, die we samen nog eens moeten spelen.

Zonder mijn gezin zou ik hier niet staan. Ze steunden mij altijd. Toen ze hoorden van deze kans reageerden ze: "Moet je doen pap, is gaaf."

Marjolein, mijn liefste oudste dochter, een master in strategisch management, je staat letterlijk bol van de leiderschapskwaliteiten en muzikaliteit. Samen met Sander ga je een prachtige toekomst tegemoet. Ik hoop dat jullie snel het huis van jullie dromen mogen vinden.

Florianne, mijn liefste jongste dochter. Net afgestudeerd als arts, werkzaam op de IC van het Maasstad ziekenhuis in Rotterdam. De geschiedenis herhaalt zich, ik ben immers ook begonnen in het Clara ziekenhuis. Met Oscar samen ga je nog veel prachtige reizen maken. Ik hoop dat je droom om anesthesioloog te worden spoedig mag uitkomen.

Lieve Anita, deze dag draag ik op aan jou. Je runt je eigen bedrijf, bent recent met een academische studie begonnen. Je bent voor mij de belangrijkste steun in de rug. We hebben een prachtig gezin, een fantastisch leven samen. Fijn dat ik altijd mijn dromen mocht verwezenlijken. Welke mooie avonturen gaan we samen nog beleven? Dank voor wie je voor me bent. Ik hou van je.

Ik heb gezegd.

References

1 Cardenas D. Let not thy food be confused with thy medicine: The Hippocratic Misquotation. e-SPEN Journal 8 (2013) e260ee262.

2 Lafont O. Du saule a l'aspirine [From the willow to aspirin]. Rev Hist Pharm (Paris). 2007 Jul;55(354):209-16. French. doi: 10.3406/pharm.2007.6334. PMID: 18175528.

3 https://www.stichting-nice.nl/datainbeeld/public?year=2020&subject=SMR&hospital=-1&icno=0. Last accessed 22 May 2022.

4 Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014 Apr 2;311(13):1308-16. doi: 10.1001/jama.2014.2637. PMID: 24638143.

5 Wischmeyer PE. Are we creating survivors…or victims in critical care? Delivering targeted nutrition to improve outcomes. Curr Opin Crit Care. 2016 Aug;22(4):279-84. doi: 10.1097/MCC.0000000000000332. PMID: 27327244.

6 https://healthcarenutrition.org/methods-of-nutrition/ Last accessed 22 May 2022.

7 Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol. 2013 Dec;13(12):862-74. doi: 10.1038/nri3552. Epub 2013 Nov 15. PMID: 24232462; PMCID: PMC4077177.

8 Moonen HPFX, Beckers KJH, van Zanten ARH. Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. J Intensive Care. 2021 Jan 12;9(1):8. doi: 10.1186/s40560-021-00524-0. PMID: 33436084; PMCID: PMC7801790.

9 Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Phadke R, Dew T, Sidhu PS, Velloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SD, Hart N, Montgomery HE. Acute skeletal muscle wasting in critical illness. JAMA. 2013 Oct 16;310(15):1591-600. doi: 10.1001/jama.2013.278481. Erratum in: JAMA. 2014 Feb 12;311(6):625. Padhke, Rahul [corrected to Phadke, Rahul]. PMID: 24108501.

10 Weijs PJ, Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Oudemans-van Straaten HM, Beishuizen A. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. Crit Care. 2014 Jan 13;18(2):R12. doi: 10.1186/cc13189. PMID: 24410863; PMCID: PMC4028783.

11 Treskes N, Koekkoek WAC, van Zanten ARH. The Effect of Nutrition on Early Stress-Induced Hyperglycemia, Serum Insulin Levels, and Exogenous Insulin Administration in Critically Ill Patients With Septic Shock: A Prospective Observational Study. Shock. 2019 Oct;52(4):e31-e38. doi: 10.1097/SHK.0000000000001287. PMID: 30407371.

12 Fliers E, Boelen A. An update on non-thyroidal illness syndrome. J Endocrinol Invest. 2021 Aug;44(8):1597-1607. doi: 10.1007/s40618-020-01482-4. Epub 2020 Dec 15. PMID: 33320308; PMCID: PMC8285315.

13 Moonen HPFX, Van Zanten ARH. Mitochondrial dysfunction in critical illness during acute metabolic stress and convalescence: consequences for nutrition therapy. Curr Opin Crit Care. 2020 Aug;26(4):346-354. doi: 10.1097/MCC.0000000000000741. PMID: 32487844.

14 Singer M. Critical illness and flat batteries. Crit Care. 2017 Dec 28;21(Suppl 3):309. doi: 10.1186/s13054-017-1913-9. PMID: 29297363; PMCID: PMC5751585.

15 Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, Fruhwald S, Hiesmayr M, Ichai C, Jakob SM, Loudet CI, Malbrain ML, Montejo González JC, Paugam-Burtz C, Poeze M, Preiser JC, Singer P, van Zanten AR, De Waele J, Wendon J, Wernerman J, Whitehouse T, Wilmer A, Oudemans-van Straaten HM; ESICM Working Group on Gastrointestinal Function. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017 Mar;43(3):380-398. doi: 10.1007/s00134-016-4665-0. Epub 2017 Feb 6. PMID: 28168570; PMCID: PMC5323492.

16 Koekkoek KWAC, van Zanten ARH. Nutrition in the ICU: new trends versus old-fashioned standard enteral feeding? Curr Opin Anaesthesiol. 2018 Apr;31(2):136-143. doi: 10.1097/ACO.0000000000000571. PMID: 29351143.

17 Fraipont V, Preiser JC. Energy estimation and measurement in critically ill patients. JPEN J Parenter Enteral Nutr. 2013 Nov;37(6):705-13. doi: 10.1177/0148607113505868. Epub 2013 Oct 10. PMID: 24113283.

18 Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care. 2016 Nov 10;20(1):367. doi: 10.1186/s13054-016-1538-4. PMID: 27832823; PMCID: PMC5105237.

19 Bousie E, van Blokland D, Lammers HJ, van Zanten AR. Relevance of non-nutritional calories in mechanically ventilated critically ill patients. Eur J Clin Nutr. 2016 Dec;70(12):1443-1450. doi: 10.1038/ejcn.2016.167. Epub 2016 Sep 14. PMID: 27623980; PMCID: PMC5153455.

20 De Waele E, van Zanten ARH. Routine use of indirect calorimetry in critically ill patients: pros and cons. Crit Care. 2022 May 5;26(1):123. doi: 10.1186/s13054-022-04000-5. PMID: 35513872; PMCID: PMC9069947.

21 van Zanten ARH. Changing paradigms in metabolic support and nutrition therapy during critical illness. Curr Opin Crit Care. 2018 Aug;24(4):223-227. doi: 10.1097/MCC.0000000000000519. PMID: 29901462.

22 Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomised controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med. 2013 Feb 1;187(3):247-55. doi: 10.1164/rccm.201206-0999OC. Epub 2012 Nov 29. PMID: 23204255.

23 Koekkoek WACK, van Setten CHC, Olthof LE, Kars JCNH, van Zanten ARH. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study. Clin Nutr. 2019 Apr;38(2):883-890. doi: 10.1016/j.clnu.2018.02.012. Epub 2018 Feb 17. PMID: 29486907.

24 Choi AM, Ryter SW, Levine B. Autophagy in human health and disease. N Engl J Med. 2013 Feb 14;368(7):651-62. doi: 10.1056/NEJMra1205406. PMID: 23406030.

25 Andréasson C, Ott M, Büttner S. Mitochondria orchestrate proteostatic and metabolic stress responses. EMBO Rep. 2019 Oct 4;20(10):e47865. doi: 10.15252/embr.201947865. Epub 2019 Sep 18. PMID: 31531937; PMCID: PMC6776902.

26 Allingstrup MJ, Kondrup J, Wiis J, Claudius C, Pedersen UG, Hein-Rasmussen R, Bjerregaard MR, Steensen M, Jensen TH, Lange T, Madsen MB, Møller MH, Perner A. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. Intensive Care Med. 2017 Nov;43(11):1637-1647. doi: 10.1007/s00134-017-4880-3. Epub 2017 Sep 22. PMID: 28936712.

27 van Zanten AR. Nutritional support and refeeding syndrome in critical illness. Lancet Respir Med. 2015 Dec;3(12):904-5. doi: 10.1016/S2213-2600(15)00433-6. Epub 2015 Nov 18. PMID: 26597130.

28 Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, Reade MC, Harrigan PW; Refeeding Syndrome Trial Investigators Group. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015 Dec;3(12):943-52. doi: 10.1016/S2213-2600(15)00418-X. Epub 2015 Nov 18. PMID: 26597128.

29 Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. Clin Nutr. 2018 Oct;37(5):1609-1617. doi: 10.1016/j.clnu.2017.08.001. Epub 2017 Aug 10. PMID: 28866139.

30 Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, Hiesmayr M, Mayer K, Montejo JC, Pichard C, Preiser JC, van Zanten ARH, Oczkowski S, Szczeklik W, Bischoff SC. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019 Feb;38(1):48-79. doi: 10.1016/j.clnu.2018.08.037. Epub 2018 Sep 29. PMID: 30348463.

31 Chan-Yeung M, Xu RH. SARS: epidemiology. Respirology. 2003 Nov;8 Suppl(Suppl 1):S9-14. doi: 10.1046/j.1440-1843.2003.00518.x. PMID: 15018127; PMCID: PMC7169193.

32 https://coronavirus.jhu.edu/map.html. Last accessed 8 June 2022.

33 Arbov E, Tayara A, Wu S, Rich TC, Wagener BM. COVID-19 and Long-Term Outcomes: Lessons from Other Critical Care Illnesses and Potential Mechanisms. Am J Respir Cell Mol Biol. 2022 Mar 29. doi: 10.1165/rcmb.2021-0374PS. Epub ahead of print. PMID: 35348443.

34 Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Simons KS, Westerhof B, Rettig TCD, Jacobs C, van Santen S, Slooter AJC, van der Woude MCE, van den Boogaard M, Zegers M. Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19. JAMA. 2022 Feb 8;327(6):559-565. doi: 10.1001/jama.2022.0040. PMID: 35072716; PMCID: PMC8787680.

35 Slingerland-Boot H, van der Heijden I, Schouten NE, Driessen L, Meijer S, Mensink MR, van Zanten ARH. PRospective Observational cohort Study of reached Protein and Energy Targets in general wards during the post-intensive care period: the PROSPECT-I study. Submitted for publication.

36 Ridley EJ, Chapple LS, Chapman MJ. Nutrition intake in the post-ICU hospitalisation period. Curr Opin Clin Nutr Metab Care. 2020 Mar;23(2):111-115. doi: 10.1097/MCO.0000000000000637. PMID: 31977335.

37 Wischmeyer PE. Tailoring nutrition therapy to illness and recovery. Crit Care. 2017 Dec 28;21(Suppl 3):316. doi: 10.1186/s13054-017-1906-8. PMID: 29297385; PMCID: PMC5751603.

38 Bendavid I, Singer P, Theilla M, Themessl-Huber M, Sulz I, Mouhieddine M, Schuh C, Mora B, Hiesmayr M. NutritionDay ICU: A 7 year worldwide prevalence study of nutrition practice in intensive care. Clin Nutr. 2017 Aug;36(4):1122-1129. doi: 10.1016/j.clnu.2016.07.012. Epub 2016 Aug 9. PMID: 27637833.

39 van Zanten AR, Sztark F, Kaisers UX, Zielmann S, Felbinger TW, Sablotzki AR, De Waele JJ, Timsit JF, Honing ML, Keh D, Vincent JL, Zazzo JF, Fijn HB, Petit L, Preiser JC, van Horssen PJ, Hofman Z. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomised clinical trial. JAMA. 2014 Aug 6;312(5):514-24. doi: 10.1001/jama.2014.7698. PMID: 25096691.

40 Hofman Z, Swinkels S, van Zanten ARH. Glutamine, fish oil and antioxidants in critical illness: MetaPlus trial post hoc safety analysis. Ann Intensive Care. 2016 Dec;6(1):119. doi: 10.1186/s13613-016-0220-y. Epub 2016 Dec 12. PMID: 27957725; PMCID: PMC5153384.

41 Buijs N, Brinkmann SJ, Oosterink JE, Luttikhold J, Schierbeek H, Wisselink W, Beishuizen A, van Goudoever JB, Houdijk AP, van Leeuwen PA, Vermeulen MA. Intravenous glutamine supplementation enhances renal de novo arginine synthesis in humans: a stable isotope study. Am J Clin Nutr. 2014 Nov;100(5):1385-91. doi: 10.3945/ajcn.113.081547. Epub 2014 Oct 1. PMID: 25332337.

42 Koekkoek WA, van Zanten AR. Antioxidant Vitamins and Trace Elements in Critical Illness. Nutr Clin Pract. 2016 Aug;31(4):457-74. doi: 10.1177/0884533616653832. Epub 2016 Jun 16. PMID: 27312081.

43 Wesselink E, Koekkoek WAC, Grefte S, Witkamp RF, van Zanten ARH. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. Clin Nutr. 2019 Jun;38(3):982-995. doi: 10.1016/j.clnu.2018.08.032. Epub 2018 Aug 31. PMID: 30201141.

44 Crowley JJ, Ball L, Hiddink GJ. Nutrition in medical education: a systematic review. Lancet Plan Health 2019; 3: e379–89.

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'Food is not medicine. However, nutrition is essential to recover from acute metabolic stress. Metabolic stress induced by critical illness markedly changes the metabolism of patients and interacts with nutrition therapy. Therefore, feeding patients during metabolic stress and convalescence cannot easily be compared with the anabolic-catabolic changes observed in health. Optimal timing and dosing of macronutrients and micronutrients is paramount to do no harm, enhance recovery and achieve the maximum functional performance and quality of life for patients after acute metabolic stress. Personalised, tailored nutrition strategies throughout the patient journey are essential to improve outcomes.'

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