Nutritional Support in Intensive Care Unit (ICU) Patients

Topic 18

Module 18.1

Energy in the ICU

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Learning Objectives

- Energy status of the critically ill;
- Energy production;
- Energy and substrate;
- Energy utilisation measurement: indirect calorimetry;
- Modifying factors for energy utilization;
- Refeeding syndrome: relation to energy metabolism.

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Key Messages

- ATP is the energy of the human body generated via oxidation of substrates;
- Substrate oxidation is impaired in acute illness;
- The body is able to produce all substrates from within the body;
- Total substrates are the sum of substrates from within and given as nutrition from outside;
- Progressive nutrition allows a proper adaptation of metabolism;
- Refeeding syndrome is frequent and needs prevention and treatment.

1. Introduction

All human activities and the maintenance of cell integrity and function necessitate energy. Energy utilized in mammalian cells is exclusively delivered by adenosine-tri-phosphate (ATP), that liberates 7 kcal.mol^{-1} when one phosphate group is split off. The energy is stored in substrates like the typical macronutrients glucose, fatty acids, proteins or alternative substrates like alcohol or organic anions like citrate, lactate, acetate and malate which in the process of mitochondrial oxidation generate ATP in the respiratory chain. Thus the energy production in human mitochondria and utilization process for cellular processes has an efficiency of 50%.

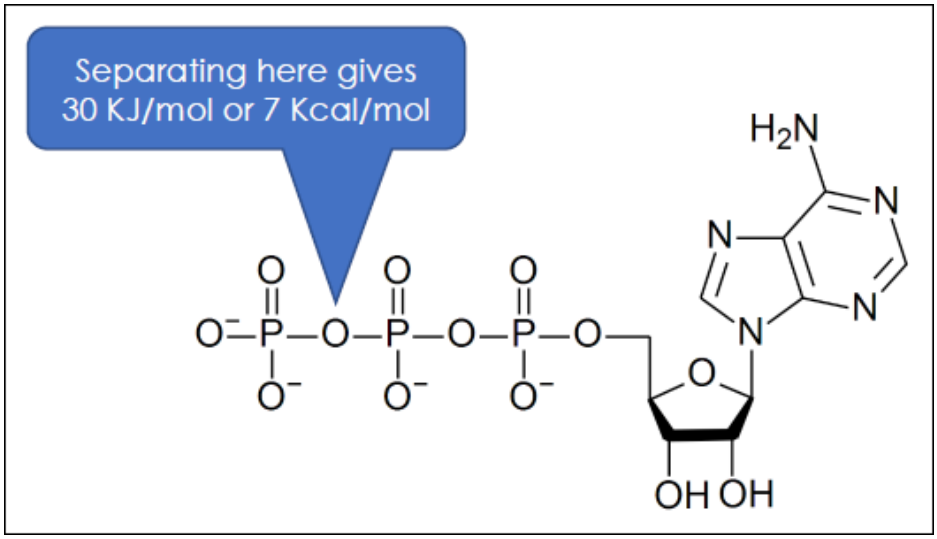

Fig. 1 ATP molecule (1 mol=507.81 g)

FADH2 and NADH2 are the substrates for respiratory chain, they are produced by the oxidation/dehydrogenation of various metabolites, their availability is required to produce energy in the respiratory chain. Creatine-phosphate in muscle stores at rest are approximately 26 mmol/kg wet weight, the energy utilized within the first 8-15 seconds of starting maximal muscle force development.

The ATP content of an adult human body is 50-100g whereas ATP production is 50-75 kg in any 24 hour period. Over a 24 hour period 100 moles of ATP are synthetized from ADP which is equivalent to 1000 times recycling of ATP daily. Thus the ATP content of human tissues is just sufficient to sustain all energy consuming processes for 1-2 minutes. ATP needs to be continuously produced from oxidation of glucose or β-oxidation of fatty acids

via oxidative phosphorylation in mitochondria, because ATP storage capacity is minimal and ATP is never produced in excess. Glycolysis occurs without oxygen, produces only 2 ATP per molecule of glucose and is associated with the accumulation of lactate in tissues whereas oxidative degradation of glucose yields (32)-36 ATP.
Humans are dependent on the availability of substrates and oxygen to generate the amount of energy necessary for life.
During an average day a healthy human ingests about 2500 g of food composed of 200-300 g of carbohydrate, 50-100 g of fat and 50-100g of protein equivalent to 1800 Kcal. During this day about 14 kg of air is inhaled and 14.1 kg of air with a lowered oxygen content and a higher CO_2 content is exhaled. In terms of weight 375 g of macronutrients are oxidized with 375 g of O_2 to 450 g of CO_2 and 240 g of H_2O.

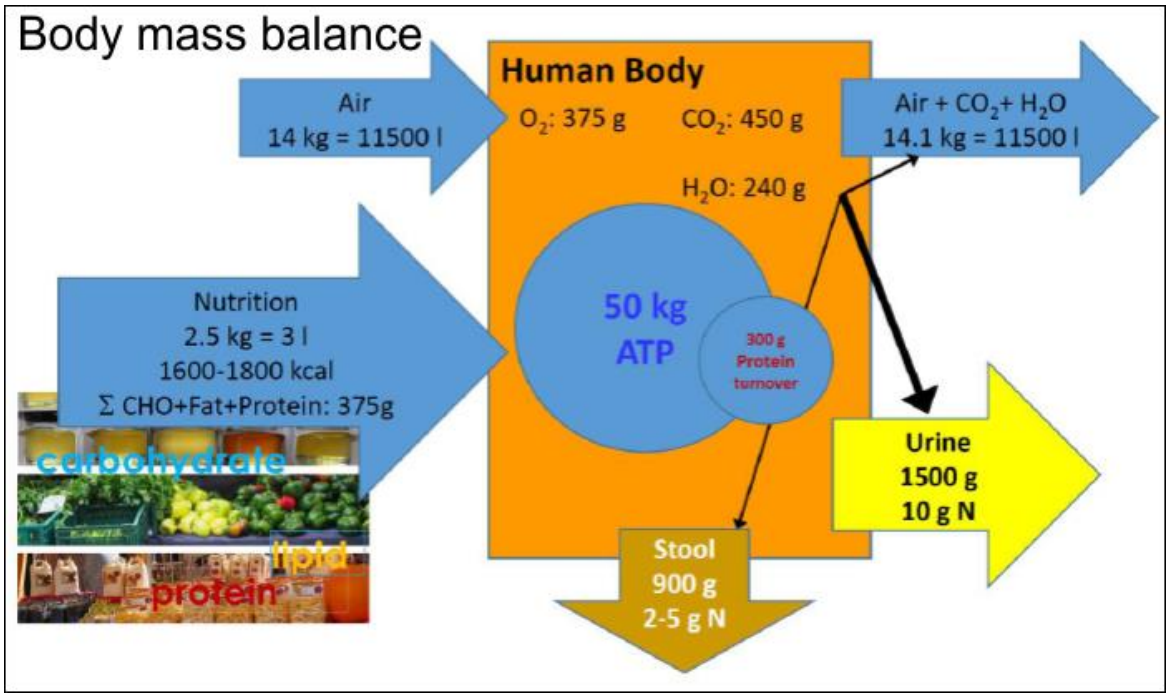

Fig. 2 Substance flow through the human body.
All input needs to match output in energetic equilibrium.

1.1 Regulation of Energy Production

Energy production is primarily governed by demand. When demand cannot be satisfied there is a central sensor adenosine-mono-phosphate-kinase (AMPK) that is activated and downregulates energy-consuming processes such as ribosome biogenesis, translation, protein synthesis, sterol synthesis and glycogen storage (1). In general autophagy related mechanisms are also activated and may supply the ATP producing machinery with substrates, and the repair mechanisms with amino acids, and degrade defective proteins and organelles (2-4). AMPK is not only activated by reduced oxygen and substrates but also by accumulation of CO_2 and increased H^+ as result of decreased blood flow to tissues (1). Thus an impaired energy production induces a catabolic response with the ultimate goal to reduce the active tissues to a level that can be served by the actual energy production capacity. One example in chronic diseases is the catabolic response to heart failure or chronic renal failure.
In acute illness, especially in infection, the body reacts with "sickness associated anorexia" (SAA) (5). The reduced intake of nutrients, especially meat aversion, may strongly

stimulate autophagy which has been associated with an improved immune response and broader antigen presenting capacity. The role of SAA in trauma and non-infectious inflammation is not clear. The debate on how to adapt artificial nutrition to phases of illness is still ongoing. Blocking autophagy was associated also with greater loss of muscle mass (6).

1.2 Which Processes Are Involved in Energy Utilization

Table 1
Relative contribution of energy (ATP) consuming processes (in bold: processes that can be temporarily reduced without compromising cell viability)

• **Protein turnover**	**20-30%**
• Na^+/K^+ ATPase	20-28%
• Mitochondrial proton leak	20-25%
• Triacylglycerol turnover	<3%
• Calcium cycling	4-10%
• Gluconeogenesis	5-10%
• Ureagenesis	<3%
• Actinomyosin ATPase	<8%
• **DNA/RNA turnover**	**<2%**
• Substrate cycling	<5%

Mervyn Singer has proposed that the ICU-patient may be considered to have flat batteries (7). Protein turnover may be reduced to spare energy for Na^+/K^+ ATPase and other cell wall pumps that maintain cell membrane potential and cell hydration is more important for cell survival at the price that function may be impaired. In fact cells in failing organs in patients with severe sepsis do not typically show necrosis when examined after death.
There is an organ priority for loss of function in case of limitation of substrates or oxygen. The brain is the most preserved organ and typically does not lose mass in acute illness. To be fed sufficiently with glucose, an essential nutrient for the brain, the brain is able to induce even insulin resistance in peripheral muscles to increase glucose availability. The high protein turnover organs such as intestine and liver may react with atrophy and loss of function that can be recovered within a few days but carries the risk of severe complications. In the muscle, a slow protein turnover tissue, critical illness may be associated with persistent impaired function.

2. Energy in Critical Illness

ATP production is impaired in critical illness especially in the non-survivor. The ATP content is reduced in association with the severity of illness and the need for supportive treatment (8). Several complexes of the respiratory chain are reduced in relation to tissue weight. The structure and function of mitochondria is impaired (9, 10). The capacity to produce ATP is reduced to as low as 50%. A critical process is the impaired repair of mitochondria and the recycling of defective mitochondrial material. Several repair mechanisms are important such as mitochondrial elongation and fragmentation that aims to create a pool of functional mitochondria at the price of a reduced number. This repair and maintenance mechanism is dependent on functioning autophagy (see below).

2.1 Substrate Availability in Acute Illness

In acute illness necessitating admission to intensive care intake of nutrients is impaired by several factors including: sickness associated anorexia, impaired cognition, intubation and artificial ventilation, sedation, pain treatment.

2.2 Substrate "Stores" in the Adult Human

All three macronutrients can be provided from within the body. Glycogen and body fat are real substrate stores, whereas amino acids are generated from breakdown of proteins that must all be considered functional. Thus any utilization of amino acids from within the body is associated with a loss of protein from the body (see **Module 18.2**).

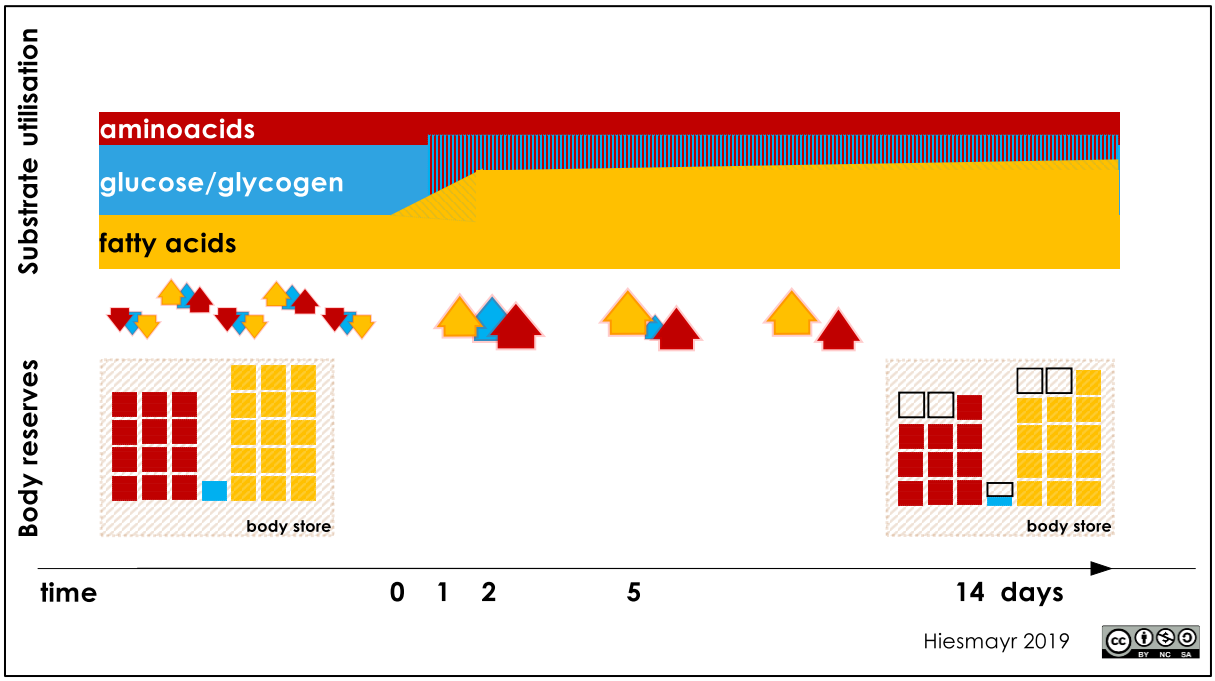

Fig. 3

Fig. 3: Relative size of substrate "stores" and depletion after 2 weeks of starvation (each block is equivalent to 1 kg). Time 0 is the timepoint of injury. Before injury patients eat meals. After each meal stores are refilled and the body is anabolic. The proportional substrate utilization is 15-20% amino acids (red), 30-40% lipids (yellow) and 45-55% carbohydrates (blue). With start of illness glucose metabolism is replaced by lipid metabolism and the minimal requirements of glucose are generated via gluconeogenesis from amino acids (blue red striped). The full substrate needs are supplied by breakdown of body reserves. Protein reserves are from muscle, visceral and thoracic organs and skin. After 2 weeks reserves are depleted by several kg (open squares).

2.3 Mobilisation of Energy Reserves

An average adult of 75 kg body weight will have postprandial body reserves of about 700 g of glycogen, 15 kg of fat and 12 kg of protein. The glycogen reserves are distributed between the liver (200 g) and the muscle (500 g). The muscle glycogen is preferentially used locally in the muscle whereas the liver glycogen serves all glucose dependent tissues.

The main glucose dependent organ is the brain that uses 100 g per day when food is available regularly. With starvation the brain switches progressively to ketones as a substrate to generate energy, a process that takes several days. A minimum amount of 30-40 g of glucose is always needed by the brain. There are two sources for glucose production in starvation, glycerol from fat breakdown and amino acids from protein breakdown. A minimal amount of 10-15 g of glucose needs to be produced via gluconeogenesis in prolonged starvation (> 1 week starvation). To produce 1 gram of glucose about 2-3 grams of protein have to be broken down to get enough glucoplastic amino acids.

In acute severe illness two mechanisms are activated to secure glucose availability. Firstly the brain triggers down-regulation of GLUT-4 receptors on the muscle thus cutting the muscle off from its glucose supply by creating insulin resistance, and secondly gluconeogenesis from amino acids is strongly stimulated. Even after 10 days of ICU stay and adequate supplementation with glucose containing nutrition gluconeogenesis cannot be suppressed completely (personal communication M. Berger) (11). In addition lipogenesis in the liver is also maintained at a higher level than in healthy subjects when continuous enteral nutrition is provided (12, 13).

After two weeks of starvation the glycogen stores are depleted, 1.5-2 kg of protein equivalent to 7-10 kg of muscle and other protein-rich tissues, and 1.5-2 kg of fat have been lost and caloric deficit of 25000 kcal has accumulated. If this process continues until 30-40% of lean body mass is lost death is inevitable. This may occur before all fat substrate reserves are depleted because the main component to be considered is protein.

Similar protein loss has been found in the critically ill even with the use of a relatively high amount of substrates via parenteral nutrition (14). The catabolic response to injury was described by Cuthbertson more than 80 years age (15, 16) but it is unclear how the response to critical illness is modulated by current intensive care treatments that were not used at that time.

It is essential to separate starvation from the metabolic reaction to injury, both being associated with provision of substrates for energy production from within the body. Whereas starvation, fasting or overnight sleep is associated with hunger and a nearly immediate return to an anabolic situation with eating, the metabolic reaction to injury and critical illness is associated with "sickness associated anorexia" (5, 17), insulin resistance (18) and activated lipolysis. This metabolic emergency program appears to be started with the aim that it continues for several days and it is not designed to abate immediately upon external provision of nutrients (11). If full nutrition is given in this situation this nutrition adds to the persisting internal substrates (19) and may cause harm associated with poorly controlled hyperglycaemia and storage of excess substrates as fat possibly also in organs that usually do not have such fat stores (20). Furthermore external substrates in the acute phase of critical illness may impair autophagy (see below).

The amount and composition of substrates to prevent the loss of lean body mass and enhance recovery has not been defined and may need phase specific nutrition adaptation (ESPEN ICU guideline (21)).

There is one organ, the brain, that is preserved from protein loss in starvation. All other organs decrease in weight and functional capacity. Thus patients with recent weight loss and low nutrient intake are at risk of "refeeding syndrome" due to insufficient capacity by organs such as the heart to maintain a higher cardiac output triggered by the higher metabolic load necessitating more oxygen and substrates for ATP production and more removal of CO_2.

2.4 Autophagy: Substrate Provision from Within

Autophagy is the key mechanism to generate substrates from within the body (17). Autophagy has a central role in clearing the cell of defective organelles, proteins and mitochondria but also in generating substrates for energy production and synthesis of proteins within the cell (4). Autophagy is thus key for cell vitality and function. Suppression of autophagy is not compatible with independent life and thus newborns without autophagy die shortly after birth. Downregulation of autophagy has been associated with chronic diseases and higher muscle loss in acute illness.
Autophagy is stimulated by starvation and suppressed by glucose and protein (17, 22). Stimulated autophagy may also be beneficial in infective inflammation because autophagy may "digest" infective agents and stimulate immune cells. The role of autophagy in non-infective inflammation is less clear. Our understanding of autophagy in critical illness is still limited but it is clear that major perturbations of this highly preserved safety and house-keeping mechanism may have unforeseen consequences.

2.5 Substrate Provision from Outside

Substrate provision is thus a life saving treatment that is necessary in all patients staying in ICU for more than 1 or 2 days (ICU guidelines). About 25% of patients in ICU may be able to eat but oral intake may often be insufficient due to sedation, delirium, tachypnoea, weakness and swallowing disorders (23). Thus most patients need artificial nutrition as enteral or parenteral nutrition.
The current ESPEN guidelines indicate that nutrition should be introduced progressively over 3-7 days to reach the target quantities (**Fig. 4**). Such an approach is recommended because the injured body needs several days to downregulate the stimulated mechanisms. Over several days a normalization of substrate flow should occur (**Fig. 5**) and loss of lean body mass will be reduced.

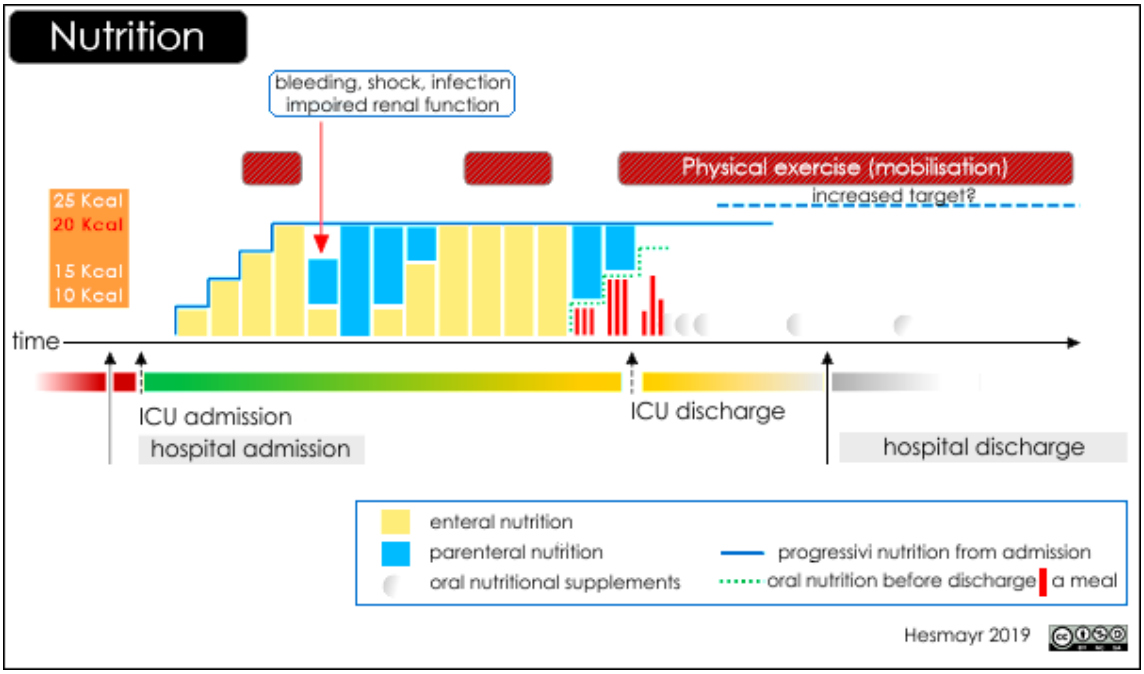

Fig. 4

Fig. 4: Time course of nutrition build-up and use of supplemental parenteral nutrition during complications with poor tolerance of enteral nutrition during a severe illness. Towards the end of the ICU stay a strategy for liberating the patient from artificial nutrition and sustaining continuity of care after discharge is schematically illustrated.

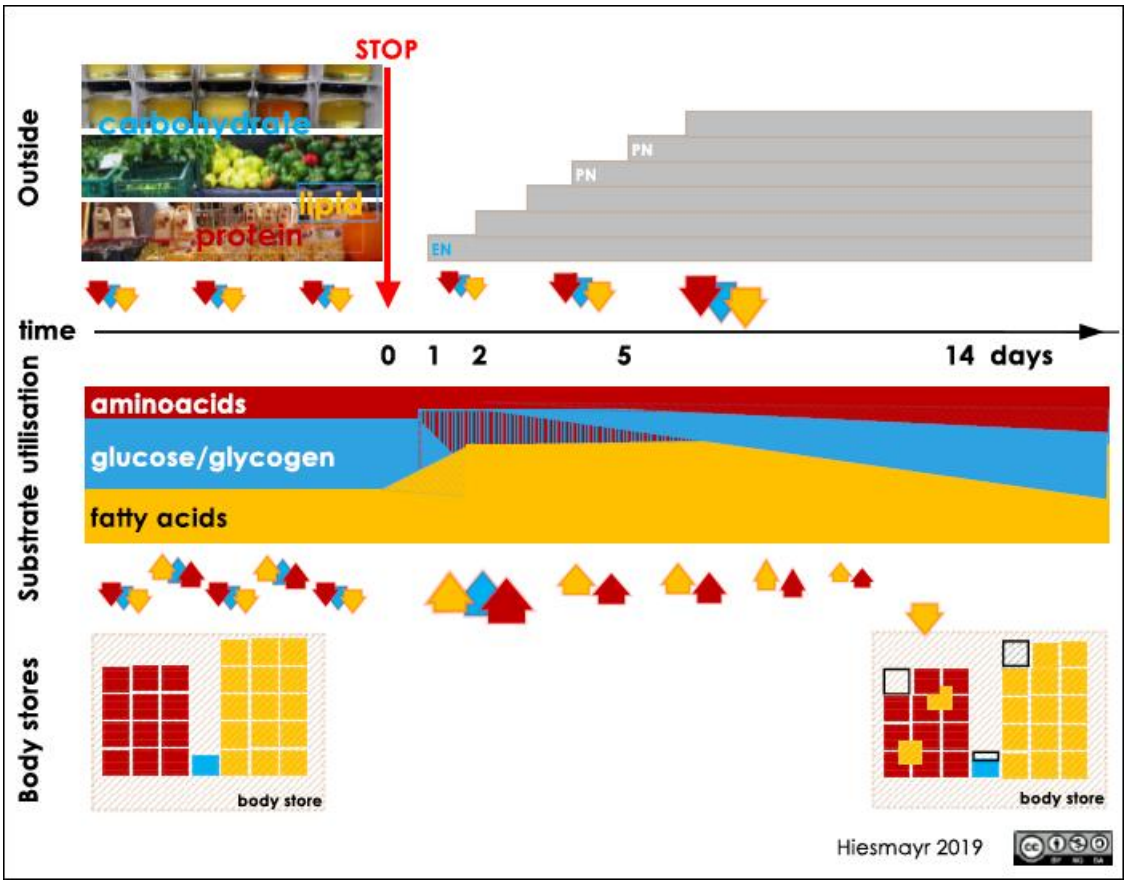

Fig. 5

Fig. 5: Adaptation of metabolic reaction to injury to artificial nutrition from outside.
The time axis separates the outside of the body from the inside. Before injury, substrate utilization is supplied from intermittently absorbed substrates from meals and breakdown from body reserves when the interval between meals is longer, e.g. overnight. When eating stops and the metabolic reaction to injury is initiated all substrates are provided continuously from body reserves. With the use of progressive artificial nutrition (substrates from outside the body) the flow of substrates from reserves decreases, insulin resistance resolves and the proportion of substrates utilized more closely resembles the situation before injury.
Enteral nutrition may be introduced with a minimal amount, once shock has resolved, within the first 24-48 hours.

2.6 Substrate Need Versus Energy Consumption/Production

In long-term nutrition it is logical that substrates have to match energy consumption and nitrogen losses in order to maintain lean body mass and function. The body has potential for increased efficiency of substrate utilization that can be considered as an adaptation to the available resources and the mix of substrates. Such a process is slow. To adapt from

low to high protein and back usually needs a minimum of 5 days for each step. The consequence is that daily large changes in substrate provision may not benefit patients.
In acute critical illness where generation of substrates from within the body is active the ideal amount of energy to be given from outside is around 70% of measured energy consumption (24, 25).

3. Measuring Energy Production

The measurement of energy used can be done either directly via the temperature generated by the body or indirectly via the consumption of oxygen, the production of CO_2 and the loss of nitrogen via the urine, stool and skin. Because there is only little ATP stored the temperature generation from ATP production and its utilization are nearly simultaneous. The calculation of energy expenditure from indirect calorimetry is based on the Weir equation:
EE (kcal.day^{-1}) = 1.44 (3.94 x V'O_2 + 1.11 x V'CO_2) – 2.17 x N-excretion
V'O_2 and V'CO_2 are given in ml.min^{-1} and N-excretion in g.day^{-1}.
Depending on the techniques only V'O_2 and V'CO_2 may be measured and calculation of energy consumption necessitates an assumption about the respiratory quotient RQ (RQ= V'CO_2 / V'O_2). Typically 0.85 is assumed. During a metabolic steady state the actual RQ could also be derived from the RQ of the substrates given but this approach ignores the substrates generated within the body.

Table 2
RQ of typical nutrients

• **Glucose (180 g/mole)**	
$C_6H_{12}O_6 + 6\ O_2 = 6\ CO_2 + 6\ H_2O + 4.2$ kcal/g	RQ = 16/23 = 0.7
• **Fat (Palmitic acid 256 g/mole)**	
$C_{16}H_{32}O_2 + 23\ O_2 = 16\ CO_2 + 16\ H_2O + 9.4$ kcal/g	RQ = 6/6 = 1
• **Amino acids (89-204 g/mol, Alanine 89 g/mole)**	
$2(C_3H_7O_{2N}) + 6\ O_2 = 5\ CO_2 + 5\ H_2O + CH_4ON_2$ 4.6 kcal/g	RQ = 5/6 = 0.83
PHA	RQ =17/23 = 0.74
• Citrate	RQ = 1.33
• Alcohol	RQ = 0.67

The energy generated by volume of oxygen utilized is slightly higher for glucose 5.6 kcal.L^{-1}, fat 4,7 Kcal.L^{-1} and for alanine 6 Kcal.L^{-1}.
In the critically ill only indirect calorimetry is done as thermic isolation of patients is impossible.

3.1 Indirect Calorimetry

Indirect calorimetry (IC) typically measures inspired and expired gas concentrations and expired gas volume. The following variables need to be measured: inspired gas volume (V'$_i$), inspired O_2 concentration (F_iO_2), expired respiratory volume (V'$_e$), expired O_2 (F_eO_2) and CO_2 concentration (F_eCO_2). Inspired CO_2 is assumed to be zero.
V'O_2 = V'$_i$ x F_iO_2 - V'$_e$ x F_eO_2
V'CO_2 = V'$_e$ x F_eCO_2

Inspired gas volume is derived from expired volume by using the calculated nitrogen concentration in inspired and expired gas to estimate the difference between inspired and expired gas volume that originates in the RQ. The formula applied is called Haldane transformation.
From the formulae it is obvious that $V'CO_2$ is much more reliably measured because only 2 variables need to be measured instead of 4. This is unfortunate since $V'CO_2$ contributes only 20% to total energy expenditure in the Weir formula. The problem of measuring precisely $V'O_2$ is technically slightly circumvented by measuring F_iO_2 and F_eO_2 with the same sensor. Thus measuring F_iO_2 is only done intermittently at intervals of several minutes. This adds some caveats if the oxygen supply is not stable in the hospital in terms of pressure because slight fluctuations in delivered O_2 may occur. A further problem originates in the fact that measuring O_2 is more difficult than CO_2 and has a much slower response time. Thus several transformations are needed to obtain reliable results when a breath-to-breath method is used for IC. The reference (Deltatrac, Datex/GE, Finland) used a mixing chamber technique for exhaled gas concentrations and used a very robust gas dilution technique to obtain expired gas volume once a minute.
Typically, expired volume is lower than inspired volume by about 1%, or 3-6 ml per breath. Such a small difference in gas volume is technically very difficult to measure directly.
IC can be used in intubated patients and in extubated patients who can be put under a hood without any respiratory aid and can oxygenate sufficiently on room air.
Validation and comparative studies have demonstrated that some calorimeters appear to deviate substantially from each other, especially from the device that is often considered the gold standard but which is neither manufactured nor maintained anymore (Deltatrac, Datex / GE, Finland) (25-27).

3.2 Partial Calorimetry

Calorimetry can also be done by either measuring only $V'CO_2$ or $V'O_2$.
$V'CO_2$ is obtained from ventilators that have an integrated CO_2 concentration measurement in expiration and measure tidal volume near the Y-piece. This method is also called quantitative capnometry. The formula is given above. Of note EE is derived from a small portion of the variables that is used for extrapolation (see above). Simply EE ($kcal.d^{-1}$) = $V'CO_2$ ($ml.min^{-1}$) x 8 when the RQ is assumed to be 0.89. A diet with 20% protein, 30% lipids and 50% glucose would have an RQ of 0.87.
$V'O_2$ is obtained from simultaneous measurement of cardiac output and arterial and venous content for oxygen. The variables needed are cardiac output, arterial or venous haemoglobin concentration, arterial and mixed-venous blood gas analysis with pO_2 and O_2 saturation. The largest part of O_2 is transported bound to haemoglobin and only a minimal amount is transported physically dissolved in the blood. 100 ml of blood fully saturated with O_2 contains about 13.9 ml of O_2. There is a linear relation between content and saturation. Simply EE ($kcal.d^{-1}$) = $V'O_2$ ($ml.min^{-1}$) x 7 when an RQ of 0.83 is assumed.
The rounded numbers 7 & 8 are proposed for partial calorimetry because it is always an approximation and thus simple calculations may be practical. Of course in computerized systems a similar RQ would be recommended. Given the complexity of the measurement partial EE from O_2 is less precise than from CO_2. Unfortunately it has been shown that the RQ of ICU patients is more variable than expected and thus partial calorimetry does not correlate very well with full IC (28,29). For patients on ECMO the combination of IC with partial methods allows an approximation (30, 31).

4. Estimation of Energy Production

4.1 Body Composition

The three main determinants of energy consumption/production (EE) at rest are lean body mass, gender and age. There is linear increase of EE with FFM in adults with a slightly higher value of EE per kg FFM at lower FFM than at higher FFM. The reason is that with increasing FFM less energy demanding tissues such as muscle and skin contribute to FFM (32). Females have 10% less EE per kg body weight and similar amounts to males if an adjustment for FFM is done. After 60 years of age EE decreases by 1% per year of age (33). The basis for this is probably decreased protein turnover.

4.2 Modifier of Energy Consumption in Critically Ill

In the critically ill many factors related to disease or treatment can modify EE. In phases of shock EE is typically decreased independently of the body temperature (34). Sedation, pain treatment and anti-inflammatory treatments may decrease EE but seizures, delirium, shivering and ventilator asynchrony will increase EE.

4.3 Formulae: Harris-Benedict and More

Estimating EE from formulae has been proposed by many groups. The formulae work well for groups of individuals but are of much less help in individual patients. Most formulae work well in the originating centre and much less so in other centres with different patient populations. In the critically ill none of the formulae can prevent over- and undernutrition much more effectively than simple rules as 20 $kcal.kg^{-1}$ BW (35).
Some formulae are displayed below but their use is discouraged.

- Harris-Benedict 1919
  - Male: 14 x weight + 5 x height-7 x age + 66
  - Female: 10 x weight + 185 x height- 5 x age + 655
  - Stress factor usual but not recommended anymore
- PENN State 2010
  - Male: 0.71 (10 x W+6.25 x H-5 x Age + 6)+ 64 x VE + 85 x Temp – 3085
  - Female: 0.71 (10 x W+6.25 x H-5 x Age -15)+ 64 x VE + 85 x Temp – 3085
- Faisy-Fagon
  - 8 x weight + 14 x height + 32 x minute volume + 94 x Temp – 4834

4.4 Adjusting Substrate Supply to Measurements

Measurement of EE does not directly indicate the amount of substrates to be given in the early phase of critical illness. The production of nutrients within the body needs always to be considered. In this view it is logical that it has been found that the best outcome is associated with giving 70% of measured EE (36). A similar careful approach is recommended when EE is estimated with formulae. In stable ICU patients, after 1-2 weeks and with controlled inflammation, production of substrates from within the body may be decreased to a level where meeting measured EE with substrates given is safe. This may be indicated by decreasing insulin resistance.

5. Refeeding Syndrome

The refeeding syndrome is a potentially lethal and often forgotten condition associated with feeding of chronic malnourished individuals or individuals with little or no nutrient intake for 5-10 days. The hallmark biochemical feature is hypophosphataemia but many other clinical signs are possible. The route of feeding does not have a specific effect on the refeeding syndrome (37, 38).

Table 3
Key pathophysiological features of the refeeding syndrome

- Fluid balance
- Glucose homeostasis
- Vitamin B1 deficiency …. Hyperlactataemia
- Hypophosphataemia
- Hypomagnesaemia
- Hypokalaemia

The incidence of the refeeding syndrome may be as high as 25% for cancer patients, and as many as 34% of intensive care patients experience hypophosphatemia within 2 days of starting artificial nutrition (39). The clinical presentation may be variable; some symptoms are even compatible with other disease processes and a poor general condition. Based on case reports the syndrome is potentially fatal, often unrecognized and poorly treated especially outside areas with close monitoring such as intensive care units.

Table 4
Refeeding syndrome: high risk patients (37)

- Patients with anorexia nervosa
- Patients with chronic alcoholism
- Cancer patients
- Postoperative patients
- Elderly patients
- Patients with uncontrolled diabetes mellitus
- Patients with chronic malnutrition
  - Marasmus
  - Prolonged fasting or low energy diet
  - Morbid obesity with profound weight loss
  - High stress patients unfed for > 7 days
  - Inflammatory bowel disease
  - Chronic pancreatitis
  - Cystic fibrosis
  - Short bowel syndrome
- Long term antacid use
- Long term diuretic use

Table 5
NICE recommendation to identify high risk patients based on cases and expert opinion (38)

- One or more
  - BMI < 16
  - Unintentional weight loss > 15 % in 3-6 months
  - Little or no nutritional intake for > 10 days
  - Low potassium, phosphate, magnesium before feeding
- Two or more
  - BMI <18.5
  - Unintentional weight loss > 10 % in 3-6 months
  - Little or no nutritional intake for > 5 days
  - History of alcohol misuse or chronic drug use (insulin, antacids, diuretics)

5.1 Pathophysiology

The pathophysiology is determined by the occurrence of starvation followed by refeeding. During starvation the basal needs in glucose are supplied by gluconeogenesis from protein when glycogen stores have been depleted. The metabolic and hormonal changes aim to minimize protein break-down. The main source of energy is lipids, and increased levels of ketone bodies stimulate the brain to utilize ketone bodies instead of glucose. The metabolic rate progressively decreases by 20-25%. During this phase cells tend to shrink and lose large amounts of intracellular electrolytes. The serum levels may remain normal despite severe depletion.
With refeeding, insulin levels increase and glucagon levels decrease. Protein, glycogen and fat synthesis is stimulated and cell volume increases again. This anabolic phase necessitates nutrients but also large amounts of phosphate and magnesium as well as cofactors such as thiamine. The role of depletion of micronutrients has not yet been well investigated.
Insulin stimulates glucose uptake into cells with the help of the Na-K ATPase symporter. Magnesium and phosphate are also taken up by the cells. Water follows by osmosis, and cell volume tends to increase. This is by itself a strong anabolic signal. As a consequence, the serum levels of these electrolytes may decrease dramatically within a short period of time and the metabolic rate may increase above the physiological tolerance of the cardio-respiratory system.

5.2 Clinical Symptoms

5.2.1 Fluid Equilibrium

Refeeding with carbohydrate can induce reduced sodium and water excretion with extracellular volume expansion and weight gain. Volume expansion and poor fluid tolerance due to the reduced cardiac mass of malnutrition may result in cardiac failure (40, 41). Refeeding predominantly with protein and lipid may result in fluid loss.

5.2.2 Glucose and Lipid Metabolism

The capacity to metabolize glucose decreases within a few days of even partial starvation. During refeeding with glucose gluconeogenesis will be suppressed or at least reduced in critically ill patients but tolerance for glucose is limited. Hyperglycaemia with osmotic diuresis and metabolic acidosis is possible and should be detected early with proper monitoring. Thus relative overnutrition and insufficient treatment of the insulin-resistance of starvation may promote lipogenesis. The maximal lipid tolerance is 3.8 $g.kg^{-1}.day^{-1}$ and can be much lower during critical illness (42).

5.2.3 Thiamine Deficiency

Thiamine is a cofactor of several enzymes such as transketolases. The vitamin deficiency of malnutrition may be exacerbated with refeeding and the increasing intracellular need for vitamins. Thiamine deficiency is associated with Wernicke's encephalopathy (confusion, ocular disturbance, ataxia, coma) and Korsakov's syndrome (short-term memory impairment and confabulation). Thiamine deficiency is also associated with hyperlactataemia without other shock symptoms but may also present like heart failure with signs of pulmonary oedema (43).

5.2.4 Hypophosphataemia

Hypophosphataemia is the most frequent sign of the refeeding syndrome. Phosphate is the major intracellular anion and is involved in energy storage in the form of ATP, in intracellular buffering, as an essential initial step of glycolysis, and as a structural part of cell membranes. Many enzymes are activated by phosphate binding (44, 45).

Table 6
Phosphate functions

- General cell function
    1. Metabolic pathways
    2. Intracellular buffer
    3. Control of enzyme function
- Excitation-stimulus coupling and nervous system conduction
- Chemotaxis & phagocytosis of leucocytes
- Platelets: clot retraction
- Erythrocyte oxygen affinity
- Muscle function
- Neurological function
- Avoidance of thrombocytopenia

Phosphate is the major intra-cellular anion and is shifted rapidly between the intracellular and extracellular compartments. The driving forces for these shifts are the metabolic rate, ingestion of carbohydrates and lipids and finally the acid-base balance. The majority of phosphate (85%) is stored in the organic matrix of bone as hydroxyl-apatite crystals, 14% is in cells and 1% in blood. The normal intracellular concentration is 100 $mmol.L^{-1}$. A small proportion is in the inorganic form and the majority is bound to intermediary carbohydrates, proteins and lipids. In the blood, phosphate is present in organic and

inorganic forms at a concentration together of 3.5-4 mmol.L^{-1}. Typically only the inorganic form is measured by standard laboratory methods and the normal reported concentration of phosphate is thus 0.9-1.3 mmol.L^{-1}. Phosphate is present in sufficient amounts in a mixed diet; phosphate balance is determined by the kidneys.
Hypophosphataemia is categorized into

- Mild 0.6-0.85 mmol/L
- Moderate 0.3-0.6 mmol/L
- Severe < 0.3 mmol/L

In moderate and severe hypophosphataemia immediate intravenous replacement therapy is indicated. Current guidelines recommend the administration of 9 or 18 mmol respectively within a 12 hour period (38). The next dose should be given after rechecking serum phosphate. In the setting of intensive care units supplementation of 45 mmol over a 3 hour period normalized phosphate in 98% of patients with moderate or severe hypophosphataemia (46). The amount proposed should always be seen in addition to continuous phosphate supplementation with typically 0.5 mmol.kg $BW^{-1}.d^{-1}$. Either inorganic phosphate or organic phosphate has been used. KPO_4^- has often been used when concomitant hypokalaemia has existed. Organic preparations such as glucose-1-phosphate or fructose-1-6-diphosphate have the advantage of minimizing the risk of precipitation when calcium is also present in the solution. In all cases where phosphate is added to parenteral nutrition mixtures the organic preparations should be preferred. Unfortunately organic preparations have not received approval in all countries.
Nutrition therapy should not be delayed until hypophosphataemia has been corrected. Both interventions - nutrition and correction of electrolytes - should be done in parallel (47).

5.2.5 Hypomagnesaemia

Hypomagnesaemia is also frequent with refeeding and several acute severe disease states. Magnesium is a predominantly intracellular divalent cation. Magnesium levels < 0.5 mmol.L^{-1} are considered to be severe and are often accompanied by clinical symptoms. Magnesium is an important cofactor in many enzyme systems such as those involved in ATP production, it maintains the structural integrity of DNA, RNA and ribosomes, and affects the membrane potential.
The most prominent clinical symptoms are cardiac arrhythmias including torsade de pointes, abdominal discomfort and anorexia, and neurological manifestations such as tremor, paraesthesiae, tetany, seizures, weakness, etc. (48, 49).
Supplementation is best achieved with a continuous infusion until normalization. The maintenance dose is 4-8 mmol.d^{-1}. Oral magnesium supplementation can be associated with diarrhoea.

5.2.6 Hypokalaemia

Hypokalaemia is frequently present in acute disease states especially those associated with increased catecholamine release, but also during aggressive refeeding and CRRT. Potassium is the most abundant monovalent intracellular cation. Its main function is to maintain the electrochemical membrane potential. A potassium < 3 mmol.L^{-1} is considered to be severely low. The most severe features are cardiac arrhythmias, but many other systems are also affected. Gastrointestinal symptoms include ileus and constipation, the kidney has impaired concentration capacity, compensation of metabolic alkalosis is

delayed, neuro-muscular function is impaired but endocrine function is also affected with impaired glucose tolerance.

Sign & symptoms ↓ $PO_4^{=}$, K^+, Mg^{2+}, …..				
Muscle & Bone	**Heart & Circulation**	**Lung & Ventilation**	**Neurology & Mood**	**Metabolism & Hematology**
Chronic myopathy	Cardiomyopathy	Ventilatory insufficiency	**Delirium**	**Glucose intolerance**
Rhabdo-myolysis	**Arrhythmia** (ventricular)	Weaning failure	Seizures	Reduced peripheral O2 release
Bone not resistant		**Gut & Motility**	Encephalo-pathy	Metabolic acidosis
Osteoporosis		**Ileus**	Hallucinations	Hemolysis
	Heart failure	Anorexia Discomfort	Peripheral neuropathy	Leucocyte function Impaired

Fig. 6 Symptoms of hypophosphataemia and refeeding syndrome related deficits. Symptoms in red are associated with increased risk of death.

5.3 Treatment and Prevention

According to the most recent NICE recommendations, refeeding should not be delayed until biochemical abnormalities have been corrected (47). Progressive increase in nutrient intake, correction of biochemical abnormalities and close monitoring allow early and safe refeeding (50, 51).

Table 7
Treatment and prevention of the refeeding syndrome: a stepwise approach

- Identify patients at risk
- Check electrolytes
- Start refeeding with 25% of recommended energy intake
    1. 5-8 $kcal.kg^{-1}.d^{-1}$ (actual body weight)
    2. Increase gradually to reach recommendations within 3-5 days
- Rehydrate carefully and monitor cardio-circulatory function
- Replace electrolytes in sufficient amounts
    1. Potassium 2-4 $mmol.kg^{-1}$
    2. Phosphate 0.3-0.6 $mmol.kg^{-1}$
    3. Magnesium 0.05-0.1 $mmol.kg^{-1}$
    4. Calcium 0.05-0.1 $mmol.kg^{-1}$
- Monitor electrolytes, metabolic tolerance and clinical situation closely during the first 5-10 days of refeeding

6. Summary

Energy in the human body is exclusively ATP. ATP needs to be produced continuously from substrates. The stores of ATP are so low that recycling from ADP needs to be done about 1000 times every day at rest. Substrate oxidation in impaired in severe acute illness because of modified mitochondria with lower level of some complexes of the respiratory chain. The body is able to produce all necessary substrates from within the body. The mechanism of internal substrate production is based on autophagy. This mechanism normally is adapting to nutrient supply for example during overnight fast. This mechanism is started during acute illness and does not stop upon resumption of nutrient supply. In this situation the total amount of substrates is the sum of internal production and artificial nutrition provided via EN or PN. Closely monitoring of nutrient tolerance allows to safely and progressively to increase artificial nutrition and to reach the metabolic target.
Energy expenditure is poorly estimated by formulae but can be accurately measured via indirect calorimetry. Partial indirect calorimetry from the ventilator may offer an alternative if a normal RQ of about 0.85 can be assumed.
Refeeding syndrome is a clinical situation with substantial risk if full nutrition is maintained despite signs of intolerance. Electrolyte deficits mainly phosphate and potassium need proper replacement together with progressive nutrition. All organ systems can be affected by the refeeding syndrome.
Overall energy consumption and total substrate availability need to be considered to support homeostasis during acute illness.

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