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Opinion paper

Meta-analysis is not enough: The critical role of pathophysiology in determining optimal care in clinical nutrition

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SUMMARY

Evidence based medicine has preferably been based on prospective randomized controlled trials (PRCT's) and subsequent meta-analyses in many fields including nutrition and metabolism. These meta-analyses often yield convincing, contradictory or no proof of effectiveness. Consequently recommendations and guidelines of varying validity and quality have been published, often failing to convince the medical, insurance and government worlds to support nutritional care.

Causes for lack of adequate proof of effectiveness are manifold. Many studies and meta-analyses lacked pathophysiological depth in design and interpretation. Study populations were not homogenous and endpoints not always clearly defined. Patients were included not at nutritional risk, unlikely to benefit from nutritional intervention. Others received nutrients in excess of requirements or tolerance due to organ failure. To include all available studies in a meta-analysis, study quality and homogeneity were only assessed on the basis of formal study design and outcome rather than on patient characteristics.

Consequently, some studies showed benefit but included patients suffering harm, other studies were negative but contained patients that benefited. Recommendations did not always emphasize these shortcomings, confusing the medical and nutritional community and creating the impression that nutritional support is not beneficial.

Strong reliance on meta-analyses and guidelines shifts the focus of education from studying clinical and nutritional physiology to memorizing guidelines.

To prevent or improve malnutrition more physiological knowledge should be acquired to personalize nutritional practices and to more correctly value and evaluate the evidence. This also applies to the design and interpretation of PRCT's and meta-analyses.

1. Introduction

Over the last decades evidence for effectiveness of therapy has been increasingly and rightfully required to justify diagnostics and treatment in medicine. This has led to small as well as huge prospective randomized controlled trials (PRCT's), often including thousands of patients. In general this has been beneficial, deleting useless and ineffective practices and instituting practices that were likely to be beneficial on a population basis. However, there is an increasing recognition that the positive effects of this practice is limited by the fact that, although there is an overall benefit in the total population, in many studies in these populations subgroups of patients exist that do not benefit from the treatment modality studied. Alternatively, in some studies only a small subgroup benefits whereas the remaining population is not malnourished and cannot eat normally for only a few days and therefore is either unaffected or even harmed, for instance by instituting TPN [1]. Even worse, negative multimodal nutritional interventions (studying the effect of addition of more than one different nutrient) have led to suggestions that all the supplemental nutrients should be withheld,

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despite ample evidence that supplementation of one or more of the individual nutrients is safe and even beneficial in some circumstances and in specific subgroups [2]. Care should be taken to not ascribe the benefits of a multimodal intervention to a single component, especially in the absence of or incomplete insight into the metabolic mechanisms involved.

Consequently it has been difficult to convince doctors, hospital managers and governments that nutritional practices in hospitals, nursing homes and in the community should be promoted and supported. In this review we will use examples to try to explain why effectiveness has not always been convincingly demonstrated and what the positive and negative consequences are of the strong emphasis of the PRCT's and meta-analyses on our daily practice, teaching and education. We will also suggest which elements should be considered to improve study designs and interpretation of the study results.

2. The difficulty of acquiring convincing proof of effectiveness of nutritional support

There are several reasons why proof of effectiveness of nutritional support in clinical practice has been difficult to obtain and has not always been convincing. These include the nature of nutritional support, the design of clinical studies, the difficulty in obtaining large, homogeneous study populations, deficient insight in the underlying pathophysiology and consequently improper identification of patients that will benefit or be harmed, when applying guidelines.

2.1. The supportive nature of nutrition

A good nutritional state is a prerequisite to generate an adequate host response to achieve recovery from disease, trauma and their treatment. A substantial part of the clinical patient population is not undernourished so that it is questionable whether short term perioperative (or during other types of treatment) nutritional support will have a significant impact on complications of treatment. This is supported by low postoperative complication rates in well-nourished patients even when starving for a few days after surgery and by the apparent lack of effect of the ERAS approach, emphasizing continuing perioperative oral intake, on postoperative complications in colorectal surgery [3]. Undernutrition can be defined as a nutritional state resulting from a truly negative nutrient balance leading to loss of body cell mass, including peripheral tissues (skeletal muscle, skin, adipose tissue), whereas malnutrition is often considered to consist of a combination of undernutrition and inflammatory activity [4]. Long standing infectious complications after surgery or accidental trauma induce loss of peripheral tissue mass (muscle, bone, skin) even when full nutritional support is instituted, which will however maintain adipose tissue mass and may at best only modestly diminish losses of fat free mass solids [5]. In the purely undernourished state, resulting solely from a decrease in intake or absorption of food (e.g. in anorexia nervosa, a benign stricture of the esophagus or short bowel syndrome) nutritional support has an immediate anabolic effect and clearly benefits outcome [6]. In clinical practice many patients are malnourished, combining a negative nutrient balance with inflammatory activity. The first priority in this last category consists of adequately eliminating the inflammatory focus.

Inclusion of many non-malnourished cancer patients in studies of the effect of (parenteral) nutrition may lead to the conclusion that nutritional support is useless in cancer patients. Subsequently such studies are included in highly quoted meta-analyses with much impact, concluding that parenteral nutrition has deleterious effects [7]. Along similar lines doubt has been expressed whether 2 weeks of starvation in critically ill patients is harmful because this has not been studied in PRCT's, as if nutrition is a drug requiring placebo controlled randomized trials [8]. Admittedly, the obligatory nitrogen and potassium losses cannot or only modestly be prevented by nutritional support, as mentioned earlier [5], but prospective randomized studies evaluating effects on body composition are lacking [9]. We can only hypothesize, that in these conditions nutrition promotes host response but will only diminish protein loss or increase protein gain when the first pro-inflammatory phase has been successful, adequately dealing with trauma, infection and other inflammatory insults.

Although the macroscopic (Celsus A.D. $\pm$ 45) and microscopic characteristics of wound healing clearly represent an adaptive inflammatory response, leading to healing ("restitutio ad integrim") it is less clear whether other symptoms like pain and anorexia are also beneficial. We nevertheless treat patients with non-steroidal inflammatory drugs because of pain and fever, and try to convince patients to eat even when they are nauseated and anorectic. One could just as well develop the view that nausea and pain force the previously well-nourished traumatized or infected individual to put the wounded area and the organism to rest, which may promote a salutary neuro-endocrine and metabolic response. The initial short proinflammatory phase prepares the damaged organism for rebuilding of biomass and is minimally 3-day long but longer, when the primary infection or trauma is not yet adequately dealt with. During this phase, overfeeding and especially the pro-oxidative stress of lipid containing nutrition may interfere with the adequacy of host response. Consequently in previously well-nourished patients there may be some logic in postponing (full) nutritional support until the regenerative anti-inflammatory phase. At present, support for this view is limited. There is much evidence in animals and humans during acute inflammation that overfeeding has short and long term harmful effects, but although meeting requirements immediately after (surgical) trauma and in critical illness has been suggested to lead to more complications than when patients receive only 60% of requirements or less [10–12], whereas other studies have claimed the opposite [13,14], the quality and art of these studies do not allow drawing definitive conclusions. Altogether the hypothesis may be tested that truly malnourished patients should be fed rather early (a few days after successful resuscitation) to support an otherwise failing inflammatory response to trauma/infection, whereas well-nourished patients may possibly not need coverage of nutritional requirements in the first proinflammatory phase after trauma/infection and that this may even be harmful [15]. Full nutritional support is required to optimally promote the regenerative phase.

Similarly, the recommendation to commence nutritional support 3–4 days (ESPEN) or 7 days (ASPEN) after admission to the intensive care if intake is insufficient, is exclusively based on expert opinion. Here assessment of the individual patient is crucial. The decision to delay or to institute complementary artificial nutritional support immediately may depend on issues such as pre-existing nutritional state, is the patient rapidly recovering or can it be foreseen that recovery and resumption of oral food intake will be delayed. An example concerns patients with multi-trauma or patients with severe infective complications (e.g. sepsis associated with anastomotic leak) following intestinal resections. Such patients will not be able to ingest and absorb sufficient amounts of food for weeks, or even longer in the case of proximal high output fistulae or temporary diverting stomata. On clinical and physiological grounds it would seem essential to provide artificial nutrition support, especially in the presence of malnutrition. Furthermore, it is unethical to undertake randomised controlled trials, which involve withholding treatment in some of these patients. Therefore, absence of trial evidence does not mean that the

intervention has no beneficial effect. Under the circumstances, it is reasonable to provide artificial nutritional support to such patients while the underlying problems such as infection are addressed, to limit catabolism and possibly to support host response during the active phase and encourage anabolism during the recovery phase of acute illness.

A guideline regarding delayed or immediate full nutritional support in critical illness is therefore not the answer to better nutritional care. Rather clinicians should integrate knowledge of the response of the body to inflammatory stresses, so that nutritional support promotes host response to trauma and acute disease in individual patients, depending upon their nutritional state, the predicted duration of illness, the adequacy of the primary treatment of trauma/infection and the inability to ingest and absorb oral food.

Altogether, the outcome of studying the effect of nutritional support depends on the number of truly undernourished patients, and on the number of patients that suffer from lingering inflammation, that will only recover after weeks or longer. However, severely malnourished patients are often excluded from studies for ethical reasons. Inflammatory activity has to be taken into account in the design of clinical trials and markers assessed (especially plasma albumin and CRP levels), recognizing that a low serum albumin is almost always due to inflammation, reflecting increased capillary leakage and edema formation, and does not result from a prolonged negative nutrient balance unless complicated by infection/inflammation [4,16]. Inflammatory markers should be taken into account in inclusion/exclusion/stratification criteria of clinical trials.

These statements need some nuance because several authors have found that nutritional support varying between 7 and 14 days before operative trauma, improves wound healing and decreases infection in previously malnourished patients but does not significantly improve body composition (fat free mass, muscle mass, total body protein) [17–19]. In one of these studies patients with Crohn's disease had experienced significant loss of body protein stores but after 4 days of IV nutrition improvement of physiological function was already observed but no significant change in total body protein [19]. Only weeks after resolution of the inflammatory process or successful excision of the inflamed bowel segment, repletion of total body protein occurs in association with further physiologic improvements [5].

2.2. Heterogeneous patient populations (Fig. 1)

Whether a population consists of individuals with similar characteristics cannot be judged on the basis of screening methods. The NRS-2002 is such an example [20], because the two different components (degree of undernutrition and disease severity) of the screening method used may vary in opposite directions and nevertheless add up to an identical score, The effect of nutritional intervention may differ substantially, when dealing with either undernutrition or severe disease. In fact, the (relatively low) nutritional risk score in a study in patients admitted to an intensive care is strongly influenced by the fact that the patients were predominantly patients that had undergone elective surgery, only staying shortly in intensive care and not requiring long term nutritional support. Another reason for a rise in the outcome of the NRS-2002 screening method was that a substantial proportion was above 70 years of age [1].

In another study, suffering from heterogeneity of the patient population, the effect of glutamine supplementation was assessed [21]. This treatment has been proven to be safe and efficient on the basis of relevant clinical end points in small trials in homogeneous patient groups [22]. In the study mentioned, glutamine with or without anti-oxidants was administered to a heterogeneous group of ICU patients with at least 2–4 failing organs. The paper raised many comments and analyses [23,24]. Although glutamine deficiency has very likely erroneously (chicken-egg problem, [25]) been claimed to exist on the basis of low plasma glutamine levels, because the latter have been found to be associated with a higher risk of complications and mortality [26], glutamine levels were not measured before including patients in the study. Only in a subset of patients (66 out of 1223 patients) levels were measured but not taken into account despite rises of 2–5 times normal values in some of these patients. In old publications hyperglutaminemia has been reported in patients with primary and secondary liver failure (acute right ventricular failure due to pulmonary embolism) [27,28], and may be aggravated by renal failure. In experimental liver failure in rats hyperglutaminemia (and generalized hyperaminoacidemia) have also been reported [29]. The investigators of the Redox-trial did not take this possibility into account and administered a pharmacological dosage of glutamine (twice more than the highest amount that has been shown to be newly produced in trauma/sepsis: see Table 1 and references) to all patients in the study. Apart from this detailed knowledge it is well known in clinical practice that patients with severe liver failure and renal failure do not tolerate excessive nitrogen loads. Even infection or drug related catabolism may precipitate liver failure and encephalopathy in patients with marginal liver function. For example, in an experimental study in diabetic and obese critically ill rats, the nitrogen load but not an isonitrogenous intake of a pharmaconutrient was responsible for increased mortality [30]. Apart from excretion of urea and other compounds the kidney metabolizes substantial amounts of glutamine in stressed conditions, producing glucose while ammonia is produced in renal tubular cells. This ammonia diffuses in the tubular lumen, where it acts as a buffer in metabolic acidosis by binding secreted protons to form ammonium ions which cannot be reabsorbed and are excreted in the urine. In renal insufficiency these pathways may fail [31].

In the REDOX study hyperglutaminemia and patient level data were not mentioned in the hard copy publication [21]. This could have shed light on the causes of the increase in mortality in this group. At present an important role is attributed to high intracerebral glutamine levels in liver failure, leading to brain swelling and neurologic disturbances [32]. However, the authors of the REDOX study suggested that glutamine supplementation was dangerous in general, raising worldwide concern and leading to withholding glutamine containing formulas to ICU patients. Only in a later analysis of the data the authors suggested that glutamine should be withheld in patients in shock and with multi-organ failure [33]. A more specific recommendation can be that in well resuscitated hyperdynamic inflammatory states physiological amounts of glutamine (not more than 0.35 g/kg bodyweight are safe when there is no overt liver insufficiency and severe renal failure or when plasma glutamine levels are normal or low, which exclude the presence of these disease states.

In conclusion, not considering heterogeneity on the basis of pathophysiology may harm a subset of patients with liver or/and renal failure not being able to metabolize pharmacological dosages of certain supplements like glutamine, whereas it is likely that a lower more physiological glutamine intake in patients that are not in severe multiple organ or isolated liver and kidney failure may be beneficial.

2.3. Logical endpoints

Nutrition is a prerequisite to remain healthy. It maintains body composition and function, including the ability to raise an adequate immune response in case of trauma and illness. This implies that,

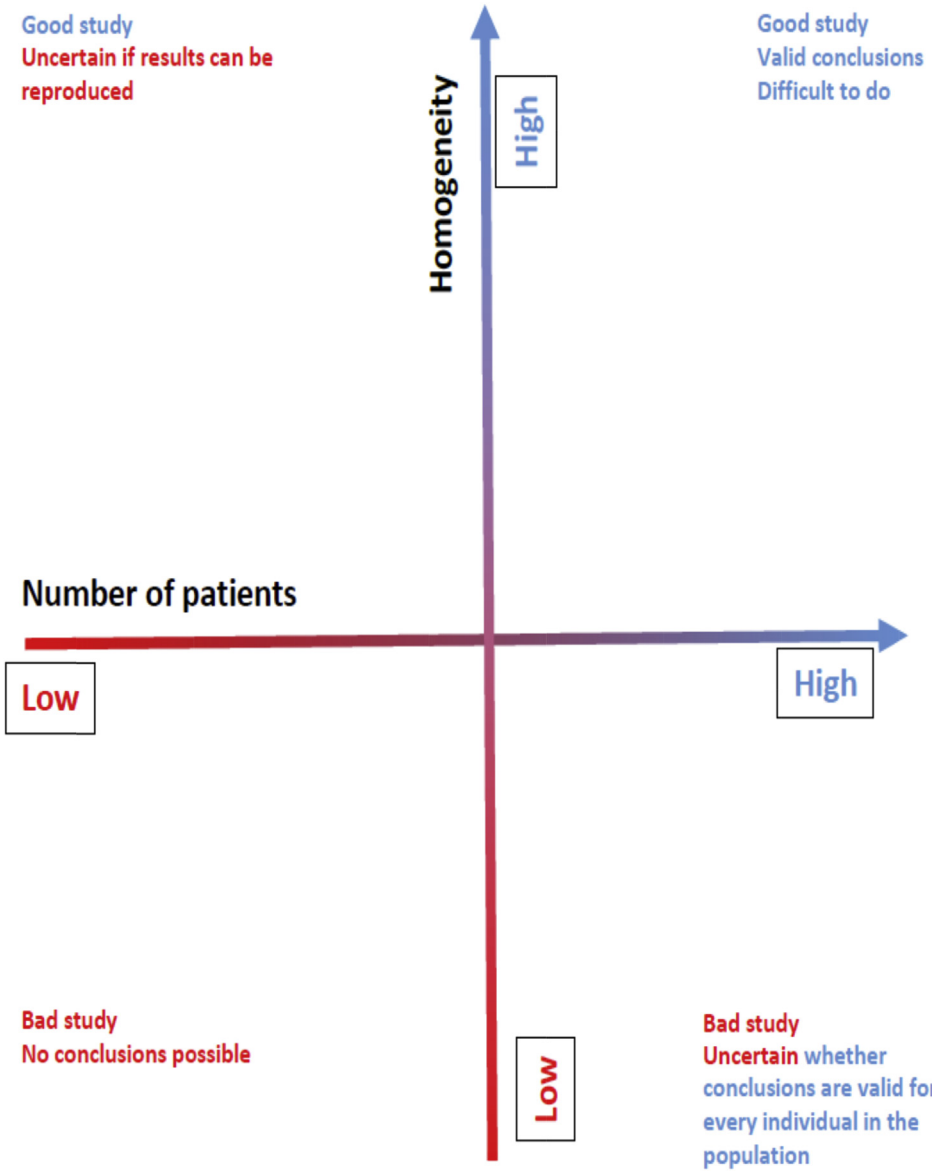

Fig. 1. Influences of number of patients (horizontal axis) included in a PRCT and the homogeneity of the population (vertical axis) on the validity of the conclusions.

Table 1
Net peripheral release of glutamine in Control, Trauma, Sepsis and Septic survivors (Clowes: g/m^2/24 h in black; ***g/1.7 m^2/24 h***; other investigators: g/100 ml muscle and skin mass/24 h in black; ***total g/24 h extrapolated to 40 L of assumed muscle and skin mass***). Data derived and recalculated from references [62–67].

Net peripheral release of GLUTAMINE (g/m^2/24h or ***g/1.7m^{2}24h***) or (g/100 ml muscle and skin mass/24h or ***g/40 L of assumed total muscle and skin volume/24h***)						
First authors	Unit of measurement	Control	Trauma	Sepsis	Septic survivors	Septic non- survivors
Clowes (Ann. Surg.) [62]	g/m^2/24h				13.8	12.2 (NS)
	g/1.7m^2/24h [62]				***23.6***	***20.8***
Fong (Surgery) [63]	g/100 ml leg volume/24 h or ***total g/24h (extrapolated to 40 L of assumed muscle and skin mass)***	0.056		0.065		
		22.3		***25.8***		
Vesali (Clin Nutr) [64]	Data derived from: references [63–67]			0.020		
				8.2		
Gore (JPEN) [65]				0.014		
				5.4		
Carli (Clin Sci Lnd) [66]		0.048		0.083		
		19.1		***33 0***		
Mjaaland (Ann Surgery) [67]		0.012		0.029		
		4.9		***11.5***		

when a study is performed, in which the effect of nutritional support is assessed, we should define endpoints which include relevant indicators of body composition and function [34]. In disease and after trauma the adequacy of the immunological response is in principle an appropriate endpoint. Unfortunately there are no reliable or precise functional indicators of innate and acquired immunological function. Delayed cutaneous hypersensitivity reactions once were promising but unfortunately their use was not further developed. We therefore revert to measuring the result of the response, including adequate wound, anastomotic, bone healing or healing/prevention of infection. In abdominal surgery, endpoints should therefore consist of surgical site infection and, when there is enough power, mortality. Surgical site infection is the direct result of a failing healing/immune response to the surgical trauma as well as of surgical technique, but this last factor is very difficult to assess reliably.

It is important to exclude nosocomial infections like ventilator associated pneumonia or urinary tract infections and in any case not to include them together with true surgical site infections, because nosocomial infections are liable to interpretation and the diagnostic criteria used [35]. They are therefore imprecise indicators of whether there is a true pneumonia or urinary tract infection. This is highlighted by the fact that depending on these criteria they have no, only modest or strong influence on complications and mortality [35]. The difficulty of diagnosing nosocomial infections is highlighted by two recent studies in intensive care. One claimed to show benefit because optimizing administration of calories and protein increased the rate of nosocomial infections but decreased mortality [14], whereas the second study claimed benefit showing fewer nosocomial infections but no difference in mortality after optimizing energy provision [13]. Also other endpoints like myocardial infarction or heart failure are problematic because it is difficult to establish a cause-effect relationship between the nutritional intervention and cardiovascular events. In the first study showing benefit of glutamine in intensive care patients, significance of parenteral glutamine supplementation was only reached 3 months later when 4 or 5 patients in the no-glutamine arm died of non-infectious causes [36]. Many find it hard to conceive that there is a causal relation between the 100–200 g less glutamine, received by these patients while in intensive care 3 months earlier, and their demise. This makes the study appear less convincing and it had less or only modest impact on daily practice in intensive care. The same is true for a multimodal (supplement with two or more different supplemental nutrients) study in which significance was only reached when mortality was assessed after 6 months follow-up [2]. The authors conclude that this showed harm induced by administering immune-modulation formula in general, implicitly also suggesting that glutamine supplementation was harmful despite only ingesting 20 g/day of glutamine enterally, which would also be reached when eating liberal amounts of wheat products and is of the same order of magnitude as what the body newly produces itself in inflammatory states (see Table 1) [37]. This not only creates confusion, but also promotes the idea that glutamine is toxic. The result is that it may lead to withholding of glutamine and other 'immunonutrients' in multicomponent interventions, when they could actually produce benefit.

In view of the difficulty to study reliable clinical endpoints, surrogate endpoints may be considered. For example, the early work of Souba et al. suggested that glutamine was a preferred substrate for the gut and would promote intestinal integrity [38,39]. Van der Hulst et al. [33,34] undertook a study in patients predominantly with exacerbations of inflammatory bowel disease receiving parenteral nutrition and used function and tissue composition as endpoints. Intestinal integrity, assessed by dual sugar tests was promoted in the glutamine enriched group. Villus height was negatively influenced by nutritional state as indicated by percentage ideal fat free mass or percent ideal body weight [40,41]. In a later similar study it was found that inflammatory activity was associated with an increase in mucosal permeability and decreases in plasma glutamine concentration whereas villous height was largely associated with undernutrition alone [42]. The findings suggest that glutamine typically affects situations of rapid cell proliferation as in inflammatory situations [42]. This is supported by the general finding that in cell or tissue culture, proliferation is only optimal when glutamine (and glucose) are added to the culture medium. In an endotoxemia model in pigs, substrate fluxes were measured across the spleen after a trauma, and confirmed the preferential uptake of glucose and glutamine in immune cells [43].

These findings support our earlier claim that nutritional interventions should logically aim for the direct functional and morphological target of the intervention [34]. Important additional goals (i.e. surrogate markers, which are not clinical endpoints) of the study may include assessment of the hypothesized metabolic working mechanisms of the intervention. Such studies support conclusions and confirm or reject hypotheses regarding the physiological cause- effect relationship of the intervention.

2.4. The pathophysiological logic of the intervention

Effects of interventions should make sense pathophysiologically. Studies, in which one of the macronutrients is supplied in excess, constitute another example. The problem then is to make the mix equicaloric or equinitrogenous, which repeatedly raises questions whether the effects observed are due to the primary intervention or to the process of adding macronutrients to achieve a mix with similar amounts of calories or nitrogen [30]. How to create isonitrogenous diets is as yet an unsolvable problem since almost all amino acids have, besides their role as building blocks in protein, physiological or pharmacological properties in the generation of modulators, neurotransmitters, growth factors etc. when provided in large amounts. The best option to reach an isonitrogenous and iscocaloric control group appears to consist of supplementation with 5 or 6 non-essential amino acids in amounts not causing substantial pharmacological effects.

Even more problematic is how to decide which component(s) of a "multimodular immunonutrition mix" (i.e. Arginine, RNA, ω-3 fatty acids, antioxidants) is/are responsible for a decrease in infectious complications in surgical patients. This knowledge would allow supplementation with the effective component and most likely decrease costs. For many years, the benefit of a trimodular nutritional supplement containing arginine, omega-3 fatty acids and RNA in surgical patients was attributed to arginine by top clinicians and investigators. This led to recurrent debates questioning the beneficial role of arginine. The turnover of arginine via protein synthesis and degradation is at least an order of magnitude larger than the amount required to produce nitric oxide (NO), which is a general mechanism ensuring the availability of substrate (for instance phenylalanine/tyrosine, tryptophan and arginine) to produce mediators like catecholamines, indole amines and NO.

An important consideration to attribute beneficial effects of Impact® to omega-3 fatty acids is that our genome developed millions of years ago in an omega-3 rich environment in the Rift valley in East-Africa whereas we migrated only rather recently (40.000 years ago) to an ω-6 fatty acid rich world [44]. Still today breast milk of nursing women in the Rift valley contains a docosahexanoic/arachidonic acid ratio of approximately 1 whereas in the Western world this ratio amounts to 8–20: 1, to which our genome may not be optimally adapted [44]. The view that

predominantly enrichment with omega-3 fatty acids is beneficial is supported by a meta-analysis showing that feedings containing only extra ω-3 fatty acids increased nutritional benefit especially decreasing postoperative infections [45]. The authors of one paper claimed benefit of arginine but showed in the same paper that "non-Impact® formulas", containing arginine and no ω-3 fatty acids (personal communication of the author) showed no benefit [46]. In recent years the message concerning the effectiveness of the same multimodular studies changed, stressing beneficial effects of ω-3 fatty acids, which now appears more likely to produce benefit on the grounds mentioned. However, in recent years the view that arginine supplementation may be harmful in septic ICU patients, has not been confirmed [47], but its benefit is uncertain. It is enigmatic why RNA is still part of Impact® despite the fact that its role is not elucidated.

One area where understanding the metabolic consequences of an intervention is crucial, is the practice to aim for tight glucose control in intensive care. The focus is to control glucose levels to prevent the potential complications of hyperglycemia. To do that insulin is administered without controlling for the amounts of carbohydrates administered, which are high in some studies [48,49] and low in other studies [50]. The fact that modest hyperglycemia and insulin resistance may be a beneficial adaptation has not been taken into account [51]. The influence of tight glucose control on the beneficial anabolic pathways, that in the presence of insulin resistance and elevated glucose levels support the synthesis of biomass and maintenance of redox potential, have not been considered [51–53]. More specifically, insulin resistance results from the "metabolic switch", which includes inhibition of glycogen synthesis and glucose oxidation, and upregulation of gluconeogenesis and lactate formation (Cori-cycle). This leads to elevated glucose and lactate levels, which benefit other pathways, which are upregulated during insulin resistance, in which glucose or its products are utilized to produce cell elements and matrix, and to produce NADPH maintaining redox balance and supporting synthesis of DNA, fatty acids and other building stones for the synthesis of biomass. Maintaining glucose levels around 4–6 mmol and administering modest amounts of glucose (120 g/24 h or less) promote glucose oxidation and deprive these anabolic pathways from substrate.(Manuscript under review by Critical Care Medicine) This may explain the deleterious effects on infection and mortality rates in studies aiming for low glucose levels and administering little glucose [50,54].

3. The emphasis on PRCT's and meta-analyses: a collection of bad vegetables does not make a good soup

Meta-analyses strongly influence our daily practice. However, the limitations of PRCT's also limit the validity of the conclusions of the meta-analyses. In an effort to ensure that conclusions are valid, homogeneity as well as other elements of the study are assessed. Unfortunately, studies are often included in meta-analyses based on assessment of study quality in terms of formal design and not on adequate selection of patients. Despite reservations regarding suboptimal homogeneity between the outcome of studies mentioned in the discussion of the papers, the title, abstract and conclusion often give far stronger messages than is justified on the basis of the composition of the patients included. The question is, who are the patients, not following the general result of outcome of the other studies and why do they not follow the average pattern? Should we go back to the medical records and scrutinize these patients one by one, hopefully learning why they react negatively to the intervention? We would learn from such an exercise identifying subgroups that respond positively and groups that respond negatively and in this way clear erroneous conclusions due to insufficient homogeneity and conduct better trials the next time.

3.1. Recommendations based on meta-analyses

In an ideal world patients in an intensive care population would be homogeneous and meta-analyses would convincingly give direction to treatment and effect should be linear. At present, meta-analyses are the cornerstone of grade A recommendations formulated in consensus conferences. Regrettably, populations studied and interventions performed are not homogeneous. The recommendations are therefore only valid for a majority of the population, whereas a sometimes sizeable minority does not benefit or is even harmed. Alternatively, recommendations based on negative studies may deprive a minority (or even a majority) of the population from a treatment that may be beneficial. Negative studies in which a majority of the population is not malnourished and requires short term care are examples [1,7,55]. These study results may suggest however to the non-critical reader and the hospital manager that there is no benefit at all, leading to inadequate care of truly under- and malnourished patients.

3.2. Emphasis on meta-analyses and consequences for education

The strong emphasis on meta-analyses, consensus statements and protocols has shifted the focus of teaching to some degree from trying to make therapy understandable on the basis of knowledge of pathophysiology to emphasizing recommendations and protocols. This is highlighted by answers to the question how to treat, including "that it is in the guidelines or in the protocol" whereas there are often good clinical or metabolic reasons why a certain type of treatment should not be implemented, or a treatment not in the guidelines should be applied. This knowledge facilitates therapeutic decision making, when the clinical condition of a patients changes or is not fit to tolerate the intervention as recommended in the protocol.

Guidelines or protocols are generally based on conclusions of consensus groups, but some of them are not based on pathophysiological thinking, the composition of the consensus group can be questioned as well as the way decisions are made by such groups. In the nutrition field these consensus statements shift the character of learning from acquiring knowledge and understanding to memorizing road maps.

Another element causing diminished interest and education in pathophysiology is the shifting focus of intensive care journals to publishing predominantly clinical studies whereas experimental more fundamentally oriented studies are not accepted or are published on line only, depriving the readership from more fundamental knowledge. Although many institutions and societies carry the flag of translational research, in practice the gap between basic research and clinical practice in nutritional sciences appears to widen.

3.3. Emphasis on meta-analyses and consequences for research

The emphasis on Meta-analyses and PRCT's has put epidemiologists and epidemiologically oriented clinicians in the lead. More metabolically oriented clinicians and pure scientists have on the whole been rather absent in constructing the design of clinical studies and the same is, possibly with the exception of the "lipidologists", true for their participation in the big nutrition societies. This is clearly visible in some of the large studies recently published and partly mentioned in earlier parts of this manuscript.

These views are not only relevant for constructing valid research designs but also for the interpretation of the results. Where

epidemiology sometimes fails to pinpoint the contribution of a specific nutrient to outcome or to explain a negative overall outcome, more in depth knowledge and expertise might allow the emergence of clues for treatment failure, which could subsequently serve as a starting point for further research. Alternatively, the epidemiologist will, due to lack of metabolic knowledge, for safety reasons, recommend that all elements in a multimodular feed should be discouraged when the study is negative despite the fact that one of the elements is unmistakably safe in patients with adequate organ function.

It is unfortunate that different expert groups looking at the same literature material arrive at different conclusions and recommendations [56,57]. It may be questioned whether this is due to selection bias, interpretation bias, vested interest bias or differences in methodology. As mentioned earlier some authors have seriously questioned the claims of ESPEN and ASPEN that enteral nutrition should be administered early even in well-nourished patients in the ICU. They ascribe this to bias, showing that especially the lower quality studies show benefit whereas the high quality studies do not [8,58]. It seems likely that professionals performing research in patients, hope to show benefit of interventions in his/her field of interest in large patient groups and therefore may be seduced to stretch the conclusions to suggest more benefit than the data should allow. Alternatively, even an unexpected but significant negative result is welcome because it adds to the quality of care and may lead to publication in highly quoted journals. In both cases bias may skew the conclusions and harm the field, because conclusions will be not convincing in the first case and concern of harm will deprive parts of the population from beneficial treatment in the second case.

4. How should we obtain proof of effectiveness?

Several aspects of research determine the suitability of clinical studies to generate results that are solid and therefore convincing.

4.1. Physiology and study design (Table 2a)

Nutritional intervention studies should be performed in a population that is likely to benefit from the intervention based on physiology and on the observation that the population is at risk to develop adverse events due to nutritional deficiencies. In situations, where immunonutrition or single nutrient intervention is applied, the role of the specific nutrient in metabolism should be known in detail and taken into account. Elements of metabolism (i.e. surrogate markers) should preferably be assessed if possible to confirm working hypotheses why benefit (or harm) is achieved. Study populations should be as homogeneous as possible and subgroups should be identified a priori and not included if, based on physiologic knowledge, reasonable suspicion exists that the intervention may be harmful. Criteria for non-inclusion of patients in the study must be defined and percentage of subjects excluded presented. For instance severe organ failure (liver and kidney) should be excluded in trials in which the effect of nutritional interventions are studied containing differing amounts and compositions of amino acids and/or protein.

In studies in intensive care, patients included should be genuinely critically ill and stratified for the expected duration of critical illness. The Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II or III scores have limitations because they are a measure of the severity of illness and are therefore predictive of the risk of mortality, but do not necessarily predict the duration of critical illness, which can be short. The predicted duration of illness and inability to ingest and absorb adequate amounts of food should be substantial e.g. at least 7 days. It is not feasible nor necessary to limit the inclusion to patients with one specific disease. This would make large studies impossible. The presence and duration of comorbidity should be assessed but will have effect on inflammatory activity, body composition and functional capacity, the final common results of disease. These elements should therefore be assessed as well as possible before and at the end of the study. In elective major surgery a great majority of patients rapidly recovers from the operative trauma and can eat after a few days. This is therefore a different group compared with truly critically ill patients with abdominal catastrophe and long term lingering inflammation/infection. Such patient groups should be identified and be separately evaluated either via non-inclusion or via stratification.

4.2. Endpoints (Table 2b)

The immediate goal of nutritional intervention is to improve or maintain nutritional state [4,34]. This consists of two elements: body composition with emphasis on fat free mass solids, and function. Function usually includes at least three major components: muscle, immunological and cognitive function, of which muscle function is most easily measurable. These function domains determine together our quality of life, longevity and the ability to respond adequately to trauma or acute illness. They are therefore suitable endpoints of studies, taking into account that cognitive and immune function are difficult to measure precisely especially in severe illness, because they have several complex aspects e.g. innate versus adaptive immunity and because methods to assess cognitive function in critically ill patients have not been developed and applied in great detail.

Infectious complications and bad wound or anastomotic healing are the direct result of compromised immunological function and are also convincing endpoints. Nevertheless care should be taken to define infectious complications well beforehand. In surgery site related infections like wound infection, anastomotic leakage, abscess formation and sepsis are complications that can be reliably be assessed and they have a major impact on outcome and should therefore be separately assessed and reported.

Ultimately mortality after elective surgery and in critical illness is to a significant degree the end result of severe infection and a most convincing endpoint, when it is likely that nutritional intervention improves infectious complications, which in turn improve mortality. As mentioned earlier, in most studies mortality after elective surgery is low and also determined in part by other factors than nutritional state (cardiovascular events, end stage cancer), which therefore requires large studies to achieve significance.

Finally, surrogate markers should be considered to provide insight in positive or negative effects of the intervention. For example, a persisting negative nitrogen balance does not immediately lead to mortality, but indirectly reflects continuing failing resolution of the primary inflammatory focus and lack of effect of nutritional support and other measures to overcome inflammation. Plasma levels of single nutrients that are supplemented to study their potential benefit should preferably be measured at the start and at the end of the study as well as potential functional effects that are hypothesized to arise from their supplementation.

It is essential that endpoints are well defined at the start of the study and accessible for reviewing.

4.3. Interpretation of study results

The interpretation of study results is hazardous when the regimens differ in more than one nutrient (which may even counteract each other's effect) but should be based on adequate

Table 2a
Factors to consider when performing nutritional studies. (Not all factors mentioned have to be included in every study).

Type of study	
Observational (cross sectional, cohort)	
Interventional (randomized, non-randomized, blinded, non-blinded)	
Representativeness of population sample (= relevant for generalizability of the findings)	
Nutritional state (nutritional assessment at start of the study)	
Undernourished	(body weight loss, very low BMI, insufficient uptake of food, body composition)
	(Prealbumin: only in the absence of inflammation and liver failure)
	(anemia: sensitive but not specific)
Inflammation	(chronic/acute)
	(trauma/illness)
	(infectious/non-infectious)
	(plasma Albumin; edema, ESR, CRP only in acute stage)
Function	(muscle handgrip strength, physical activity at home)
	(cognitive function: mood, memory, alertness, interest)
	(immune function: no easy parameter; wound healing, immune tests)
Predicted duration	
Inability to eat	
Pro-inflammatory phase	
Depends on treatability	(trauma major/minor)
	(inflammation: infectious or non-infectious)
Proliferative/regenerative phase	(longer when initial event more severe)
Organ function	
Renal function	(relevant for nitrogen intake, specifically glutamine but also total nitrogen intake)
Hepatic function	(relevant for nitrogen intake, all amino acids except BCAA and citrulline)
Cardiac/pulmonary function	(relevant for energetic efficiency/CO_2 production)
Intervention (nutritional, metabolic)	
Blinding	(as well as possible)
Duration	(preferably minimally a week or longer)
Exposure	(compliance to the intervention must be controlled, is intended nutritional intake successful?)
Enrichment with nutrients	Not more than physiological amounts, newly produced and utilized by the healthy organism in stressed conditions
	Isonitrogenous with 5-6 NEAA's as control in amounts not having major non-nutritive effects
	Isolipidogenous. (E.g. extra ω-9 fatty acids in control group when extra ω-3 FA's are administered; similar amounts of ω-6 FA's in both groups)
	(Exceptions are studies, in which ingesting more of a nutrient is compared with less of that nutrient)
	Preferably monomodular
	(Expert knowledge required regarding intermediary metabolism)

Table 2b
Factors to consider when performing nutritional studies. (Not all factors mentioned have to be included in every study).

Endpoints
Mortality
Related to primary disease, (surgical) trauma and their treatment (out of hospital mortality after discharge may be relevant to consider; not when due to other causes and occurring after healing of the primary event)
Morbidity
Primary infection persisting
Infection new but directly related to intervention and treatment (trauma, surgical, chemotherapy, wound healing)
Not directly related to primary treatment (nosocomial infection, VAP's, urinary infection; these are unreliable; different types of nosocomial infection should not be added)
Wound healing
Health care use
Length of stay in the hospital (strict standards to define discharge required)
Health care costs
Nutritional state
Body composition, muscle mass (Anthropometry, BIS?), weight in critical illness not reliable
Inflammation (Alb, CRP, IL-6, edema, ESR)
Function (muscle strength, handgrip strength, maximal inspiratory mouth pressure (Pimax); immune tests, cognitive function, intestinal permeability)
Other outcomes
Quality of life, independence, mobility, functional limitation, activities of daily living
Mechanisms (no real endpoints but potentially hypothesis supporting)
Cytokines, lipid modulators, dyslipidemia, amino acid levels, nitrogen balance, redox state GSSG/GSH, myeloperoxidase, TBAR's etc.
Interference with metabolism
(glucose and insulin dosage)
(growth hormone)
(non-steroidal anti-inflammatory agents)
(oral anti-diabetics)
(steroids)
(biologicals)
(Expert knowledge required of effects on adaptive physiology)
Type of analysis
Intention to treat
Per protocol analysis
Available data analysis

knowledge of changes in metabolism due to the specific disease of the patient and the role of the nutrients in intermediary metabolism. To pinpoint the effective nutrient ideally studies should be carried out in which only the effect of the potential responsible nutrient is assessed.

To increase power, patients are sometimes included in intervention studies that are not (or not at risk to become) malnourished, or alternatively are at risk to be harmed by the intervention [7,55]. Harm inflicted in a subgroup of patients with organ failure by administering supraphysiological quantities of single nutrients may send a message to the medical community that the particular nutrient is harmful for the total population. This causes confusion, for safety's sake depriving suitable patients from nutrients that may be beneficial [59]. Patient level data should be scrutinized and made available to all authors to learn which patients were harmed by the intervention and why. On this basis limitations of the study should be outlined in the article.

A final problem is that some trials in the clinical nutrition literature are published in parts in different journals without mentioning this. This obscures complete insight in the data acquired, their pathophysiological significance and consequences for treatment. Different primary endpoints are reported in individual publications although the main study only had one primary outcome. These endpoints are often defined post-hoc or as multiple secondary endpoints, reducing the validity or robustness of the conclusions, while raising potential statistical concerns. Correction for multiple tests are not always made, increasing the chance of a positive result. This issue has been discussed in some of the recent literature [60,61].

5. Conclusion

PRCT's and meta-analyses are in principle suitable elements to provide evidence for the presence or absence of proof of effectiveness of interventions. Proof of effectiveness in a total population analyzed may however not apply to all patients in the population due to the fact that inevitably different subgroups make up the total population. Similarly negative results may be found in the total population, whereas a subgroup may benefit. To prevent harming a particular subgroup, study designs should be far more rigorously constructed and adapted to clinical and physiological characteristics. The same is true for the interpretation of results and for reaching consensus and formulating recommendations. Post-hoc analyses of patient level data should be performed to investigate which patients benefit and which are harmed and why. The acquired knowledge may help to optimize the design of new studies and furnish insight, which patients should not receive the treatment. The meta-analysis should therefore only be the starting point in determining the type of treatment of a patient, after which treatment may be individualized on the basis of knowledge of metabolism and pathophysiology. To decide whether or not a particular patient will benefit from a certain type of intervention, the focus of teaching should be much more on clinical metabolism and on the role the specific nutrient or intervention plays in metabolism, in the adaptive response to trauma and disease and in the causal pathways that lead to clinical benefit. Ignoring these considerations risks to diminish the credibility of clinical nutrition and to deprive a discernible group of patients from the benefits of nutritional support.

Conflict of interest

None.

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