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Overview of Pharmaceutical Aspects of Artificial Nutrition: Simple Review

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Abstract

Artificial nutrition therapy is recognized as a key aspect in the management of critically sick patients, but there is still debate about the appropriate route and timing, particularly in the acute phase. It is a convenient, effective, safe, and well-tolerated method of clinical nutrition in the hospital and at home. When appropriate oral diet fails to supply the body with the required nutrients. EN is normally delivered by a nasogastric technique, whereas PN is usually administered through a central venous access, directly into the bloodstream. The injected nutrients can then be immediately absorbed by the various organs. Early mixed enteral nutrition (EN) and parenteral nutrition (PN) may be an appealing alternative in certain critically sick patients to meet recommended calorie and protein targets. PN is related with potentially serious or even deadly consequences when handled and administered incorrectly. Patient observation and treatment regimen adaptation are required.

Keywords: Parenteral Nutrition, Enteral Nutrition, Artificial Nutrition, Home Management, Pharmaceutical Aspects.

INTRODUCTION

It is imperative that healthcare professionals comprehend the pharmacological facets of artificial nutrition. Enteral or parenteral nutrition, another name for artificial nutrition, is a life-sustaining treatment that gives nutrients to patients who are unable to consume or digest food properly. Patients in severe condition, those with gastrointestinal issues, and those receiving cancer treatment frequently receive this medication. The two types of artificial nutrition that were created and released in the 1960s are called EN and PN [1].

Enteral nutrition (EN) is utilized when the gastrointestinal system is functional but oral access is limited. Nutrient absorption from the gut may be inadequate in patients suffering from partial or complete intestinal failure. Parenteral nutrition (PN) must thus be given in a formulation that has all the required substrates and is prepared for use in the intermediate metabolism. An substantial surgical colon resection or a condition causing decreased intestinal function or impairment of motility, digestion, or absorptive ability can cause intestinal failure. PN can ensure survival and a high quality of life by providing complete or partial nutritional assistance in terms of both amount and quality [2].

The preparation, administration, and supervision of the therapy are included in the pharmacological elements of artificial nutrition. When preparing enteral nutrition, the right formula must be chosen taking into account the patient's health, dietary requirements, and digestive system. In varied amounts, the formula may include proteins, lipids, carbs, vitamins,

and minerals. Because parenteral feeding requires the manufacture of a sterile solution that is injected directly into the circulation, the pharmaceutical component of the procedure is considerably more intricate. An customized nutrition plan that takes into account the patient's needs and unique condition is necessary for patients with EN and PN, or both. Unlike in the past, EN and PN are now primarily based on industrially produced, physico-chemically thoroughly specified, balanced, and stable goods [2].

For patients who are hemo-dynamically stable and cannot finish an oral meal in three days, current recommendations advise early enteral nutrition (EN) [3]. Parenteral nutrition (PN) should be added as soon as possible to patients who are not able to receive adequate food through the enteral route. European guidelines recommend starting PN as soon as possible [4], while American guidelines recommend delaying PN until days 7 to 10 if there hasn't been any malnutrition in the past [5].

While EN medicines can be supplied in stable, ready-to-use formulations, whole or partial PN must be manufactured in accordance with pharmaceutical good manufacturing practise (GMP) guidelines and compounded or made ready-to-use for administration. The stable nutritional components in the industrial PN premixes that are now on the market are mechanically separated from one another in chambers with breakable sealing. When the product is ready to use as an all-in-one admixture in a single, practical container for daily PN treatment on a single line, the sealing is broken automatically, and the contents are shaken by hand. In order to ensure the safety and tolerability of administering typically hypertonic PN admixtures with osmolality levels above 2000 mosm/kg, a central intravenous access must be introduced or maintained [2]. As such, in comparison to EN, PN and its precursors are more difficult, costly, and prone to difficulties. However, a patient who receives PN that is well-indicated in accordance with current standards exhibits good effectiveness and safety, both in long-term home PN and when aided by a nutrition support team [6].

To make sure the patient is getting the right amount of nutrients and that there are no side effects, the administration of artificial nutrition needs to be closely watched. Enteral nutrition recipients may have gastrointestinal distress, including diarrhoea, vomiting, and nausea. Conversely, problems include infections, metabolic imbalances, and liver dysfunction can occur in individuals receiving parenteral nourishment. Consequently, in order to modify the course of treatment as necessary, medical personnel must keep an eye on the patient's vital signs, lab results, and clinical symptoms [7].

The pharmaceutical components of artificial nutrition also entail the right delivery equipment selection, including infusion pumps, feeding tubes, and catheters. The medical practitioner is responsible for making sure the therapy is administered safely and successfully and that the device is implanted appropriately. The patient's dietary requirements, anticipated length of therapy, and medical status all play a role in choosing the right equipment [7].

For patients who require artificial nutrition therapy to be managed successfully, the pharmacological components of the therapy are essential. To give safe and effective treatment, healthcare workers need to be well-versed in the administration, monitoring, preparation, and equipment selection processes. Additionally, they need to be aware of the possible drawbacks and negative consequences of artificial nourishment and take the necessary precautions to avoid and control them [7]. This article's goal is to clarify the pharmacological elements of artificial nourishment.

Basic and theoretical scientific considerations

PN proponents will point out that PN provides calories far more consistently than EN, implying that this is harmful. There is no denying that prolonged hunger has negative effects. But those that get EN have continuously had superior results [8].

Numerous studies on animals show that animals getting EN vary physiologically from those receiving PN. These have led researchers to conclude that gut flora plays a critical role in maintaining normal physiology, particularly in relation to immune response and systemic inflammation. It is hypothesized that PN is less advantageous because patients may experience harmful alterations in physiology in addition to not receiving the advantages of food in the stomach. Numerous significant immunological and systemic inflammatory pathways have been clarified by research in this field. Thus, there is mounting evidence that suggests bacteremia may not be the cause of septic shock syndrome, but rather a process involving the interaction of gut-dwelling, activated pathogenic bacteria with the mucosal cells they attach to. The inflammatory mediators that cause the syndrome are secreted by these cells [9].

Here are a few more fascinating instances of animal research: Data from *Kudsk and colleagues* show that when mice are given PN instead of EN, their lung immunoglobulin A production significantly decreases. In addition, mice given PN and immunized against influenza show a 60% viremia rate in response to influenza virus exposure. After being exposed to PN for a while and then switching back to an oral diet, immunized mice showed no viremia [10].

Clinical studies from humans indicated that when patients get EN early after surgery, as opposed to receiving nothing, the lung is protected. Despite a concomitant tendency towards an increase in vomiting, there is a trend towards a reduction in pneumonia in

some evaluations of data on early postoperative feeding [11].

Omata *et al.,* demonstrated that mice on PN exhibited a reduction in the number of hepatic mononuclear cells, a drop in lipopolysaccharide receptor expression, and a decrease in survival following intraperitoneal injection of pseudomonas. Resuming an oral diet corrected the decline in survival as well as the immunological changes [12]. Human research has demonstrated a decrease in the height of the jejunum in healthy volunteers when they are given PN and nil orally for two weeks [13]. After four days without food, the intestinal mucosa of critically sick patients showed signs of atrophic and leaky conditions compared to normal volunteers [14]. Studies have looked into mucosal antigen leakage as a potential explanation for hepatic fibrosis in hepatic cirrhosis, for obesity-related elevated inflammatory states, and as a backup to the mucosal adherence theory of septic shock syndrome [8].

Artificial Nutrition Access Points

After inadequate oral and/or enteral feeding for five to seven days, PN should be started as soon as possible. In the event of acute starvation, this might begin much sooner [15]. For instance, it has been demonstrated that preoperative PN and EN enhance surgical outcomes in Crohn's disease patients having abdominal surgery [16].

Recent prospective trials have also established the usefulness of supplementary PN in critically unwell patients [17]. Depending on the indication and expected length of the EN therapy, EN may be given using nasogastric tubes, nasojejunal tubes, endoscopic or radiologic percutaneous gastrostomy/jejunostomy, Witzel fistulas, or tiny needle catheter jejunostomy. One can easily see the necessity of a central venous access for PN when calculating each person's daily demand for electrolytes, which must be included in an all-in-one PN admixture. The maximum value for an intravenous infusion given peripherally is 600–800 mosmol/kg, and they alone raise the tonicity by more than that [15]. Peripherally inserted central venous catheters (PICCs), implanted port systems, or tunnelled subclavian or jugular catheters (e.g., Hickman catheters) are used in long-term PN [18].

Peripheral PN admixtures can be administered via peripheral venous catheter for a brief time of extra PN. In order to sustain a patient who was previously well-nourished, to act as a stopgap measure before centrally administered infusions, or until sufficient enteral feedings can be established, peripheral PN may be considered for short-term usage or as a supplement [19]. Because peripheral PN has a lower osmolarity than PN, there is a larger chance of microbial contamination and subsequent growth [20]. Additionally, there is a substantial risk of phlebitis and extravasation, which results in catheter removal [21].

The benefits and drawbacks of nutritional support

Without a doubt, nutritional deficiency in the ICU is related with worse outcomes (an relationship that may be causative or coincidental), and chronic starvation eventually leads to death. The essential question, however, is whether artificial nutrition, delivered during critical illness, can avoid or repair this nutritional shortfall and, as a result, the related negative effects. Artificial nutrition is a drug given to anorectic patients that is un-physiologic and may cause issues and undesired side effects that should be evaluated against any intended benefit. Without a doubt, artificial nutrition increases calorie and protein intake, but it is uncertain if it also prevents rapid muscle catabolism in immobilized critically sick patients with systemic inflammation. Because the processes driving muscular atrophy and weakness in critical illness are exceedingly complicated [22], anticipating atrophy and weakness to be curable by just supplying calories and protein is an oversimplification.

Instead of preventing muscle loss or lowering proteolysis and gluconeogenesis, aggressive nutritional assistance in critically sick patients resulted in fat increase [23].

Aspiration pneumonia, feeding tube dislocation, diarrhoea, abdominal hypertension, intestinal ischemia, catheter sepsis, hepatic steatosis, hyperglycemia, dyslipidemia, and re-feeding syndrome are all complications of artificial nutrition [24]. Autophagy, a survival process that recycles intracellular resources and maintains energy balance during nutritional scarcity, is likewise suppressed by nutrition. Recent data shows that autophagy is required for immune response and housekeeping tasks such as the elimination of toxic protein aggregates and damaged organelles, and that it may be necessary for organ failure recovery [24]. A recent study of critically ill rabbits found that early PN, particularly protein and lipid provision, suppressed the ubiquitin-proteasome pathway, thereby contributing to muscle mass preservation, but also elicited an autophagy deficiency phenotype in liver and skeletal muscle, suggesting that muscle mass preservation may come at the expense of toxic protein aggregate accumulation, compromising function [25]. The similar pattern was discovered in the liver and muscle of fed critically sick individuals [26], and it was recently demonstrated to lead to vital organ failure in an animal model of critical illness [27]. Autophagy-deficient animals exhibit muscle atrophy as well as the buildup of toxic proteins and defective organelles [28], indicating that nutrition-induced autophagy suppression may potentially have a deleterious influence on fat-free mass.

In a series of animal tests assessing the influence of different dietary regimens on ischemia-reperfusion damage in the kidney, a direct relationship between nutrition and organ failure was also

demonstrated. Nutrition, namely protein rather than glucose, appears to exacerbate the amount of renal damage in these tests [29]. Given the benefits and drawbacks of artificial nutrition in critical illness, clinical trials should focus on clinical outcomes (morbidity, death, and long-term functional result) rather than nutritional or other surrogate endpoints.

Mixture of parenteral and enteral nutrition

Current international nutrition recommendations consistently suggest early EN in critically sick patients who cannot continue to take enough oral intake, 24-48 hours after ICU admission [30]. EN's physiological benefits translate into fewer infectious complications, shorter ICU and hospital lengths of stay, and lower overall mortality [31]. However, during the acute phase of critical illness which primarily occurs in the first week following ICU admission EN alone is frequently insufficient to meet energy and protein requirements [32]. Hemodynamic instability, gastrointestinal intolerance, and frequent EN interruptions are factors adding to the sluggish advancement of EN into a full feeding rate, which ultimately may result in severe nutrient deficits [33].

The routine use of PN in the early stages of critical illness has not been recommended by international nutrition guidelines, and concerns regarding PN-associated complications such as overfeeding, hyperglycemia, and hyperlipidemia have hindered its frequent use in clinical settings in recent years [34].

Recent studies, however, have demonstrated that PN alone, or a combination of EN and PN, may provide outcomes equivalent to or even superior than EN alone in critically sick patients with protracted hemodynamic instability. There is a growing body of evidence suggesting that in the early acute phase of critical illness, less energy and protein administration may be more advantageous. However, recommended protein and energy targets remain contentious and controversial due to conflicting outcomes from recent randomized and observational trials [34].

However, combining EN with PN may assist reach the appropriate nutrition objectives more quickly and safely, and it may be explored in patients with high nutrition risk whose nutrition targets cannot be fulfilled by EN alone. Several randomized controlled studies (RCTs) have explored the effect of combining EN with PN on clinical outcomes in critically sick patients and have shown considerable therapeutic significance for critically ill patients. However, there is significant variation amongst these studies in terms of patient demographic, time, and MNT dose, which may explain why earlier meta-analyses produced contradictory results. Another possible explanation is that none of the existing analyses distinguish between two techniques of administration: supplementary PN (SPN), which is PN supplied to EN after a certain amount of time if full EN is not achievable or does not meet nutrition objectives, or early combined EN and PN [34].

Pharmaceutical Management Specifics

NSTs are multi-professional teams that include at least a physician, a specialized nurse, a dietician, and a pharmacist who are trained to manage PN and provide the optimum nutritional assistance. The majority of people on artificial nourishment also require medication to treat their underlying disorders. This complicates the overall treatment regimen, which aims to combine parenteral nutrition and drug administration in specific cases, such as when the indication for PN is extended to malignant chronic diseases or severe functional deficiency, requiring additional complex medication in addition to the artificial nutrition. This is a difficult endeavor that needs a rigorous examination of compatibility, particularly with regard to precise and appropriate dose of both nourishment and medication over time in order to assure safe and efficacious therapy requiring pharmacological expertise. One of the primary responsibilities of the chemist within the NST is to confront and examine PN and drug related problems from a pharmacological standpoint. The chemist also helps to establish a suitable nutritional and medical care plan, eliminate prescription mistakes, and ensures that the proper patient receives the right goods provided in the right method [7].

Artificial nutrient Monitoring

Regular, defined, and appropriate evaluation may assist to avoid or reduce the metabolic problems of artificial feeding. In addition to the standard clinical evaluation, this should encompass the identification of (particular) individual nutrients, the tracking and progression of the underlying illness, and laboratory tests. Haematological testing, lipid status, liver and renal function (particularly in PN), glucose, sodium, potassium, calcium, magnesium, phosphate, CRP, and iron status are examples of laboratory tests of artificial nutrition-associated parameters. To guarantee that artificial nutrition is metabolically tolerated, anthropometric measurements including body weight, body mass index (BMI), and hydration status should also be tracked. For a maximum of two months after PN beginning, extensive and regular monitoring is needed. Long-term, clinically stable PN patients should be monitored every 3 to 6 months [7].

Home artificial nutrition (HAN) management

Home artificial nutrition (HAN) management is a complex procedure including technical skills and a variety of professions. HAN necessitates the collaboration of dietitians, doctors, nurses, chemists, psychologists, social workers, and administrative personnel [35]. Professionals must follow operational standards and procedures defined in compliance with national and international criteria to guarantee effective treatment. According to the Italian Institute's

demographic statistics, which was last updated on December 31, 2004, regional law unique to HAN is in existence in just 10% of Italy and for only 1.6% of the Italian population. Regional general resolutions exist in 65% of the land and 78.6% of the people, and they might be extremely distinct from one another. There is a lack of regulatory processes that ensure the commencement of HAN therapy in about 25% of the nation, encompassing 20% of the population [36]. According to the findings of the Italian Society for Parenteral and Enteral Nutrition (SINPE) in April 2005, the global prevalence of HAN is approximately 152.6 cases/million inhabitants, with 83.9% undergoing home enteral nutrition (HEN) and the remaining 16.1% undergoing home parenteral nutrition (HPN). However, there are considerable regional disparities in both prevalence and the appropriateness of indications and implementation methods [37]. Despite the high frequency of HAN users in this region [38], nothing is known about the extent of the territory or the existence of a multidisciplinary team specifically tasked with managing HAN patients at home. The organizational management of care delivery in the different Italian regions exhibits notable regional variations as well, underscoring the necessity of examining the HAN knowledge and management practices of professional care providers at the local level [39].

CONCLUSION

In situations where oral feeding is inadequate or not feasible, artificial nourishment must be provided. With the advancement of artificial nutrition, administration of EN and, in particular, PN became more easy and safer in the ICU, and even at home. However, whether and to what degree artificial nutrition might prevent/attenuate muscular weakness or expedite recovery is unknown. Furthermore, artificial feeding during critical illness has negative consequences that must be balanced against any putative advantage. Hard clinical outcomes should be included in future clinical studies. Well-controlled methods and consistent patient monitoring by an experienced NST are critical factors in the effective administration of artificial nutrition. The early trophic enteral feeding is at least as beneficial as full EN in patients without significant previous malnutrition, and that early addition of PN to insufficient EN provides little benefit and worsens morbidity.

REFERENCES

1. Mühlebach, S. F. (2019). Diets and diet therapy: parenteral nutrition. *Encyclopedia of Food Security and Sustainability (FOSS)*, 2, 131-142.
2. Pironi, L., Steiger, E., Brandt, C., Joly, F., Wanten, G., Chambrier, C., ... & Group, C. I. F. S. I. (2020). Home parenteral nutrition provision modalities for chronic intestinal failure in adult patients: an international survey. *Clinical Nutrition*, *39*(2), 585-591.
3. Kreymann, K. G., Berger, M. M., Deutz, N. E., Hiesmayr, M., Jolliet, P., Kazandjiev, G., ... & Spies, C. E. S. P. E. N. (2006). ESPEN guidelines on enteral nutrition: intensive care. *Clinical nutrition*, *25*(2), 210-223.
4. Singer, P., Berger, M. M., Van den Berghe, G., Biolo, G., Calder, P., Forbes, A., ... & Pichard, C. (2009). ESPEN guidelines on parenteral nutrition: intensive care. *Clinical nutrition*, *28*(4), 387-400.
5. McClave, S. A., Martindale, R. G., Vanek, V. W., McCarthy, M., Roberts, P., Taylor, B., ... & American College of Critical Care Medicine. (2009). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). *Journal of parenteral and enteral nutrition*, *33*(3), 277-316.
6. National Collaborating Centre for Acute Care (UK. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition.
7. Reber, E., Messerli, M., Stanga, Z., & Mühlebach, S. (2019). Pharmaceutical aspects of artificial nutrition. *Journal of clinical medicine*, *8*(11), 2017. doi:10.3390/jcm8112017
8. Seres, D. S., Valcarcel, M., & Guillaume, A. (2013). Advantages of enteral nutrition over parenteral nutrition. *Therapeutic Advances in Gastroenterology*, *6*(2), 157-167.
9. Alverdy, J. C., Laughlin, R. S., & Wu, L. (2003). Influence of the critically ill state on host-pathogen interactions within the intestine: gut-derived sepsis redefined. *Critical care medicine*, *31*(2), 598-607.
10. Kudsk, K. A., Li, J., & Renegar, K. B. (1996). Loss of upper respiratory tract immunity with parenteral feeding. *Annals of surgery*, *223*(6), 629.
11. Lewis, S. J., Egger, M., Sylvester, P. A., & Thomas, S. (2001). Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *Bmj*, *323*(7316), 773.
12. Omata, J., Fukatsu, K., Maeshima, Y., Moriya, T., Murakoshi, S., Noguchi, M., ... & Hase, K. (2009). Enteral nutrition rapidly reverses total parenteral nutrition-induced impairment of hepatic immunity in a murine model. *Clinical Nutrition*, *28*(6), 668-673.
13. Buchman, A. L., Moukarzel, A. A., Bhuta, S., Belle, M., Ament, M. E., Eckhert, C. D., ... & Vijayaroghavan, S. R. (1995). Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. *Journal of Parenteral and Enteral Nutrition*, *19*(6), 453-460.
14. Hernandez, G., Velasco, N., Wainstein, C., Castillo, L., Bugedo, G., Maiz, A., ... & Vargas, C. (1999). Gut mucosal atrophy after a short enteral fasting period in critically ill patients. *Journal of critical care*, *14*(2), 73-77.
15. Aeberhard, C., & Mühlebach, S. (2017). Parenterale Ernährung-Grundlagen und Durchführung (Parenteral nutrition-basics and good practice). *Aktuelle Ernährungsmedizin*, *42*(01), 53-76.
16. Dreznik, Y., Horesh, N., Gutman, M., Gravetz, A., Amiel, I., Jacobi, H., ... & Rosin, D. (2018). Preoperative nutritional optimization for Crohn's disease patients can improve surgical outcome. *Digestive surgery*, *35*(5), 442-447.

17. Heidegger, C. P., Berger, M. M., Graf, S., Zingg, W., Darmon, P., Costanza, M. C., ... & Pichard, C. (2013). Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *The Lancet*, *381*(9864), 385-393.
18. Bischoff, S. C., Arends, J., Dörje, F., Engeser, P., Hanke, G., Köchling, K., ... & das DGEM Steering Committee. (2013). S3-Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin (DGEM) in Zusammenarbeit mit der GESKES und der AKE. *Aktuelle Ernährungsmedizin*, *38*(05), e101-e154.
19. Gura, K. M. (2009). Is there still a role for peripheral parenteral nutrition?. *Nutrition in clinical practice*, *24*(6), 709-717.
20. Omotani, S., Tani, K., Nagai, K., Hatsuda, Y., Mukai, J., & Myotoku, M. (2017). Water soluble vitamins enhance the growth of microorganisms in peripheral parenteral nutrition solutions. *International journal of medical sciences*, *14*(12), 1213.
21. Sugrue, D., Jarrell, A. S., Kruer, R., Davis, S., Johnson, D., Tsui, E., ... & Crow, J. (2018). Appropriateness of peripheral parenteral nutrition use in adult patients at an academic medical center. *Clinical Nutrition ESPEN*, *23*, 117-121.
22. Derde, S., Hermans, G., Derese, I., Güiza, F., Hedström, Y., Wouters, P. J., ... & Vanhorebeek, I. (2012). Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. *Critical care medicine*, *40*(1), 79-89.
23. Schwarz, J. M., Chioléro, R., Revelly, J. P., Cayeux, C., Schneiter, P., Jéquier, E., ... & Tappy, L. (2000). Effects of enteral carbohydrates on de novo lipogenesis in critically ill patients. *The American journal of clinical nutrition*, *72*(4), 940-945.
24. Moreau, K., Luo, S., & Rubinsztein, D. C. (2010). Cytoprotective roles for autophagy. *Current opinion in cell biology*, *22*(2), 206-211.
25. Derde, S., Vanhorebeek, I., Güiza, F., Derese, I., Gunst, J., Fahrenkrog, B., ... & Van den Berghe, G. (2012). Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. *Endocrinology*, *153*(5), 2267-2276.
26. Vanhorebeek, I., Gunst, J., Derde, S., Derese, I., Boussemaere, M., Güiza, F., ... & Van den Berghe, G. (2011). Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. *The Journal of Clinical Endocrinology & Metabolism*, *96*(4), E633-E645.
27. Gunst, J., Derese, I., Aertgeerts, A., Ververs, E. J., Wauters, A., Van den Berghe, G., & Vanhorebeek, I. (2013). Insufficient autophagy contributes to mitochondrial dysfunction, organ failure, and adverse outcome in an animal model of critical illness. *Critical care medicine*, *41*(1), 182-194.
28. Masiero, E., & Sandri, M. (2010). Autophagy inhibition induces atrophy and myopathy in adult skeletal muscles. *Autophagy*, *6*(2), 307-309.
29. Peng, W., Robertson, L., Gallinetti, J., Mejia, P., Vose, S., Charlip, A., ... & Mitchell, J. R. (2012). Surgical stress resistance induced by single amino acid deprivation requires Gcn2 in mice. *Science translational medicine*, *4*(118), 118ra11-118ra11.
30. Elke, G., Hartl, W. H., Kreymann, K. G., Adolph, M., Felbinger, T. W., Graf, T., ... & Bischoff, S. C. (2019). Clinical nutrition in critical care medicine–Guideline of the German Society for Nutritional Medicine (DGEM). *Clinical nutrition ESPEN*, *33*, 220-275.
31. Marik, P. E., & Zaloga, G. P. (2001). Early enteral nutrition in acutely ill patients: a systematic review. *Critical care medicine*, *29*(12), 2264-2270.
32. Villet, S., Chiolero, R. L., Bollmann, M. D., Revelly, J. P., Cayeux, M. C., Delarue, J., & Berger, M. M. (2005). Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clinical nutrition*, *24*(4), 502-509.
33. Doig, G. S., Heighes, P. T., Simpson, F., Sweetman, E. A., & Davies, A. R. (2009). Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive care medicine*, *35*, 2018-2027.
34. Hill, A., Heyland, D. K., Ortiz Reyes, L. A., Laaf, E., Wendt, S., Elke, G., & Stoppe, C. (2022). Combination of enteral and parenteral nutrition in the acute phase of critical illness: an updated systematic review and meta-analysis. *Journal of Parenteral and Enteral Nutrition*, *46*(2), 395-410.
35. Paccagnella, A., Baruffi, C., Pizzolato, D., & Conte, N. (2001). Il team nutrizionale: dal mito personale alla specificazione dei ruoli. *Rivista Italiana di Nutrizione Parenterale ed Enterale*, *19*, 36-43.
36. Guglielmi, F. W., Mazzuoli, S., Regano, N., Fregnan, S., & Guglielmi, A. G. (2005). Nutrizione artificiale domiciliare: analisi delle differenze tra le regioni italiane. Ruolo del ministero della salute. *Rivista Italiana di Nutrizione Parenterale ed Enterale*, *23*, 205-212.
37. Sulla Situazione Attuale Della Nutrizione, R. (2008). Artificiale Domiciliare (NAD) in Italia, Ministero della Salute, Marzo 2004.
38. Pironi, L., Candusso, M., Biondo, A., Bosco, A., Castaldi, P., Contaldo, F., ... & Toigo, G. (2005). Prevalenza della Nutrizione Artificiale Domiciliare in Italia nel 2005: indagine epidemiologica SINPE. *Rivista Italiana Di Nutrizione Parenterale Ed Enterale*, *23*, 99-104.
39. Guglielmi, F. W., Mazzuoli, S., Regano, N., Fregnan, S., & Guglielmi, A. G. (2005). Nutrizione artificiale domiciliare: analisi delle differenze tra le regioni italiane. Ruolo del ministero della salute. *Rivista Italiana di Nutrizione Parenterale ed Enterale*, *23*, 205-212.