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ESPEN endorsed recommendations: Nutritional therapy in major burns☆

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SUMMARY

Background & aims: Nutrition therapy is a cornerstone of burn care from the early resuscitation phase until the end of rehabilitation. While several aspects of nutrition therapy are similar in major burns and other critical care conditions, the patho-physiology of burn injury with its major endocrine, inflammatory, metabolic and immune alterations requires some specific nutritional interventions. The present text developed by the French speaking societies, is updated to provide evidenced-based recommendations for clinical practice.
Methods: A group of burn specialists used the GRADE methodology (Grade of Recommendation, Assessment, Development and Evaluation) to evaluate human burn clinical trials between 1979 and 2011. The resulting recommendations, strong suggestions or suggestions were then rated by the non-burn specialized experts according to their agreement (strong, moderate or weak).
Results: Eight major recommendations were made. Strong recommendations were made regarding, 1) early enteral feeding, 2) the elevated protein requirements (1.5–2 g/kg in adults, 3 g/kg in children), 3) the limitation of glucose delivery to a maximum of 55% of energy and 5 mg/kg/h associated with moderate blood glucose (target $\leq$ 8 mmol/l) control by means of continuous infusion, 4) to associated trace element and vitamin substitution early on, and 5) to use non-nutritional strategies to attenuate hypermetabolism by pharmacological (propranolol, oxandrolone) and physical tools (early surgery and thermo-neutral room) during the first weeks after injury. Suggestion were made in absence of indirect calorimetry, to use of the Toronto equation (Schoffield in children) for energy requirement determination (risk of overfeeding), and to maintain fat administration $\leq$ 30% of total energy delivery.
Conclusion: The nutritional therapy in major burns has evidence-based specificities that contribute to improve clinical outcome.

1. Introduction

Severe burn injuries remain a major health care problem through the World. There are good news though: the first is that the vast majority of injuries are small "bagatelle" injuries that can be treated as outpatient, with a little less than 10% of the victims requiring hospital admission, and only a few requiring intensive care (ICU) treatment[1,2]; the second is that burn care has improved tremendously over the last 3 decades, resulting in a reduction of both mortality and of sequelae. Major burn injuries, i.e. those affecting more than 20% total burn surface area (TBSA) with or without inhalation injury, represent a specific condition when compared to the general intensive care pathologies. Critically ill burned patients are characterized by a strong oxidative stress, an intense inflammatory response, and a prolonged months-long hypermetabolic and catabolic response, all of which are proportional to the severity of injury (depth and extent). Nutrition therapy constitutes an integral part of the treatment, from the early start of the initial resuscitation.

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The body of literature concerning burns' nutrition has increased over the 3 last decades, while some important trials should be completed during 2013. The American Burn Association (ABA) published guidelines for the management of burn injuries in 2001,[3] based on a Medline search including years 1966 through 1998. As many aspects of management have evolved since that date, and particularly those concerning energy requirements, the French speaking societies included a revision of nutritional therapy in major burns in their upcoming global nutrition guidelines.

2. Material and methods

Experts in charge of burns' nutrition were nominated based on their experience by delegates of three scientific societies: Société Française d'Anesthésie-Réanimation (SFAR), Société de Réanimation de Langue Française (SRLF) and Société Francophone de Nutrition Clinique et Métabolisme (SFNEP).

Based on a PUBMED search including human studies 1979 through 2011, the experts produced a review of the literature and elaborated a French version of recommendations using the GRADE methodology (Grade of Recommendation, Assessment, Development and Evaluation),[4] that was validated by the widened non-burn specialized expert group. This method takes into account the quality of evidence study limitations, inconsistency of results, indirectness of evidence, Imprecision, reporting bias, the balance between benefits versus harms, and endpoint relevance.

The quality of evidence of each study used to support the recommendations was systematically specified (the supplemental online Table provides the list of the studies included in the analysis). The global evidence quality was therefore up- or down-modulated by the weight of these three additional factors. Each recommendation was thus allocated a final level of evidence which determined its wording: "we recommend" (or "we do not recommend") for a strong recommendation, "we strongly suggest" (or "we strongly do not suggest") for a moderate recommendation, "we suggest" (or "we do not suggest") for a weak recommendation. Each recommendation was then rated by all experts on a scale from 1 to 9 (1 = disagreement, 9 = agreement). A median score was calculated (after exclusion of the highest or lowest ratings, if necessary) that could fall into one of 3 zones: [1–3] = disagreement; [4–6] = indecision; [7–9] = agreement. If the confidence interval of the median was within the first or last zone, the strength of the recommendation was considered to be weak or strong, respectively. With this methodology, strength of recommendation has to be distinguished from the level of agreement (or disagreement) obtained from the vote of the experts: for example, it is possible to propose a weak recommendation with a strong agreement, or inversely a strong recommendation with weak agreement (e.g. for the use of rhGH in children).

3. Recommendations

Major burn patients are first of all critically ill. By default general ICU recommendations apply. Many high quality human studies, i.e. randomized and placebo controlled with reasonable number of patients, were published during the period, investigating major burn specific issues, enabling a reasonable GRADE rating (Table 1).

3.1. Route of feeding

The gastrointestinal tract is particularly at risk during the early burn resuscitation phase due to the major stress resulting from burn injuries and from the treatment required to maintain life. As a result of the early massive capillary leak causing an hypovolemic shock, large amounts of crystalloids are required during the first 24–48 h to maintain blood pressure. The fluid resuscitation causes generalized edema, including in the gut, contributing to the development of a paralytic ileus in case the gastrointestinal tract is not used early on. Intestinal permeability is also significantly increased shortly after injury compared to other ICU conditions.[5] Very early enteral feeding, i.e. initiated within the first 6–12 h after injury by the gastric route is associated with numerous clinical and biological advantages, such as attenuation of the stress hormone levels, of the hypermetabolic response,[6] results in increased immunoglobulin production,[7] reduction of stress ulcers, while reducing the risk of malnutrition and of energy deficit.[8,9]

The gastric route should be attempted first, keeping the post-pyloric access option or even percutaneous endoscopic gastrostomy (PEG) as backup in case of pyloric dysfunction in the most severely burned patients.

The choice of the feeding solution does not differ from other critically ill patients with preference of polymeric, high energy, high nitrogen solutions.[10] Fibers are recommended from the start as these patients are exposed to a high risk of constipation due to the important fluid movements and high doses of sedatives and opioids frequently required for analgesia. Parenteral nutrition (PN) is an alternative that is indicated only in case of enteral feeding

Table 1
Summary of statements.

Topic		Grade	Agreement
Indication	Nutritional therapy should be initiated early within 12 h of injury, preferentially by the enteral route.	B	strong
Route	We recommend to give priority to the enteral route, parenteral administration being rarely indicated	C	strong
Energy requirements & predictive Equations	We recommend considering indirect calorimetry as a gold standard to assess energy requirements. If not available or not suitable, we recommend using the Toronto equation for burn adults. For burn children, we suggest to use Schoffield formula	D	weak
Proteins	Protein requirements, are higher than in other categories of patients, and should be set around 1.5–2.0 g/kg in adults and 1.5–3 g/kg/day in children.	D	strong
	We strongly suggest to consider glutamine supplementation (or ornithine alpha-ketoglutarate) but not arginine	C	weak
Glucose and glycemia control	We strongly suggest to limit carbohydrate delivery (prescribed for nutritional and drug dilution purpose to 60% of total energy intake, and not to exceed 5 mg/kg/min in both adults and children.	D	strong
	We strongly suggest to keep glucose levels under 8 mmol/l (and over 4.5 mmol/l), using continuous intravenous infusion of insulin	D	strong
Lipids	We suggest to monitor total fat delivery, and to keep energy from fat <35% of total energy intake	C	weak
Micronutrients	We strongly suggest associating, in both adults and children, a substitution of zinc, copper and selenium, as well as of vitamin B1, C, D and E.	C	strong
Metabolic modulation	We strongly recommend using non-nutritional strategies to attenuate hypermetabolism and hypercatabolism in both adults and children (warm ambient temperature, early excision surgery, non-selective beta-blockers, and oxandrolone).	B	strong
	Unlike adults, we recommend to administer rhGH to burn children with burns TBSA >60%	B	weak

failure, or contraindication to the latter. PN implies an even stricter monitoring of glycemia and adherence to the patient's energy requirement to avoid overfeeding. The deleterious effects attributed to PN were observed in the late 80ies in the context of "hyperalimentation"[11] which was delivered without tight glucose control.

These access issues do also apply to children in whom post-pyloric tube placement is even easier, occurring nearly automatically with gastric placement attempts.

3.2. Energy requirements

Patients with severe burn injuries develop an important and prolonged hypermetabolic response, grossly proportional to the severity of the injury: this response is caused by the important endocrine stress response, the inflammatory response (multiple mediators), the classical factors age and sex, and the extent and timing of the wound healing. The energy requirements after major burns are significantly increased above basal resting energy expenditure (REE), but the increase is variable over time,[12] and grossly proportional to the burned body surface area (TBSA). In the late 70ies, while burn care was developing, the clinical observation of massive weight loss and the metabolic measurements lead to the development of the concept of "hyperalimentation" which frequently resulted in massive overfeeding, as the delivery of 5000 kcal/day was considered normal with the historical Curreri equation.[13] But the early weight based plus TBSA based equations did not consider the changes over time: several studies have shown that the REE increase was most pronounced during the first weeks, decreasing progressively thereafter. Advances in burn care have reduced the magnitude of the hypermetabolic response, resulting in more moderate feeding targets.

On the other hand, nutritional requirements calculated on the usual ICU fixed weight based equations (25–30 kcal/kg/d) result in underfeeding.[14] Further the stress factors used to modulate the Harris & Benedict equation have been shown to be either very inexact, or totally wrong. Overfeeding causes morbidity such as fatty liver infiltration and increased infectious morbidity.[11,15] In children the Hildreth and Galveston equation incur the same risk of overfeeding.

For the above reasons, indirect calorimetry is the gold standard for determination of energy requirements both in adults and children. Practically, the measurements are made in the fed state, and the results of the analysis are rounded to the upper 100 value, without exceeding +10% of the measured value. In absence of this tool, the Toronto equation (Table 2), which is based on multiple regression analysis of an important number of calorimetric studies, is a well validated alternative.[16,17]

In children, and in absence of calorimetry, the Schofield equation appears as a reasonable alternative, while keeping in mind it might underestimate the requirements,[18] and that the result of the calculation should be rounded upwards. For clinicians used to the older equations the results of the Schoffield equation might seem very low: this feeling should be attenuated by the knowledge that children have been massively overfed until the late 80s with severe related complications.[15] The major drawback of the Schofield equation is to be a fixed equation, not integrating changes over time.

Patients with major burns appear to be as sensitive to overfeeding as other critically ill patients. Due to the important volumes of dextrose 5% solutions delivered during the first week to treat hypernatremia, and/or to the use of the fat solubilized sedative propofol in many centers it is particularly important to include these non-nutritional sources of carbohydrates and lipids in the total energy count.[19]

Table 2
Best predictive equations according to the burn literature.

Age category	Equation	Requirement (kcal/day)
Adults	Toronto	−4343 + (10.5 × % TBSA) + (0.23 × caloric intake) + (0.84 × REE by Harris-Benedict «crude») + (114 × t°) − (4.5 × days after injury)
Girls 3–10 yrs	Schoffield	(16.97 × weight in kg) + (1618 × height in cm) + 371.2
Boys 3–10 yrs	Schoffield	(19.6 × weight in kg) + (1033 × height in cm) + 414.9
Girls 10–18 yrs	Schoffield	(8365 × weight in kg) + (4.65 × height in cm) + 200
Boys 10–18 yrs	Schoffield	(16.25 × weight in kg) + (1372 × height in cm) + 515.5

3.3. Proteins and specific amino-acids

Proteins requirements have been considered to be around 1.5–2 g/kg/d since the early 80ies.[20] Protein intakes above 2.2 g/kg/d have no further beneficial effects on net protein synthesis.[21] Protein intakes up to 3 g/kg/d have been reported in children without real advantage.[22]

Glutamine is an amino-acid becoming conditionally essential for burn patients. It is a favorite substrate for lymphocytes and enterocytes. A few small monocentric studies about glutamine supplementation in burn patients have been performed but present many variations in terms of dose, route and duration of administration, studied population or objectives. Inconstant results are observed regarding impact on infectious complications, length of stay and mortality.[23–28] A large on-going American burn trial should provide answers. Currently, it is therefore difficult to recommend a precise dose, a route, or duration of administration. Doses reported for other critical patients should probably be considered: 0.3 g/kg/d during 5–10 days. In burn children, administration during less than 3 days has been demonstrated to have no effect.[29]

Ornithine alpha-ketoglutarate, only available in France for enteral administration, is the precursor of glutamine and therefore an alternative. Administration during the acute phase of burn care seems to enhance wound healing.[30]. Daily intake of 30 g divided in 2 or 3 boluses has been shown to be efficient in improving nitrogen balance.[31,32]

Currently, there is no evidence in the literature to recommend arginine supplementation in burn patients.[33]

3.4. Carbohydrates and glycemic control

The number of recent studies investigating carbohydrate requirements in burns is limited. A few sophisticated isotopic studies conducted in adult[15] and pediatric[34] burn patients and recent reviews and guidelines[35–37] enable recommending to deliver 55–60% of energy as carbohydrates without exceeding 5 mg/kg/min both in adults and children: this number corresponds to 7 g/kg/day in a standard adult patient.

Regarding glucose control and intensive insulin therapy (ITT), the recent evidences and words of caution from other categories of critically ill patients probably apply[38]: intensive insulin therapy conveys a risk of hypoglycaemia, that is likely to be particularly elevated in burn patients as their nutritional requirements are elevated and frequently delivered over shorter periods of time (with elevated pump rates up to 150 ml/h) due to the frequent interruptions of feeding associated with the numerous interventions under anesthesia that their treatment requires.

Nevertheless, a reasonable control with glucose targets between 5 and 8 mmol/l is associated with significant clinical benefits as

shown by both retrospective[39–42] and prospective[43] burn studies. Observed benefits include better graft take, less infectious complications, and decreased mortality. The exact cut off for benefit has not yet been defined, leaving the clinician with the general ICU recommendations, of glucose 6–8 mmol/l (100–150 mg/dl).

New glucose control strategies have also been investigated in burns but can still not be recommended as general clinical practice. Metformine that reduces blood glucose by several mechanisms might be an alternative to insulin in some cases[44,45] but the risk of lactic acidosis should be considered. Exenatide, a new incretin that inhibits glucagon secretion, might reduce the exogenous insulin requirements as shown in a preliminary pediatric burn study.[46]

3.5. Lipids

Small amounts of fat are required to prevent essential fatty acid deficiency: only few studies are available regarding lipid requirements in burns. The two available studies[47,48] show that burn patients seem to be particularly sensitive to the total lipid load. Negative impact on hospital length of stay and on infection risk have been reported with total lipids intakes reaching 35% of energy requirements compared with 15%. As the current industrial preparations provide 30–52% of total energy as fat, the limitation of fat intakes requires hospital compounding. Due to this apparent sensitivity, it is also recommended to monitor the non-nutritional lipid intakes, such as delivered with the sedative propofol, which can reach 15–30 g/day in adults.

The place of omega-3 fatty acids or other mono- or poly-unsaturated fatty acids remains to be defined: in this area also, there are on-going trials.

3.6. Micronutrient requirements

Patients with major burns have increased micronutrients requirements (i.e. trace elements and vitamins) due to their hypermetabolic response, to their wound healing requirements and to the important cutaneous exudative losses which characterize burns with open wounds. An intense oxidative stress is associated with burn injury which in combination with the intense inflammatory response contributes to the exhaustion of the endogenous antioxidant defenses which are highly dependent on micronutrients.[49] The delivery of standard micronutrient intakes invariably results in clinical deficiency syndromes that become clinically visible by the end of the first month with delayed wound healing and infectious complications: the biological deficits are already detectable by the end of the first week.

The industrial enteral feeding solutions or the parenteral multivitamin and multi-trace element solutions are insufficient to cover the elevated major burn patients' requirements. The substitution of the losses and the increased nutritional requirements cannot be covered by the enteral route (due to absorption antagonism and competition between trace elements delivered in supra-nutritional doses).

Regarding vitamin requirements, the clinical studies have mainly investigated vitamin B, C, E and D.[50] Additional thiamin intake normalizes lactate and pyruvate metabolism.[51] Clinical benefits have been shown with reduction of oxidative stress, and improved wound healing using doses of vitamin C and E 1.5–3 times higher than recommended daily intakes in children and adults.[52] The results are not as clear with vitamin D, which is deficient and contributes to the development of osteoporosis in patients with major burns. Standard intakes are obviously insufficient: 400 IU/day of vitamin D2 do not improve bone density.[53]

The nutritional requirements for vitamin C have been shown to remain elevated during the entire acute phase (0.5–1 g/day). Recently Vitamin C has been administered at very high early doses (0.66 mg/kg/h for 24 h) since the early 2000s in human and animal studies. This treatment appears to stabilize the endothelium, thereby reducing the capillary leak and the fluid resuscitation requirements by about 30%.[54] This intervention is by no means conventional nutrition but an adjunctive therapy to resuscitation, and requires validation (NCT01587261).

Among trace elements, three have been shown to be particularly important in immunity and wound healing of both adult and pediatric burn casualties. Copper (Cu), selenium (Se) and zinc (Zn) are lost in large quantities with the exudative losses, the losses persisting as long as the burns wound are not closed.[55] The duration for elevated substitution requirements is therefore determined by the burned surface: 7–8 days for burns 20–40%, 2 weeks with burns 40–60% and 30 days for burns $>$ 60% TBSA. The early substitution from admission is associated with reduction of lipid peroxidation, improved antioxidant defenses, improved immunity with lower incidence of infectious complications, improved wound healing and shorter ICU stay.[56,57] Competition between Cu and Zn for intestinal absorption (metallothionein transporter) makes the administration of enteral substitution doses inefficient.

The same considerations apply to children using substitution doses calculated at the prorate of their body weight or body surface.[58]

3.7. Non-nutritional management of hypermetabolism

In addition to early enteral nutrition,[59] several non-nutritional strategies are recommended to attenuate the hypermetabolic response to burn injury: maintenance of nursing environmental temperature at 28–30 °C,[60] early excision and coverage of deep burn wounds[61] and administration of agents stimulating protein synthesis (non-selective beta-blockers, oxandrolone). Pain control and early institution of exercise therapy programme are essential additive measures for metabolic resuscitation as in any ICU patient.

Benefits of non-selective beta-blockers are best demonstrated in children,[62] they seem to be less important in adults. Use of propranolol at a dose titrated to reduced basal heart rate by 20% is noted to decrease cytokines or stress hormones release and to lessen both hypermetabolism and hypercatabolism.[63–66]

Decrease in mortality[67] and length of stay[68] has been demonstrated after administration of oxandrolone (10 mg/12 h). In addition, beneficial effects are described on weight loss, protein catabolism and healing time, as well as on bone metabolism, both during acute[68–70] and rehabilitation periods.[71,72]. Similar effects are observed in children (0.1 mg/kg/12 h). The administration of oxandrolone requires a close monitoring of liver function.

Propranolol and oxandrolone are the two best cost-effective pharmacotherapies for burns hypermetabolism. A role for combined therapy is currently under trial (NCT00675714). It is recommended to start administration after the resuscitation phase: at the end of the first week for propranolol, and a little later for oxandrolone. Of note the early administration (i.e. during the first week) of both drugs alone or in combination is under investigation. Treatment duration is currently not defined but could correspond to the hospitalization stay, except during septic events. According to sparse data,[73] a prolonged administration during the rehabilitation phase might be considered.

Administration of recombinant human growth hormone (rhGH) is not recommended in burn adults. Unlike in general intensive care population,[74] no adverse impact on mortality was observed in burn patients. However, rhGH effects are not better than oxandrolone,[69] while disclosing adverse hyperglycemia.[75] In burn children, rhGH treatment seems to be an effective and secure strategy, probably related to a proven GH deficiency associated with growth

impairment (stunting). In this population, rhGH treatment (0.05–0.2 mg/kg/d) has been demonstrated to enhance donor site healing[76,77] and to reduce hypermetabolism and growth deficit.[78,79] Ideal duration of treatment is still to be determined: until now treatments for up to one year have been tested and shown to be safe.

4. Conclusion

Artificial nutrition of patient suffering major burns is a highly specific therapy. Early enteral feeding, started within the first 12 h after injury, is an integral part of initial resuscitation. Nutrient requirements are not constant over time but are generally substantially higher than those of other critically ill patients: weight based predictive formula are consequently inaccurate. In addition, trace elements deficiencies develop early on in the most severe burn patients because of the cutaneous exudative losses. Major burns need an early supplementation with supra-nutritional amounts of zinc, copper and selenium to prevent deficiency related complications. Nutritional and metabolic problems related to burn injury require the early implementation of complementary strategies. Non-nutritional therapies are essential to reduce hypermetabolism and hypercatabolism (high ambient temperature, early wound excision and coverage, non-selective beta-blockers and anabolic agents). The routine use of propranolol and oxandrolone has reached a very high level of evidence. Further large studies are needed to precise some of their optimal modalities.

Conflicts of interest

Authors have no conflict of interest to declare. There was no industrial sponsoring of the guideline process.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2013.02.012.

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