Clinical Nutrition 28 (2009) 359–364

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

The ESPEN clinical practice guidelines on Parenteral Nutrition: Present status and perspectives for future research

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ARTICLE INFO

Article history:
Received 11 May 2009
Accepted 11 May 2009

Keywords:
Guidelines
Methodology

SUMMARY

The ESPEN Guidelines on Parenteral Nutrition (PN) reflect current scientific knowledge in the field of clinical nutrition in adults. They summarize the indications for PN and its anticipated outcomes in respect of the underlying disease, nutritional status and quality of life. They are companion documents to the ESPEN Guidelines on Enteral Nutrition and follow the same general format. They address the influence of the underlying disease on the patient's nutritional status, and that of malnutrition on the outcome of the disease. Contraindications to and complications of PN are considered, together with comparative analyses of the roles of the parenteral and enteral routes in different illness states.

The quality and strength of the supporting literature has been graded according to the criteria of the Scottish Intercollegiate Guidelines Network (SIGN) and the Agency for Health Care Policy and Research. Hence, meta-analysis of randomised clinical trials (level of evidence Ia) or at least one randomised clinical trial (level of evidence Ib) translate to a Grade A recommendation. Levels of evidence IIa, IIb and III are attributed respectively to: at least one well-designed controlled trial without randomisation; at least one other type of well-designed, quasi-experimental study; or well-designed non-experimental descriptive studies such as comparative studies, correlation studies, case-control studies; each of these sustains a Grade B recommendation. Grade C recommendations reflect expert opinion and/or the clinical experience of respected authorities (level of evidence IV).

Each of the 11 sets of PN Guidelines was devised by an international working group, the total faculty comprising no fewer than 87 experts from 16 European/Mediterranean countries, each group's contributions being co-ordinated by a designated chairman. Once each guideline had been approved by all the members of the relevant working group, this version was reviewed by at least two independent external reviewers (one selected from ESPEN's Education and Clinical Practice Committee, and at least one from outside the ESPEN committee structure). Following this review each guideline was hosted in draft form on the public pages of the ESPEN website for at least one month to permit the receipt of comments or suggestions from any interested party. At this point the Guidelines were reviewed and revised again by the original working group chairman and submitted to the Clinical Nutrition editorial process. At least 3 further reviewers were selected by the Journal's editorial office for each guideline, in line with the normal selection process. Final revisions were performed by the Chairmen of the working groups, and by ourselves as commissioning editors of the whole project.

More than 300 evidence-based recommendations are now presented. Fewer than one sixth of the recommendations are Grade A, and disappointingly, but unsurprisingly, more than 50% are Grade C. The need for more and better controlled trials in the field remains apparent.

"Knowledge is the enemy of disease"

1. Definitions and aims of the guidelines

The past decade has seen a dramatic increase in the number of guidelines produced worldwide, with literally hundreds of Clinical Practice Guidelines (CPGs) having been issued by different medical organisations. The stimulus for such proliferation has been attributed in part to the unexplained variety in medical practices in

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doi:10.1016/j.clnu.2009.05.010

different countries, and concerns about inappropriate use (over-, under- and mis-use) of interventions, and the use of interventions in the absence of established effectiveness.[1] The expansion has also been driven by evidence-based medicine and the increasing need for health care purchasers to base spending on proven effective measures. CPGs aim to improve consistency of care and cost-effectiveness. When there has been variation in practice, explicit guidelines may improve clinical practice.[2] The European Society for Clinical Nutrition and Metabolism (ESPEN), as an international organisation dedicated to all issues concerning enteral (EN) and parenteral (PN) nutrition and metabolism, therefore, among its aims, promotes the development of CPGs.

CPGs are commonly defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances".[3] The ESPEN CPGs on PN are mainly intended for physicians, but, since correct practical administration plays a fundamental role in terms of safety and efficiency, some parts are addressed more specifically to nurses and other health care workers.

These CPGs do not address the autonomy, choices and responsibilities of health professionals, since the complexity and variability of institutions, health organisations, pathologies and patients is too great to be neatly encapsulated. However, they are intended to present safe-guards for the user, by virtue of supplying guidance so as to improve the well-being of the patient and to minimise the chance of exposing the patient to hazardous or futile health interventions. The CPGs should be used flexibly with adaptation to specific situations and circumstances taking into account availability of resources, the specific medical condition to be addressed, and the characteristics (medical, social, administrative) of the clinical setting.

The present CPGs on PN reflect current scientific knowledge in clinical nutrition, and summarize the evidence for indications for PN, and the outcomes which can be attained in respect of the underlying disease, and the patient's nutritional status and quality of life. Their main aim is to guide clinicians, dieticians, nurses and other caregivers involved in the nutritional support of patients in hospital or at home, to the optimal use of PN. They are intended to be complementary to the ESPEN CPGs on enteral nutrition,[4] and accordingly, whenever possible, follow their general layout.[5]

The CPGs on PN aim to answer the following questions:

- What influence does the disease exert on nutritional state and energy and substrate metabolism?
- What influence does nutritional state exert on the outcome of the underlying disease?
- What are the goals of PN?
- When is PN indicated?
- Is PN better than EN?
- Does PN have specific contraindications or complications?

Depending on the topic concerned, there is variable availability of evidence-based literature. Consequently the proportion of practical evidence-based recommendations, compared to those based only on considerations of pathophysiology or on conflicting results from literature varies substantially. In general, the larger the number of recommendations from the evidence-based literature, the lower the requirement for explanation in the comments. As the percentage of Grade A recommendations lies between 7% and 30% for different topics it is clear that each chapter should be read and interpreted independently.

In drafting the CPGs for PN the authors had the opportunity to consider the ESPEN EN guidelines[4] as a model with regard to the methodology of scrutinizing the scientific literature, determining rationale and recommendations, scoring their strength, and in presenting the document.

The reference to the EN guidelines is in any case central to the use of PN as it so often becomes necessary only when patients requiring nutritional support cannot be fed orally or enterally. There are very few conditions where the parenteral route should have priority over the enteral one. The time-honoured dogma that the "bowel rest" achieved through exclusive PN was safe and useful in gastrointestinal disease has been progressively eroded, to be replaced by the recognition that enteral disuse contributes to mucosal atrophy, disturbances in gut permeability, disruption of enteric hormone function, and to potentially damaging alteration of the gut flora and the immune response. In only a few conditions does PN retain a privileged role over EN in the presence of a functioning gut.[6–8] The new guidelines also contain technique-specific sections on home PN, and on central venous catheters used in nutritional support.

2. Development and methodology

The present guidelines were commissioned by the Executive Committee of ESPEN in 2005, to the then current standards for guideline construction, and are now formally adopted by ESPEN.

The published literature was scrutinized carefully using such search terms as "parenteral", "TPN", "nutritional support", "intravenous", "HPN", together with terms for the disease, organ or pathological process determined by the chapter concerned. Searches were performed on general electronic databases (Scopus, PubMed, Cochrane Library, Medline, EMBASE). Existing topic-specific ESPEN CPGs and guidelines from other scientific societies were also examined, including: those of the Italian Society for Parenteral and Enteral Nutrition[9,10]; the Italian guidelines on Home Artificial Nutrition[11,12]; those from the German Society for Nutritional Medicine[13,14]; those from the Scottish Home Parenteral Nutrition Managed Clinical Network Protocols[15]; those from the Australasian Society of Parenteral and Enteral Nutrition[16]; the several publications of the American Society for Parenteral and Enteral Nutrition[17–21]; the joint recommendations of the American Society for Parenteral and Enteral Nutrition and the American Society for Clinical Nutrition[22]; and the guidelines from the UK National Institute for Health & Clinical Excellence (NICE) on Nutrition Support in Adults.[23] There was no systematic attempt to search for "grey literature" such as abstracts, theses, conference reports, and unpublished literature. The search strategy was restricted to adult patients given the recent comprehensive reviews of parenteral and enteral nutrition in pediatrics.[24–26]

The quality and strength of the supporting literature was graded according to the Scottish Intercollegiate Guidelines Network (SIGN) criteria[27] and those of the Agency for Health Care Policy and Research.[28] The grade of recommendation depends on the scientific quality of the studies reported (Table 1).

Table 1
Grades of recommendation and levels of evidence.

Grade of recommendation	Level of evidence	Requirement
A	Ia	Meta-analysis of randomised controlled trials
	Ib	At least one randomised controlled trial
B	IIa	At least one well-designed controlled trial without randomisation
	IIb	At least one other type of well-designed, quasi experimental study
	III	Well-designed non-experimental descriptive studies such as comparative studies, correlation studies, case-control studies
C	IV	Expert opinions and/or clinical experience of respected authorities

Prospective randomised controlled trials (RCTs) minimise bias in the selection and grouping of patients, the practical conduct of the protocol, and in the final interpretation and presentation of results, while systematic reviews and meta-analyses provide "*an efficient scientific technique to identify and summarize evidence on the effectiveness of interventions and to allow the generalizability and consistency of research findings to be assessed and data inconsistencies to be explored*".[29] On the contrary, the flaws and pitfalls of non-RCTs have been widely recognized and reported.[30] RCTs are therefore considered as the gold standard for the determination of the overall efficacy of clinical therapies, and their use underpins the assignation of a Grade A recommendation, either from a single strong and relevant study (level Ib evidence) or through meta-analysis of multiple RCTs (level Ia evidence). Levels of evidence IIa, IIb and III are attributed to: at least one well-designed controlled trial without randomisation; at least one other type of well-designed, quasi-experimental study; or well-designed non-experimental descriptive studies such as comparative studies, correlation studies, or case-control studies, respectively, and support a grade of recommendation B. Grade C recommendations reflect expert opinion and/or clinical experience of respected authorities (level of evidence IV). The differentiation of Grade A recommendations from the others is generally simple, but it may sometimes appear almost arbitrary whether a conclusion is graded B or C. A practice considered widely accepted and diffuse across the world clearly rests on more than the opinion of few experts, but in the absence of scientifically-structured reports in the literature this practice warrants only a designation of Grade C. Where there was a general lack of data, a lack of rationale, or where there was controversy or unresolved discrepancy between existing publications we have allocated the less dogmatic designation.

The PN CPG programme involved 11 international committees, each co-ordinated by a chairman (Table 2), comprising 87 experts from 16 European-Mediterranean countries. The committees were multidisciplinary, including experts in clinical nutrition from different fields of medicine, nursing and dietetics, and they were responsible for the literature research, the preparation, discussion and revisions of draft guidelines. Once each guideline had been approved by all the members of the relevant working group, this draft was reviewed by at least two independent external reviewers. In each case one of these reviewers was a member of ESPEN's Education and Clinical Practice Committee who had not previously been involved in that guideline's creation, and at least one reviewer came from outside the ESPEN committee structure (often also from outside Europe). Following this review and amendments being made each guideline was hosted in draft form on the public pages of the ESPEN website for at least one month to permit the receipt of comments or suggestions from any interested party. Comments received from representatives of the nutrition industry were addressed on their scientific merit on the same basis as those from clinical and academic colleagues. At this point the guidelines were reviewed and revised again by the original working group chairman and submitted into the Clinical Nutrition editorial process. At least 3 further reviewers were selected by the Journal's editorial office for each guideline, in line with the normal selection process. Final revisions were performed by the chairmen of the working groups, and by ourselves as commissioning editors of the whole project, which now presents more than 300 evidence-based recommendations in 11 areas of clinical practice (Table 2).

Table 2
Chairmen of the Committees of the ESPEN Parenteral Nutrition Guidelines.

Cardiology/Pneumonology	SD Anker, Germany
Central venous catheters	M Pittiruti, Italy
Gastroenterology	A Van Gossum, Belgium
Geriatrics	L Sobotka, Czech Republic
Hepatology	M Plauth, Germany
Home Parenteral Nutrition	M Staun, Denmark
Intensive Care	P Singer, Israel
Nephrology	N Cano, France
Oncology	F Bozzetti, Italy
Pancreatic disease	L Gianotti, Italy
Surgery & Transplantation	M Braga, Italy

3. European and non-European clinical practice guidelines

Other publications aiming to guide nutritional practice exist elsewhere and it may be helpful to consider where there is over-lap and where these ESPEN guidelines present distinctive features. The American Society for Parenteral and Enteral Nutrition (ASPEN) has published several guidelines,[17–21] and also a range of documents defining standards of practice in nutrition support,[31–38] which address themselves to particular members of the nutrition team (pharmacist, nurse, dietician) or to a specific patient population. The most similar to the ESPEN CPGs, in being focussed on the medical community, are the 2002 ASPEN guidelines,[21] which differ most obviously in considering the enteral and parenteral approaches in the same document. The Canadian Society of Clinical Nutrition has published the results of their meticulous work on the nutritional support of the Intensive Care Unit patient.[39] This more limited focus has allowed the authors, who work in a tightly connected national network, the unique opportunity to elaborate *ex novo* data from the literature thus creating systematic reviews and meta-analyses which are not entirely reliant on already published data.

3.1. Nutritional therapy versus nutritional support. Does the terminology matter?

The aim of CPGs is to develop recommendations which are based on good research. The term "evidence-based medicine" originated at McMaster Medical School during the 1980s[40] where it was defined as "*the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients*".[41] Despite more than 20 years of best intentions the majority of the recommendations in nutritional care remain based on low-grade research evidence or on expert consensus. This was evident in the 1993 ASPEN guidelines, in which only 16% of the recommendations were judged to be based on good research-based evidence (meta-analysis of RCTs or single RCTs), and 29% on fair research-based evidence (essentially level II and III evidence) with 55% of guidance based on expert opinion alone.[19] Sadly little progress appears to have been made as we find similar percentages in the present CPGs (Grade A, 15.8%; Grade B, 28.2%; and Grade C, 56.0%). Nonetheless we should not conclude that these guidelines are of poor-quality. A large part of the problem distinguishing nutritional studies from those of a pharmacological agent is the frequent impossibility of performing studies to gold standard methodology. It is rarely ethically justifiable or clinically feasible to perform a placebo controlled trial in which some patients will deliberately be denied nutritional support, and in the particular context of PN it is applied now mainly as a "substitutive" treatment for a vital function when the normal enteral route is unavailable. The ASPEN Guidelines[21] summarize this as follows: "*A major distinction between therapeutic trials of efficacy of a drug or a procedure and the feeding of nutrients known to be essential to maintenance of human health and survival must be made. Withholding a drug or invasive procedure will not produce disease in otherwise healthy humans, whereas essential nutrients must be provided to both healthy and ill people*".

In many clinical conditions (exemplified by long-term intestinal failure), it is ethically unjustifiable to randomise between nutrition and non-nutrition,[42] given the lack of "equipoise".[43] Controlled trials should always rest on a genuine uncertainty that the outcome from one intervention (or the lack of it) is better or worse than the alternative. Despite these constraints the effects of PN can be investigated in a structured, randomised fashion under certain conditions:

- when the planned duration of PN is so short that a non-nutrition arm is ethically acceptable (eg in the immediate postoperative state; it is understandable that one third of our Grade A recommendations are in this area).
- when in one arm of the study, the investigator adds one or more special substrates (eg BCAA, n-3 emulsions, etc.) to the conventional (control) nutritional regimen.
- when the investigator compares different nutritional regimens (eg glucose-based versus lipid-based PN, etc.), or different routes of administration (eg PN versus tube feeding etc.) or different times of administration (eg early versus delayed, continuous versus intermittent, etc.).

Even in these circumstances it can prove very difficult or impossible to construct blinded studies in order to minimise bias.

The assertion[44,45] that EN and PN, as medical interventions, should thus be termed "nutritional therapies" rather than "nutritional support", raises some interesting questions on the legitimacy and potential consequences of this attribution. PN is clearly a medical intervention that surpasses "ordinary care", but to equate it (as a therapy) to a drug, could lead to the assumption that the use of PN should be limited to conditions where it can be evaluated according to the pharmacological gold standard of the randomised controlled trial (RCT). An excessive emphasis on PN as "medical therapy" might paradoxically imply that in conditions in which its efficacy cannot be tested by RCT, it could only be considered as a simple "supportive" measure, even though it may then be an essential and life-saving treatment substituting for the failing gut. Nutritional intervention in fact encompasses a broad spread of clinical indications which include but go beyond the narrow definitions of "true therapy". By way of illustration Table 3 identifies some of the dichotomies in the perception of PN and how this might influence clinical actions, while at the same time indicating how often elements from the therapy and support columns co-exist. Challenges are posed in at least three domains: the scientific validation of the use of PN; its financing; and the ethical implications of withholding/withdrawing PN.

Some of the problems associated with scientific validation have already been addressed, and it will be noted that the most malnourished patients and those with a non-functional gut - those who would appear most likely to benefit - cannot normally be randomised to a no-feeding group and are therefore excluded from evaluation. Only patients who are marginal candidates for PN will satisfy the requirement for equipoise so as to be included in the study, which potentially masks any benefit of the intervention. A technical review of PN in cancer based on a meta-analysis of 26 RCTs (~1000 patients), concluded that PN was associated with increases in total and infectious complication rates.[47] This study formed the basis for an official statement from the American Gastroenterological Association to the effect that PN caused net harm in cancer patients.[48] However patients with severe malnutrition or hypophagia were excluded and the scientific credibility for PN in these patients was thus (unintentionally) diminished. The Veterans Affairs Perioperative PN Study[49] met with similar problems: of 459 patients who would accept randomisation, 97 (17%) were excluded because PN was judged to be clinically essential, such that randomisation to an unfed group would be unethical. The study showed that, overall, PN led to an increase in infectious complications. However, in the subgroup of 50 severely malnourished patients, the frequency of infectious complications was similar in the two arms, and non-infectious complications were more than 8 times more frequent in the controls than in those on PN (43% versus 5%). Similar results came from the Maastricht study.[50] It can be concluded that controlled studies of patients with marginal degrees of malnutrition will generally demonstrate the morbidity of PN, but potential benefits to those most in need will be obscured by the absence of major benefit to the majority. Restriction of trial entry to those with weight loss permitted a more persuasive positive result in perioperative patients[51] PN proving able to reduce both morbidity and mortality.

The absence of placebo-controlled trials and the uncertainties that have arisen from studies that appear to show harm from PN have added to the difficulties in funding PN research and its clinical application. In most countries now the health care system requires a clear demonstration of treatment efficacy in order for its expense to be covered, which sometimes seems to stem from a contention that treatments are guilty until proven innocent[52]! If PN is considered exclusively as a therapy, both the medical community and public health authorities will expect it to be validated by RCTs before its endorsement for public funding.

Most cultures allow for the final decision on accepting or refusing therapy to be taken by the patient. The ethical issue admittedly becomes more complicated when the caregiver has to decide whether to start or discontinue treatment in an incompetent patient, but most clinicians will feel comfortable declining the provision of a treatment sought by the patient which is considered ill-advised.[53] The ethical issues surrounding the provision of basic/essential care may however require a different approach, including the proposition that the decisional autonomy of the individual about any such element - including nutrition - must always be respected. Ultimately this controversy reflects the differences between two general beliefs which dominate modern medicine: on the one hand evidence-based medicine, which follows a positivistic, biomedical perspective that is disease-oriented and doctor-oriented, and which considers therapy from the cognitive-rational perspective; and on the other hand patient-centred holistic medicine in which the focus is humanistic and biopsychosocial combining the ethical values of the "ideal physician" with the individual perspectives and belief systems of the patient.

With respect to parenteral nutrition, the few Grade A recommendations available reflects the paucity of level I studies and might suggest that PN has been introduced in a way that we would consider suboptimal compared to other therapeutic interventions. Compelling PN to conform to methods of analysis devised for drug

Table 3
Potential implications of the dual conception of parenteral nutrition as therapy or support.

PN as a therapy	PN as support
Any chemical agent which affects living processes is a drug[46]	"Natural" nutrition affects living processes (and all humans received intrauterine PN)
Physicians prescribe PN	Patients and relatives may call for PN
Physicians and medical societies consider PN as a therapy	Nourishment is viewed by relatives as an act of love and care
PN is a medical therapy for ill people	Nutrition is essential to both the ill and the healthy
As a therapy PN should be validated by RCT	It is ethically impossible to have a no nutrition (no PN) arm and hence a Grade A recommendation is precluded

treatments is however inappropriate, as it can be seen that these methodologies will condemn it to remain poorly-proven. We will never be able to justify withholding this intervention in a patient who cannot otherwise be nourished. However to avoid the charge that PN is nonetheless a poor-quality intervention we should perform randomised trials where feasible and actively seek other approaches to validate its use in clinical settings which preclude randomisation.

Van Way[54] suggests that in such conditions a hierarchy of benefit versus risk might be the best way to discriminate whether or not a therapeutic intervention should be undertaken. With this in mind the American Preventive Services Task Force has proposed a specimen classification which permits the clinician to advise semi-objectively in favour of or against an intervention even when the data are weak (Table 4).[55] The Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research reached similar conclusions as long ago as 1983.[56] PN will continue to occupy a middle ground between high-tech medical treatment, and as natural a means as possible to secure continued provision of essential nourishment in the patient with intestinal failure. In our decisions we can do well to recall the words of Sackett – one of the fathers of evidence based medicine – who urged the integration of "individual clinical expertise with the best available external clinical evidence from systematic research".[41]

3.2. The future

Scientifically validated guidelines are developed to produce specific health gains, and must be effectively disseminated and implemented if these gains are to be achieved. Evidence suggests that they are effective in changing practice and improving outcomes, including improved patient selection, quality of life, and minimization of complications.[2] However, little will be accomplished if target users are unaware or unfamiliar with a guideline, if professional scepticism is not overcome, and when physicians resist their adoption because they feel that guidelines are eroding their role in decision making.[57]

It should be understood that while guidelines are carefully considered recommendations, they are not mandatory requirements to be applied uncritically. It may be the case that CPGs are "*the best advice about the most effective intervention in a particular clinical situation*",[58] but the clinical situation under consideration may not correspond precisely to that in the guidelines, or the recommended intervention may be unavailable or inappropriate. Nonetheless, when a strong guideline exists it should increasingly be considered to be the default from which deviations should be justifiable and documented. Hence, sponsors and endorsers of CPGs have a responsibility to disseminate them through appropriate channels to potential users, and also to try to encourage their uptake and implementation. Experience in Switzerland[59] and Canada[60] demonstrates the magnitude of the additional effort needed to achieve concordance with nutritional guidelines.

The responsibility of the originators of CPGs extends to the regular revision of the guidelines themselves, taking into account new scientific knowledge, but also review of the consequences of their inclusion in regular practice. ESPEN intends to take both these roles seriously. Despite their foundation on systematic, structured reviews of the literature, guidelines retain elements of controversy and disagreement, as is almost inevitable with the nature of pathology and human intervention. If unequivocal factual analyses existed we would have little need for guidelines. The high proportion of Grade C recommendations in the PN guidelines indicates to what degree our guidance is dependent on experience and expert opinion. The guidelines can therefore be considered to be hypothesis-generating, and to act as a specific stimulus for targeted future research. Now the work "on the guidelines" is over, the true work "of the guidelines" has to begin.

Table 4
Classification proposed by the American Preventive Services Task Force to guide clinicians in contexts of varying robustness of evidence.[55]

- Level A: good scientific evidence suggests that benefits of the clinical service substantially outweigh the potential risks. Clinicians should discuss the service with eligible patients.
- Level B: at least fair scientific evidence suggests that the benefits of the clinical service outweigh the potential risks. Clinicians should discuss the service with eligible patients,
- Level C: at least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close to make general recommendations. Clinicians need not offer it unless there are individual considerations.
- Level D: at least fair scientific evidence suggests that the risks of the clinical service outweigh potential benefits. Clinicians should not routinely offer the service to asymptomatic patients.
- Level E: scientific evidence is lacking, of poor quality, or conflicting, such that the risk:benefit balance cannot be assessed. Clinicians should help patients understand the uncertainty surrounding the clinical service.

Acknowledgments

The creation of the ESPEN PN guidelines has been dependent on the contributions of many of our colleagues to whom we are most grateful. We acknowledge also the support and assistance of the editorial team at Clinical Nutrition. We confirm that there has been no financial involvement of the nutrition industry in the development of the guidelines.

Conflict of interest

Conflict of interest on file at ESPEN (espenjournals@espen.org).

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