Supporting a Knowledge Base With Evidence Retrieved From Randomized Controlled Clinical Trials: A Case Study

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ABSTRACT

This work describes a methodology based on Evidence-Based Medicine for finding literature–based evidence for a clinical decision support system. As an illustration, we applied this method to parenteral nutrition therapy (PNT). PNT requires expertise and experience and is prone to errors. The Pico's strategy was used to built structured clinical questions, which considered 11 PN clinical indications plus a PN nutrient (amino acid, glucose, lipid, electrolyte, trace elements and vitamins), and an outcome. 211 PICO strategies were structured, and 447 searches at PubMed were performed. The results were classified in levels of evidence and recommendation grades according to criteria of the Oxford Centre for Evidence Based Medicine.

Keywords: Evidence Based Medicine, Systematic Search, Power of Evidence, Parenteral Nutrition, PICO Strategies.

1. INTRODUCTION

According to Eddy, "Scientific evidence in clinical literature is not presented in a way that allows it to be directly applied in the health care setting. Evidence must be synthesized before being applied, and this synthesis, which is the basis for understanding reality and making decisions, is decisive for the future" [1]. Randomized Controlled Clinical Trials – RCTs – are the best source of evidence for scientific medical practice. Millions of dollars are spent annually on such clinical trials. There remains, however, a discrepancy between routine practices and "best practices" because the results of extensive and important trials are published as scientific papers that are difficult to understand and be used by both physicians and researchers in clinical settings. As a result, there is an inefficient transfer of evidence from the research context to the clinical practice along with the mobilization of valuable resources [2].

Since Evidence-Based Medicine (EBM) has been promoted as a means of improving clinical prognostics, many computer-based approaches have been proposed to manage clinical literature. However, most approaches designed to simplify evidence-based practice involve electronic distribution of vast unwieldy quantities of general and statistical data. For instance, the National Guideline Clearinghouse [3] has more than 2,100 guidelines, which supports searches by Disease/Clinical Status, Treatment/Procedure, or by Institutions responsible for the guidelines. Furthermore, it does not support adaptations to the guidelines made by the user concerning a specific individual or population.

Clinical Decision Support Systems (CDSS) are another example of a computer-based approach and are considered a tool with a high potential for reducing error [4] and enhancing quality and efficiency of health care [5]. In theory, it would be expected that associating CDSS with EBM increases quality health care since it is intended to provide discrete contextualized evidence in the manner clinical practitioners prefer. The effectiveness of such a system will be proportional to the power of evidence of the knowledge base supporting it.

However, the challenge of developing and adopting CDSS simplified by EBM is considerable. The initial difficulty is that clinical research results are published only in text format and computers are effectively illiterate. Other challenges exist, such as providing the most current and highest quality of evidence. This presupposes the development of a dynamic knowledge base and the institutionalization of well established protocols to analyze the effectiveness of the RCTs.

This work presents the implementation of EBM methods for a systematized search of evidence supporting the knowledge base of a CDSS, as well as proposing dynamics for updating this evidence. To illustrate this approach, this work is focused in the prescription of Parenteral Nutrition (PN) for adult patients. In the setting of Parenteral Nutrition Therapy (PNT), the large quantity of nutrients to be prescribed is a complicating factor for health professionals, resulting in a time-consuming activity requiring specialized knowledge.

2. MATERIALS AND METHODS

Considering that PN prescription is provided according to each patient's individual needs and the associated clinical

conditions, this study focused on eleven clinical settings corresponding to eleven prescriptions of PN: 1. Acquired Immunodeficiency Syndrome – AIDS; 2. Cancer; 3. Diabetes; 4. Inflammatory Bowel Disease; 5. Hepatic Disease; 6. Gastrointestinal Fistula; 7. Renal Insufficiency; 8. Pancreatitis; 9. Short Bowel Syndrome; 10. Critical illnesses, and 11. Burns.

The process of gathering information on the prescription of PN for adult patients with specific individual needs and a determined associated clinical condition will depend much on the way in which each step of this methodological process is structured. The methodology adopted for this work is described below. PubMed was used as the literature database.

Selection of the study type
The subjects of analysis were randomized controlled clinical trials (RCTs) since they are one of the most reliable sources of scientific and clinical evidence [6].

Preparation of questions structured to clinical settings
In the electronic database we found many answers to the questions posed. Some of the information retrieved, however, was not consistent and did not support a clinical decision [7]. In cases where we did not structure questions that could be applied clinically and that included the set of information required to answer them (e.g., "What is the amount of amino acid in grams per kilogram of body weight to be given per day through parenteral nutrition to critically ill patients in order to reduce mortality?") and if we did not design an appropriate strategy for performing searches in the electronic database, the search results would display either excessive information (typically unrelated to the subject of the question posed) or omit critical information. Consequently, we used a strategy known as PICO (Patient or Population, Intervention of Indicator, Comparison or Control, and Outcome) to built well-structured clinical questions.

Questions posed using the PICO strategy were made for each PN prescription combined with each nutrient (amino acid, glucose, lipid, electrolyte, trace elements and vitamins), and an outcome. Field "P" refers to the patient and his/her clinical condition (e.g. critically ill adult patient), "I" refers to the type of intervention (parenteral nutrition) and the type of a nutrient (e.g. amino acids); field "C" was not considered since the objective was not to make a comparison with other nutritional therapies; and field "O" refers to the expected outcome (e.g., reduction of mortality). The selection of outcomes initially took into account patient-oriented outcomes followed by disease-oriented outcomes.

Converting questions into search strategies
This step consisted of identifying descriptors related to each of the terms that are components of the PICO strategy, combining PICO strategy components through Boolean operators, and defining the inclusion and exclusion criteria. The descriptors are controlled vocabularies used for indexing scientific papers in a database. The descriptor for PubMed is MeSH. The selection of the descriptor used in the searches was based on an individual review of each component of the structured questions. To illustrate our method, some specificities of the identification of the descriptors are mentioned below. The term "amino acid" was initially localized in the MeSH tree as "Amino Acids". By analyzing the MeSH tree, it was noted that the descriptor "Amino Acids, Peptides, and Proteins", which is located in a higher position in the tree, would be more appropriate since the search would retrieve references describing the protein source as "Amino Acids", "Peptides" , and, "Proteins". The term "diabetes" is not presented alone as a MeSH descriptor. For this reason, we used the descriptor "diabetes mellitus" [MeSH Terms] combined with the descriptor "diabetes insipidus" [MeSH Terms].

Search strategies were structured for each associated clinical condition versus kinds of nutrients versus outcome.

Search Process
For each clinical question posed, there were two searches. The first used the MeSH terms previously identified. The second used a term mapped from the PubMed database. This procedure had the following purposes: to validate the search methodology and prevent potential exclusions of important references. The search strategies were refined by filters to include, only randomized controlled clinical trials with adult human subjects.

Using the tools available in PubMed's Entrez, all validated search strategies were recorded in PubMed. Consequently when new studies are identified, Entrez sends a notification by e-mail and we can make the updating of evidence.

Pre-selection of studies
This pre-selection was based on the review of the abstract of each of the citations retrieved in the search.

Review of articles and assessment of the methodological quality of studies
The pre-selected articles were read and reviewed, and for each, we made a summary including important information on the methodology, results, conclusions and information regarding the clinical setting, such as nutrient concentrations, administration regimen, indication and restrictions of the formulation presented.

The Jadad's score was used as the "gold standard" to assess the methodological quality of studies.[9] This validated score lies in the range 0-5. Studies are scored according to the presence of three key methodological features of randomization, blinding and accountability of all patients, including withdrawals. For example, the score is two if appropriate methods of randomization are described, one if the study is merely described as "randomized", and zero when no details are provided to evaluate randomization. Two points can be given for blinding in the study: a score of two is allocated if patients and investigators are made blind by appropriate methods, one if the study is described merely as double blind and zero if details about blinding are not provided. The third item to be scored is the reporting of withdrawals. The study receives a score of one if all patients are accounted for in the analysis and reasons for withdrawals are provided. A score of zero is given when information regarding withdrawals is incomplete. Studies should be scored as high quality if they received a Jadad's score of four or five (of a possible five points)

Classification of studies according to level of evidence and grade of recommendation
The classification was based on criteria of the Oxford Centre for Evidence-Based Medicine (CEBM), available at http://www.cebm.net/index.aspx?o=1025. According to these criteria, studies with Jadad's score ≥ 3 were classified as Grade

of recommendation: A, Level of Evidence: 1b; on the other hand, studies with Jadad's score < 3 were classified as Grade of recommendation: B, Level of Evidence: 2b.

The results of the searches were recorded in a database of bibliographical references using the software tool Reference Manager™. For each citation recorded in the database, the following information was entered: review of the article; methodological quality of study; level of evidence; recommendation grade and evidence obtained about PN prescription.

3. RESULTS

For this work, 211 clinical questions were structured using PICO strategies, which took into account one clinical indication of the PN, one nutrient, and one outcome (refer to Table 1). In order to search for answers to the clinical questions posed, 447 searches were done in the databank. These searches resulted in retrieving 4,037 studies. See line 1 of Table 2 for a distribution of these studies by clinical indication. The use of filters reduced the number of studies to 387 (9.6%). After the abstracts were reviewed, all citations were considered of interest (line 3 of Table 2). After reading and analyzing the articles, it was noted that only 14.2% (55 articles) answered their respective clinical questions, which represents only 1.36% of the 4,037 references retrieved (line 4 of Table 2). Lines five and six of Table 2 refer to the evaluation of the quality of the studies and their classification according to the level of evidence and grade of recommendation. To illustrate the results obtained for each of the eleven clinical indications, Table 3 summarizes the evidence for the clinical indication "inflammatory bowel disease".

Table 1 – Example of a clinical question structured with a PICO strategy

Clinical question:	What amount of amino acids should be given via PN to critically ill adult patients to reduce mortality?
Patient or Population:	Critically ill adult patient
Intervention or Indicator:	Amino acids, total parenteral nutrition
Control or comparison :	None
Outcome	Reduction of mortality

Table 2 – Results of Searches by Clinical Indication

	CLINICAL INDICATION											TOTAL
	AIDS	**DIA**	**ID**	**HD**	**GF**	**RI**	**CI**	**SBS**	**PC**	**BN**	**CA**	
No. of citations retrieved	44	369	373	481	168	536	221	379	136	274	1056	4037
No. of citations after filtering	2	15	13	51	2	20	127	9	12	13	123	387
No. of articles selected for review	2	15	13	51	2	20	127	9	12	13	123	387
No. of articles answering the clinical question	0	4	4	11	0	5	5	0	1	2	23	55
No. of articles classified with LE: 2b and RG B	0	4	1	6	0	3	2	0	0	0	18	34
No. of articles classified with LE: 1b and RG: A	0	0	3	5	0	2	3	0	1	2	5	21

LE – Level of evidence; RG – Recommendation Grade ; AIDS- Acquired Immunodeficiency Syndrome; DIA-diabetes; ID – Inflammatory Bowel Disease; HD – Hepatic Disease ; GF – Gastrointestinal Fistula; RI- Renal insufficiency; CI – Critically Ill; SBS – Short Bowel Syndrome; PC – pancreatitis; BN - Burn; CA - cancer.

Table 3: Evidence obtained for the indication "inflammatory bowel disease"

Nutrient	Recommendation	JADAD	LE	RG
Amino Acids	1.25g/kg per day	3	1b	A
Glucose	4g/kg per day	3	1b	A
Lipids	1.1g/kg /day of 20% soy lipid emulsion or structured lipids (TCM/TCL 20%.)	3	1b	A
Electrolytes	12 mEq/day of calcium	0	2b	B
Trace elements	No evidence found			
Vitamins	No evidence found			

LE – Level of Evidence
RG – Recommendation Grade

4. DISCUSSION

In a vast body of work (21,979 references) related to PN in PubMed, with the specific combination of procedures for making clinical questions and the use of filters, it was possible to obtain 387 references directly related to the clinical questions made and to exclude the ones that did not focus on the elements present in the question. The use of more than one search strategy for each clinical question aimed to evaluate the methodology of the work. In this respect, we can state that all works related to a given clinical question indexed in PubMed were retrieved by the structured search strategy.

The clinical indication of cancer was the only one for which at least one study concerning each nutrient searched was obtained. In the case of the nutrients, the amino acid, which represents the protein source of the parental nutrition, resulted in at least one study per clinical indication except from short bowel syndrome, AIDS and gastrointestinal fistula. More than the general recommendations in the Guidelines, this work identified therapeutic indications for a given patient in particular.

Regarding the quality of the evidence found, only 43.24% of the studies evaluated had a Jadad's score ≥ 3. Only 10.81% had the maximum score 5, which refers to studies with excellent methodological quality. Of 65.86% of the studies with a score below three, 29.73% had a score of 0 (zero).

5. CONCLUSIONS

This work was designed to validate a methodological strategy for identifying clinical evidence for parenteral nutrition. Besides that, it also confirms that efficient trials, which are the basis for EBM, represent only a small fraction of all literature searched.

The translation of this evidence into rules of production to the CDSS is the next step in future research.

6. ACKNOWLEDGMENTS

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