

**METHODOLOGICAL APPROACHES
TO EVIDENCE BASED GUIDELINES
IN BURN INJURY**

Summary of Ph.D. Thesis

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INTRODUCTION

Evidence-based medicine (EBM) is a scientific approach that supports the application of the best available research evidence to medical decision making. An understanding of EBM and how to implement it in practice is crucial for all professionals involved in the delivery of modern healthcare today. Guidelines are the most effective way of applying evidence into patient care. Potential increases in health costs and risks due to market-driven, uncontrolled use of novel clinical interventions also make guidelines increasingly important.

Evidence-based recommendations are particularly important in areas of health care, where costs and mortality rates are very high. Burn care is one such area and according to a WHO estimate for our region the death and mortality rates are at least ten-fold higher than in Western Europe. High-income countries have made considerable progress in lowering rates of burn deaths through combination of proven prevention strategies and improvements in the care of burn victims. Most of these advances in prevention and care have been incompletely applied in low- and middle-income countries. Increased efforts to do so would likely lead to significant reductions in rates of burn-related death and disability. For these reasons we have identified burn care as a key topic in Hungary for guideline development with an evidence based methodological approach.

Guidelines are systematically developed statements providing recommendations about the care of specific diseases. In addition, guidelines can play an important role in formulating health policy. CPGs (Clinical Practice Guidelines) potentially improve the quality and processes of care by putting research findings into clinical practice, provided the recommendations are rigorously developed and based on the best available research evidence. Many organizations produce CPGs on similar topics worldwide, but their quality is highly variable.

Good CPGs should be: outcome oriented; internally valid – *i.e.* based on high quality research evidence or formal consensus when evidence is conflicting or lacking; reliable – *i.e.* developed in an explicit, transparent and reproducible manner free from commercial influence or bias; multidisciplinary; externally valid – *i.e.* clinically applicable; flexible – *i.e.* adaptable to various clinical circumstances and patient preferences; clear – *i.e.* specific and readily understood by users; regularly reviewed and updated; appropriately disseminated and implemented; cost-effective; and amenable to measurement of their impact in clinical practice.

Guidelines can be adopted, developed *de novo* or adapted. Adoption of guidelines means that recommendations are used in the same format as issued

by the authority responsible for releasing the CPG. In *de novo* guideline development once the remit and clinical questions of the CPG are defined the critical steps in the process are how systematically the underlying research evidence is collected, selected, appraised and synthesized to give unbiased information which the CPG team can interpret further. This is probably the most time-consuming element of CPG development which needs special skills and training in systematic literature reviews and meta-analytic techniques. Often busy clinicians neither have the time, nor the necessary training to carry out such a thorough investigation.

Guideline adaptation, according to the definition of the ADAPTE Working Group, refers to the modification of a CPG produced for use in one cultural and organizational context to be applied in a different setting. Adaptation can be used as an alternative to *de novo* guideline development or for customizing an existing guideline to suit the local context. Unnecessary duplication could be avoided if high quality existing CPGs were adapted rather than developed *de novo*. This approach could be particularly beneficial for countries and organizations with limited budgets and experience or skills in evidence-based CPG development.

AIMS OF THE STUDY

Our main objectives were:

- to identify and prioritize the key clinical questions in burn care to be addressed by evidence-based recommendations for national practice;
- to systematically search for existing burn injury guideline recommendations for key questions, or in the lack of those, for the best available evidence on the topic;
- to systematically assess the scope and the quality of evidence and that of CPGs;
- to systematically synthesize the available evidence for burn care in primary studies and CPGs; and
- to highlight potential shortcomings of current burn CPGs and gaps in our knowledge that may limit the effective delivery of care in practice.

For our aims we addressed the following key questions:

- Are prioritized topics and questions covered by existing guidelines for burn injury?
- Do existing burn injury guidelines meet methodological standards?
- What are the main shortcomings of existing burns injury guidelines and how we can explain those deficiencies?

- How does the methodological quality of guidelines for burn injury compare with those of other medical fields?
- Is there sufficient evidence for formulating recommendations in burn injury guidelines?
- What methods can be used to fill in evidence gaps when formulating recommendations?

METHODS

For the adaptation of international CPGs of burn injury for local settings in Hungary, we followed the first 5 steps of the ADAPTE Working Group's methodology. Steps 6 and 7 were beyond the scope of this study. We first established a multidisciplinary research team which included experts in CPG methodology, evidence based medicine, statistics, intensive care medicine, burn and plastic surgery.

Definition and prioritization of key clinical topics and questions

Key clinical topics for the CPG were primarily determined by mapping the usual care pathway of burn patients, and secondarily refined by collecting and comparing the scope of source CPGs.

For prioritizing questions in each key CPG topic area we developed criteria which considered the potential impact of the intervention on important clinical, organizational or economic outcomes

Searching for and selection of source CPGs

Literature search was carried out between January 1990 and December 2008 systematically, screening MEDLINE and SCOPUS, the websites of several general medical burns-related journals and various burn associations, electronic databases of major CPG development and by reviewing the reference lists of review articles including CPGs. Searching in Medline was carried out using the terms of ("Burns"[MeSH] OR "Eye Burns"[MeSH] OR "Burns, Inhalation"[MeSH] OR "Burns, Electric"[MeSH] OR "Burns, Chemical"[MeSH]) AND ("CPG"[Publication Type] OR "CPGs"[MeSH] OR "Practice CPG"[Publication Type]).

CPGs published in English, German or French were selected by two independent reviewers according to the following inclusion criteria: 1/ the publications were clinically relevant to burn injuries and provided recommendations for clinical practice; 2/ the type of publication fulfilled the definition of the Institute of Medicine for practice CPGs.

Assessment of the clinical content of source CPGs

Because the guidelines varied in their scope, reviewers coded the CPGs according to whether they had recommendations for the 12 key clinical topics covered: i.e. fluid resuscitation, initial assessment and management, nutritional

support, referral, organization, delivery aspects of care, thromboprophylaxis, wound management, pain management, rehabilitation and reconstruction, electric injury, chemical burns, paediatric burn injuries and inhalation injuries. We defined recommendations as any statements that promote or advocate a particular course of action in clinical care. Two investigators working independently reviewed the guidelines for recommendations that covered the preset clinical topics. We resolved discrepancies through discussion within the study team.

Appraisal of methodological quality

We assessed the methodological quality of source CPGs by the AGREE Instrument in order to select those that are suitable for further analysis of their content and coherence before adaptation. Four assessors scored each CPG independently and reached consensus when necessary.

The AGREE Instrument critically evaluates the quality of reporting and the methodological quality of CPGs according to 23 criteria, grouped into six domains: 1/ scope and purpose; 2/ stakeholder involvement; 3/ rigor of development; 4/ clarity and presentation; 5/ applicability; and 6/ editorial independence. Each of the 23 items in the checklist were rated on a 4-point Likert scale ranging from 4 ‘Strongly agree’ to 1 ‘Strongly disagree’, with two mid points: 3 ‘Agree’ and 2 ‘Disagree’ The standardized percentage scores were calculated for each domain independently, as described in the manual of the AGREE Instrument

We used kappa statistics as a measure of the agreement among reviewers. The kappa statistics for multiple raters was applied to each of the 23 items of the AGREE Instrument. The MAGREE macro of the SAS system for Windows, that can handle the case of multiple raters, was used for calculations.

We also determined whether the CPG was evidence- or consensus-based (i.e. EB or CB). A CPG was classified as EB, when there was a documented and reproducible literature search methodology and/or some form of assessment of the quality of evidence while developing the CPG.

We compared the methodological quality of burn injury guidelines with that of other medical fields for two reasons:

1. to see if the methodological scores found were specific to this particular field only or reflect a general quality of CPGs;
2. to explore how consistent our guideline appraisal methodology is with published studies using the same critical appraisal technique.

For this investigation we carried out a systematic search of the literature for any studies which used the AGREE Instrument for the critical appraisal of any guidelines. The following search terms were used to retrieve such studies and overviews: (“guidelines” AND “AGREE”). AGREE domain scores of the

retrieved studies were listed and results synthesized and compared to domain scores found for burn injury guidelines.

Adaptation of recommendations

For efficient use of all published recommendations, in the fifth step of the framework, we have modified the ADAPTE process. The ADAPTE framework groups CPGs by similarity and uses separate tools for assessing guideline currency, consistency and applicability. As we have reviewed a large number of guidelines and wished to have each key question covered by a recommendation, we found it more practical to produce a comparative recommendation matrix for each key question with the relevant recommendations quoted from the actual source guidelines in chronological order, if available.

Survey of the evidence based background of recommendations in burn injury

Because CB guidelines were more prevalent than expected, we were interested whether this could be explained by shortcomings of the burn literature. We performed a broad search in Medline between 1967 and 2010. The following search terms were used: ("burns"[MeSH Terms] OR "Eye Burns"[MeSH] OR "Burns, Inhalation"[MeSH] OR "Burns, Electric"[MeSH] OR "Burns, Chemical"[MeSH]) NOT "sunburn"[MeSH Terms]) NOT burns [Author].

Methods for formulating recommendations when there is an evidence gap

Guideline adapting teams often face difficulties when no recommendations exist due to evidence gaps or conflicting expert opinions. Systematic reviewing techniques are used to fill in such evidence gaps. To pilot test this element of the guideline adaptation process, we chose another topical and as yet unresolved problem in dermatology, i.e. electrotherapy of melanoma metastases. We conducted a primary study and a systematic search of the medical literature to identify relevant studies on the effectiveness of bleomycin-based electrotherapy on melanoma patients. The bibliographic search was performed from 1980 to January 2010 in the PubMed database, using the keywords [electrochemotherapy AND melanoma AND bleomycin].

RESULTS

Definition of key clinical topics and questions

Two main CPG areas (i.e., general management of burn injuries and special burn injuries) and 12 key topics with 55 key questions were defined. Main reasons for prioritization were if the intervention had a high impact on clinical outcomes (A1: 38 questions, 69%; A2: 23 questions, 42%; A3: 4 questions, 7%; A4: 14 questions, 25%). Questions, related to economic (C: 9 questions, 16%) and organizational outcomes (B1: 1 question, 2%; B2: 7

questions, 13%) were given gradually lower priority. Priority scores were given from 1 (most important) to 4 (least important).

Search results, selection of guidelines

We screened 519 citations identified through computerized database searches. An additional 27 citations had been identified through hand searching in reference lists of papers, and web site searches of CPG resources. After screening for relevance and other preset inclusion and exclusion criteria, we retained 24 CPGs for further evaluation and critical appraisal. Selected CPGs were of two types: 1/ specifically oriented to burns, and 2/ other clinical CPGs in which certain chapters dealt with the management of burn injury.

Main characteristics of and clinical topics covered in selected guidelines

Of the 24 CPGs, 42% (n=10) were evidence-based (EB), and the rest consensus-based (CB). For paediatric burn injuries and pain management we found only CB CPGs, while for thromboprophylaxis and nutritional support the majority of CPGs were EB. Sixty percent of CPGs for electric and inhalation injuries were also EB. A number of CPGs addressed the topics which are most important in terms of patients' outcomes in the first 24-48 hours of burn injury. Due to the nature of burn disease most CPGs provided recommendations for initial assessment (n=15, 63%) and immediate fluid resuscitation (n=8, 29%) that are crucial for patient survival, but nearly two thirds of these were CB. In terms of outcomes it is essential that after initial assessment patients are triaged for referral to a burn centre. Six CPGs (25%) made recommendations on referral criteria, and other important organizational aspects of care, and only one third of these were EB.

Evaluation of the quality and coherence of source CPGs

Scope and purpose

Most CPGs performed well in this domain with a mean score of 74%, with only five CPGs (21%) scoring less than 60%. There was no difference between the mean scores of EB *versus* CB CPGs in this domain.

Stakeholder involvement

The mean score for this domain was 35%, with only 2 CPGs (8%) scoring slightly above 60%. Only 5 CPGs (21%) included individuals from all relevant professional groups in the development stage, and none was piloted among end-users. The average scores of EB and CB CPGs did not differ.

Rigor of development

In this domain the mean score was 38%, with 71% of CPGs scoring <60%. Only 5 CPGs (21%) described systematic methods for searching and selecting the evidence, 8 CPGs (33%) considered health benefits, side effects and risks when formulating the recommendations, and 7 CPGs (29%) described

the methods used to formulate the recommendations. Seven CPGs (29%) were externally reviewed prior to publication. Eight CPGs (33%) provided any procedure for future. The mean score in this domain was much lower in CB (22%) than in EB CPGs (61%).

Clarity and presentation

The mean score was 79%, and only two CPGs (8%) scored <60% for this domain. Three CPGs (13%) included tools for application. The average scores of EB and CB CPGs did not differ.

Applicability

In this domain the mean score was 21% with only one CPG scoring >60%. Three CPGs provided review criteria for monitoring purposes, and also 3 discussed potential organizational barriers. No CPG discussed cost implications. Consensus-based CPGs scored somewhat lower (18%) than EB ones (27%).

Editorial independence

The score in this domain was the lowest of all, with a mean of 17%. Four CPGs (17%) scored >60%. Potential conflicts of interests of CPG developers were recorded only in 3 CPGs (12%). Evidence-based CPGs scored much better but still only about one third of them reported these issues as compared to 8% of CB CPGs.

Overall recommendations

After assessing the quality of all CPGs reviewers recommended for adaptation those that were considered to influence outcomes in some form and that demonstrated acceptable quality on the AGREE instrument. In total, we recommended 16 (67%) CPGs for adaptation of which 9 (56%) were EB, and 7 (44%) CB. Two EB CPGs (8%) were strongly recommended and 14 (58%) with provisos or alterations.

Agreement among Reviewers

The kappa values indicate that overall agreement was fair to moderate for 61% of the items and was substantial to excellent for 39% of the items. In the final rating where there were some disagreements assessors based their scores on consensus.

Comparison of the methodological quality of burn guidelines with guidelines in other medical fields

In many medical fields altogether 1338 CPGs were investigated with the AGREE instrument, including results of our own systematic review of 712 CPGs along with a more recent systematic review of 626 CPGs published between 2003 and 2008. This overview revealed that in most guidelines the scope and purpose of recommendations are clearly defined and guidance is given in a clear format. There are significant shortcomings, however, in the multidisciplinary composition of guideline teams and involvement of patients

in formulating recommendations. The scores in these critical assessments were also low for the rigour (or reporting) of an evidence-based CPG methodology. Guidelines often fail the criteria of editorial independence, *i.e.* reporting on funding and potential conflicts of interest. Furthermore, all reviews found that most recommendations lack external validity, *i.e.* applicability in practice. The average domain scores in these reviews are very similar to what we have found in burns CPGs.

Modification of the ADAPTE process

For a more effective guideline adaptation and for the efficient use of all published recommendations we modified the fifth step of the ADAPTE framework and developed an algorithm. This modification enables guideline teams to address all tailored *a priori* questions, and to objectively compare the underlying evidence with final recommendations in various guidelines.

Literature review for high quality evidences in burn care

By searching MEDLINE for primary evidence in burn literature, a total number of 41.502 publications were evaluated, of which 10.830 (26%) could be classified according to the evidence hierarchy. Of these only 19 (0.04%) were meta-analyses, 606 (1.4%) randomized controlled trials, 904 (2.2%) clinical trials, 2745 (6.6%) comparative studies and 6556 (15 %) case series and case reports.

Formulating recommendations when there is an evidence gap

We performed a local primary study and compared our own findings to a systematic literature search from 1980 to January 2010 in the PubMed database. We retrieved 27 papers of which, after checking titles and abstracts, 11 were identified as being relevant for inclusion. Due to the low sample size in each study, we did not carry out a meta-analysis, even though objective response rates to treatment showed fairly homogeneous results.

DISCUSSION

Before adapting international CPGs to local practice the following questions need to be addressed: 1/ Are international guidelines of appropriate quality available? 2/ Are published recommendations based on the best available evidence, or in the lack of it on expert consensus conceived in a transparent and explicit process? 3/ Are recommendations transferable to our local settings? Our guideline adaptation study on burn care investigated all these issues and resulted in a pilot tested framework of methods that can be successfully used by guideline teams in various medical disciplines.

The assessment of guideline attributes by using the AGREE scores helped in deciding which guidelines could be trusted and used to base our local recommendations upon.

In general, as EB CPG methods have been published in the examined last 5 years or so, we expected some improvement of methodological quality of CPGs over time. In fact, neither the number of EB vs CB CPGs, nor the actual AGREE domain scores showed any tendency of improvement

Our study demonstrates that the majority of burns CPGs defined their scope and purpose reasonably well and presented their recommendations clearly. In this respect we found no difference between EB and CB CPGs. Equally, no difference could be seen between CB and EB CPGs in terms of multidisciplinary. Nevertheless, both types of CPGs often failed to involve related disciplines in the development process, even though a European survey has shown that in intensive care practice mostly plastic and trauma surgeons and anaesthetists are responsible for the management of burn injuries.

The adequacy of CPGs for adaptation is best reflected by the rigor of development and clinical applicability of the recommendations. In both domains burns CPGs achieved rather low scores (i.e., 38% and 21%, respectively). The low scores in the former are explained by the fact that most of the reviewed CPGs referred to some underlying literature, but many did not report the methodology of literature retrieval and selection or how recommendations were finally arrived at. One may argue that the large difference we found between the scores of EB and CB CPGs in the “rigor of development” domain (i.e., 61% versus 22%) is due to the fact that the AGREE Instrument is mostly applicable to evidence-based CPGs. In our assessment and according to the AGREE criteria, CB CPGs are also considered valid and may receive high scores, provided it is made explicit and transparent that authors searched for and appraised the literature, but due to the lack of suitable evidence a multidisciplinary expert team had to conceive its recommendations in a formal consensus process.

For CPG adapters, thorough documentation and reporting of such processes in source CPGs is particularly important as consensus is often influenced by local value judgements related to societal, cultural, organizational and economic aspects of care which are not directly transferable from one setting to another.

CPG validity depends not only on the rigor of its development but also on the quality of the underlying evidence base. Our literature review for high quality evidences confirmed the results of a recent study that evaluated the quantity and quality of research evidence in peer-reviewed burn care journals. We therefore conclude that burn care literature suffers from a shortage of high-quality evidence which explains why consensus based guidelines are in the majority.

There are many explanations for the lack of appropriately designed and executed trials in burn literature; patient population may grossly differ by age,

comorbidities, the extent of the injury, etc. Therefore recruiting the number of treated patients needed for a randomised controlled trial either takes a long period of time or needs a wide-scale international collaboration amongst burn centres. Because of the irreversibility of surgical treatments, randomisation can also cause ethical problems for surgeons when utilising new treatments which they have less knowledge of and/or trust in their efficacy. For the same reasons it is difficult to get patients' consent for taking part in a randomised trial. These problems do not only affect burn surgery, but in general the whole surgical field.

Nevertheless, well conducted CB guidelines proved to be valuable, especially in a field, where we are lacking a solid underlying evidence base. Good quality consensus based guidelines, which were developed with a rigorous methodology and by formal consensus techniques are worthy for adaptation.

Our study demonstrated that especially in areas where the evidence base is not particularly strong, guideline adaptation could be made more effective and explicit by following the modified ADAPTE process. The biggest advantage of this modification is that it maximizes the potential to address all tailored *a priori* questions and facilitates the objective appraisal, synthesis and comparison of the validity and consistency of the underlying evidence across various guidelines. This modified framework also assists in grading or re-grading the adapted recommendations. The strength of this process lies in its transparency and reproducibility.

Systematic overviews coupled with evidence from appropriately designed local studies can assist in making recommendations that can be applied to national practice even in areas where there is no international consensus or guidance to inform the guideline adaptation team.

Electrochemotherapy, which is a novel method in the treatment of the cutaneous metastases of malignant melanoma, was chosen as an example where clear recommendations for practice are still lacking and there are conflicting views on its effectiveness. Our example also demonstrates how to translate new knowledge into clinical practice and health decision making, which is one of the principal aims of EBM. Such systematic reviews compared to local experience on limited number of cases also help guideline teams to make informed and graded recommendations in a more objective and evidence-based fashion.

SUMMARY

- We have developed and pilot tested a contemporary, evidence-based guideline adaptation framework that meets international methodological standards and can be universally used in any medical field when international CPGs are adapted to local use in Hungary.
- We have developed prioritization criteria for defining key clinical topics and questions for guidelines. These criteria are primarily based on patient relevant clinical, organisational and economic outcome considerations, and help guideline teams in addressing high priority topics in guidelines with more rigorous and transparent evidence-based methodologies.
- We have modified the ADAPTE process to make guideline adaptation more effective and explicit. The modification maximizes the potential to address all tailored key questions and enables the objective comparison and efficient use of all published recommendations. It also provides a tool for a more transparent (re)grading of recommendations based on the quality of evidence and other pragmatic, value-based considerations.
- We have proposed and pilot tested systematic reviewing techniques coupled with local primary studies to help formulating recommendations when evidence is lacking or controversial.
- We have mapped that all high priority burn injury topics were covered by at least one CPG, but no single CPG addressed all areas. This highlights the need that guideline adaptation must be a systematic process and should not simply rely on adoption of any one preselected international CPG.
- We have shown that the majority of burn injury guidelines are consensus based and a large proportion of recommendations are based on lower levels of evidence or expert opinion. As an explanation we have found that burn care literature suffers from a shortage of high-quality evidence which is partly due to organisational and ethical barriers of performing large-scale randomised controlled trials.
- Whilst existing international CPGs for the management of burn injury may accurately reflect agreed clinical practice, most performed poorly when evaluated for methodological quality by the AGREE Instrument.
- The methodological shortcomings of burn injury CPGs are very similar to those in other medical fields.
- Critical appraisal of international burns CPGs revealed that the majority defined their scope and purpose well, but there were serious shortcomings in involving all relevant stakeholders in the guideline development process and in the rigour and editorial independence of the development of recommendations. Burn injury CPGs also failed the majority of the clinical

applicability criteria. These methodological shortcomings raise concerns about both the internal and the external validity of recommendations and therefore guideline adaptation teams must investigate the evidence or reasoning behind key recommendations before formulating and releasing local guidelines.

In conclusions, we make the following recommendations for the future:

- To improve the quality and validity of current guidelines systematic and explicit methods, based on the state-of-the art of guideline development and adaptation, are needed in burn care and any other medical fields.
- In Hungary guideline adaptation is a more pragmatic and cost-efficient approach and should adhere to a standardized framework, such as the one pilot tested in this study.
- All external CPGs should be critically evaluated for methodology and content before recommendations are adopted/adapted and endorsed for use in clinical practice.
- Guideline adaptation needs special skills and basic knowledge in evidence-based medicine and critical appraisal techniques, therefore training of guideline adapting teams should precede any such endeavours.
- Guideline adaptation should involve a close collaboration between all relevant stakeholders caring for the condition targeted by the recommendations.
- Guideline teams must disclose any potential conflicts of interest that might bias their judgment while formulating recommendations.
- Beyond the evidence the guideline adaptation team should consider the practical aspects and applicability of international recommendations, and diversions from the evidence or any other reasoning behind local recommendations should be documented explicitly and transparently.
- A standardised grading/re-grading system should be developed for adapting international recommendations in Hungary.

Future CPG efforts addressing these issues would add substantially to the improved management of burn injury and any other medical conditions in Hungary.

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