

UPDATE IN INTENSIVE CARE MEDICINE: NEWS IN RESUSCITATION

ILCOR 2010 recommendations. The evidence evaluation process in resuscitation

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Abstract The consensus document on the Science of Resuscitation and Emergency Cardiac Care with ILCOR Treatment Recommendations is an invaluable tool for quickly, simply and rigorously establishing the evidence on which the Resuscitation Guidelines 2010 are fundamented. We present a method that has been used in the review process according to evidence-based medicine, which can be considered a role model for both individual and collective use in clinical practice, not only in the field of resuscitation but also in other areas of medicine.

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PALABRAS CLAVE

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Recomendaciones ILCOR 2010. El proceso de evaluación de la evidencia en resucitación

Resumen El documento de Consenso sobre la Ciencia de la Resucitación y Cuidados Cardíacos de Emergencia con Recomendaciones de Tratamiento del ILCOR constituye una herramienta inestimable para conocer de una manera rápida, sencilla y rigurosa la evidencia en la que se basan las Guías de Resucitación 2010. Se presenta el método que se ha utilizado en el procedimiento de revisión según la medicina basada en la evidencia, que puede considerarse un modelo a seguir para la utilización tanto individual como colectiva en la práctica clínica no sólo en el campo de la resucitación, sino en otras áreas de la medicina.

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Introduction

On 18 October 2010 simultaneous online publication was made of the new American and European cardiopulmonary resuscitation (CPR) guides that serve to update those published in 2005, thus maintaining the cycle of change in the guidelines every 5 years.¹ The European guides

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were published on the website www.erc.edu and in the journal *Resuscitation*, while the American guides were published on the website www.circ.ahajournals.org and in the journal *Circulation* – these being the official publications of the European Resuscitation Council (ERC) and of the American Heart Association (AHA), respectively. From that moment the same sources also offer the International Consensus Document on the Science of Cardiopulmonary Resuscitation with Treatment Recommendations (CoSTR) 2010² of the ILCOR (International Liaison Committee on Resuscitation), which has been used by all the organizations in the world for the preparation of their guides.

The elaboration of the ILCOR Recommendation 2010 is in itself a fascinating process, considering the enormity of the effort made by hundreds of experts from all over the world, with a degree of international cooperation and global consensus never before seen in any other aspect of Medicine, and probably also not in any other area of human activity. Likewise, the methodology used for the search and evaluation of the evidence may serve as a model for advancing in the development and improved understanding of the current “Medicine based on evidence”. We therefore have considered it interesting to dedicate this first article on “News in Resuscitation” to reviewing the ILCOR and the evidence review and evaluation process that has taken body in the form of the Consensus Document on the Science of Cardiopulmonary Resuscitation with Treatment Recommendations (CoSTR) 2010.

How have we reached this point?

Modern cardiopulmonary resuscitation (CPR) has now completed its first 50 years of history. The original articles on rescue ventilation, chest compression and the effective combination of both,³⁻⁵ together with external defibrillation, established the bases for the elaboration of the first CPR training and practice guides. In 1966 the United States Medical Academy held a first conference to review the available evidence and recommend norms for the application of CPR techniques and Emergency Cardiac Care (ECC).⁶ The American Heart Association (AHA) supervised the subsequent conferences for the drafting of resuscitation standards in 1973 and 1979. At the same time, interest grew in similar organizations in other countries, inevitably leading to variations in training and in the application of techniques throughout the world. The growing awareness of this variability in resuscitation practice in turn generated interest in gathering experts from different countries with a view to establishing consensus in the field. With this aim in mind, in 1985 the AHA organized a meeting inviting CRP experts from many countries as observers for the elaboration of the Resuscitation and ECC Norms and Guides of 1986.⁷ At this conference it became clear that much could be learned and improved upon through international collaboration, though drafting of the guides continued to be supervised by experts in North America.

The change in decade witnessed the creation, development and consolidation of the European Resuscitation Council (ERC), the Australian Resuscitation Council (ARC), and the Resuscitation Council of South Africa (RCSA).

On occasion of the conference in Dallas in 1992, organized for the elaboration of the new CPR guides of the AHA, over 40% of the participants came from outside the United States. However, the ERC, in the same way as the rest of the recently created Councils, prepared and published its own Resuscitation Guide 1992 based on the evaluation of evidence by its own experts. At the mentioned conference, a panel on international cooperation underscored the need to promote Medicine based on evidence with a multinational character to serve as the basis for recommending practices in CPR. It was strongly recommended for a group of experts from all the organizations to carry out a systematic review of the world literature on CPR. Finally, after the first consensus conference for the elaboration of the first CPR guides of the ERC, the ILCOR was created on 22 November 1992 in Brighton (United Kingdom) with the mission of “providing a mechanism whereby science and the relevant knowledge for CPR and ECC (emergency cardiac care) can be internationally identified and reviewed. The ILCOR will periodically develop and publish a consensus document on the science of resuscitation. When this becomes possible, the ILCOR will publish treatment recommendations applicable to all the member organizations. This consensus mechanism can be applied by the member organizations to offer concordant resuscitation guides. The ILCOR will promote coordination of the development and publication of guides on the part of its member organizations. Although the greatest attention will center on the evaluation of the science of CPR and ECC, the ILCOR will also address topics such as effectiveness in training, and the approach to the organization and implementation of emergency cardiac care”.⁸ The founding member organizations of the ILCOR were the AHA (United States), the ERC (Europe), the HSFC (Canada), the RCSA (South Africa) and the ARC (Australia). Posteriorly, these organizations were followed by the incorporation of the Latin American Resuscitation Council (which now forms part of the Inter-American Heart Foundation [IHF], Central and South America), the New Zealand Resuscitation Council (which now forms part of the Australia and New Zealand Committee on Resuscitation [ANZCOR]), and the Resuscitation Council of Asia (RCA).

In the year 2000 the first major conference of the ILCOR was held for the definition of a single set of international guidelines, though after publication of the International Guides 2000,⁹ each member organization published its own guides, and the goal of establishing a single set of CPR guides has still not been reached. In general, consensus has been reached regarding the science of resuscitation, though local variations in treatment recommendations are inevitable as a result of epidemiological differences, the existence of different sanitary models, differences in implementation and cultural and economical factors. As an example, while medicalized ambulances supervised by physicians are common in Europe, in North America they are staffed by paramedics, etc. These variations are reflected in some differences in the local and national resuscitation guides. Undoubtedly, international cooperation has allowed more rigorous collection and analysis of the scientific evidence, though this has not always been followed by standardization of training and practice. The ILCOR methodology for the evaluation of evidence by experts from all over the world evolved during the elaboration of the

Consensus Conference 2005, and has been further refined with the elaboration of the latest Consensus Conference 2010 –the final document of which constitutes the basis of the recommendations of the different of member organization guides, including the Resuscitation Guides of the ERC 2010 and of the present article.²

Evidence review and evaluation process for the Consensus Document on the Science of CPR and ECC with Treatment Recommendations 2010¹⁰

Who does the review?

In starting the process, the ILCOR representatives established 6 working groups:

- Basic life support (BLS)
- Advanced life support (ALS)
- Acute coronary syndrome (ACS)
- Pediatric life support
- Neonatal life support
- Training, implementation and equipment (TIE)

Separate drafting groups were formed for the evaluation of evidence in topics related to defibrillation and airway devices, since these showed overlapping in both BLS and ALS

Each working group identified the topics requiring evaluation of the evidence, and invited international experts to review them. In order to secure a uniform and rigorous approach, a worksheet was drafted with step-by-step indications to help the experts to document their reviews of the literature, evaluate the studies, determine the levels of evidence (LOE) and develop the treatment recommendations.

Where possible, two expert reviewers were invited to conduct independent evaluations of each topic or subject. The authors of the worksheets submitted their search strategies to one of three experts in the reviewing of worksheets. The director of the experts in the evaluation of evidence also examined all the worksheets and helped their authors to ensure coherence and quality in evaluation of the evidence.

The evidence evaluation process from 2007 to 2009 initially included 569 worksheets with 509 authors. Some worksheets were finally merged with others, while in other cases no new evidence was forthcoming and the corresponding worksheets/ topics were eliminated. At the end of the process, a total of 313 experts from 30 countries participated in the International Consensus Conference held in February 2010. A total of 277 specific resuscitation worksheets were considered, corresponding to 356 authors who examined thousands of relevant publications. Many of these worksheets were presented and discussed monthly or every two weeks in the context of internet seminars of the different working groups.

In early May 2009 the ILCOR website (www.ilcor.org) posted the worksheets with the updated reviews and partial summaries of the evaluation of the evidence with the conflicts

Table 1 Review of the evidence relating to therapeutic hypothermia

| |
|---|
| Population / patient: In patients after cardiorespiratory arrest (CPA) with spontaneous circulatory recovery (SCR)... |
| Intervention: ...therapeutic hypothermia... |
| Comparison: ...compared with usual treatment ... |
| Objective: ...improves mortality or morbidity? |

of interest of the authors –inviting the public to comment on them. All people submitting comments were asked to issue their own statement on conflicts of interest.

Lastly, at the Consensus Conference held in February 2010 in Dallas, discussion and final adjustment of the worksheets was carried out by their authors and the corresponding working group, drafting the manuscript approved by the ILCOR member organizations and an international editorial board –with final publication in the journals *Circulation* and *Resuscitation*.

What questions have been reviewed and how have they been formulated?

The questions or issues to be reviewed were postulated from the priorities identified by the working groups, the organization and individual recommendations, with an analysis of deficiencies in research and a rigorous systematic approach referred to as the “mapping of evidence” based on the previous guides (<http://www.evidencemap.org/about>).⁸ It was admitted that not all the issues could be incorporated, and consequently some topics were not reviewed and thus remain as subjects lacking supporting or refuting evidence.

Before starting a search of evidence, it is important to clearly define the issue to be reviewed in each worksheet. A standardized structured format was used, called PICO (population / patient, intervention, comparison, objective) (<http://www.cebm.net/?o=1036>).² Table 1 provides an example of how the issue of the usefulness of therapeutic hypothermia was addressed.

What was the search strategy?

The experts in the evaluation of evidence supplied the authors of the worksheets with generic instructions on the types of search strategies and the databases to be searched, followed by review from each of the coordinators of the working groups and resubmission with suggestions and comments to the authors. The latter were required to conduct the searches at least in multiple databases, including the Cochrane library for systematic reviews and the Central Register of Controlled Trials (<http://www.cochrane.org/>), MEDLINE (<http://www.ncbi.nlm.nih.gov/pubmed/>), EMBASE (www.embase.com) and the master EndNote reference library compiled by the American Heart Association (AHA). Moreover, additional search strategies were adopted for the inclusion of articles not identified by the previous searches.

The authors of the worksheets selected studies for ulterior review based on a series of pre-established inclusion and

Table 2 Levels of evidence (LOE) for the recommendations of 2005

| |
|--|
| LOE 1: Randomized clinical studies or metaanalyses of multiple clinical trials with substantial effects on treatment |
| LOE 2: Randomized clinical studies with less or less significant effects on treatment |
| LOE 3: Non-randomized, controlled, prospective cohort studies |
| LOE 4: Non-randomized historical cohort or case / control studies |
| LOE 5: Case series; patients enrolled in serial manner, without a control group |
| LOE 6: Studies in animals or using mechanical models |
| LOE 7: Extrapolation of existing data collected for other purposes, theoretical analyses |
| LOE 8: Rational postulates (common sense); accepted common practices before the guides based on evidence |

exclusion criteria, and levels of evidence were assigned according to their relevance.

Assignment of levels of evidence (LOE)

In drafting the Consensus Document on the Science of CPR and ECC with Treatment Recommendations (CoSTR) of the year 2005, use was made of a classification with 8 levels of evidence, as shown in Table 2.

For elaboration of the CoSTR 2010, upon which the current guides are based, and following a review of the available literature on the classification of evidence, a simplified list of 5 levels of evidence (LOE) was created, adopting a series of assignment principles for the studies related to treatment interventions based on the probability of bias suppression in the control group, following the algorithm shown in Figure 1.

The 5 levels of evidence were differentiated in reference to treatment intervention studies, prognostic studies, and studies on diagnostic tests (Table 3).

Assignment of levels of quality (good, regular or poor)

In addition to the level of evidence, a process was developed to assign a level of methodological quality (good, regular or poor) to each study, according to greater or lesser compliance with a list of specific quality factors applied to the different LOE in relation to treatment interventions studies (LOE 1, LOE 2, LOE 3, LOE 4 and LOE 5), studies of diagnostic procedures (LOE D1, LOE D2, LOE D3, LOE D4, LOE D5) or studies of prognostic aspects (LOE P1, LOE P2, LOE P3, LOE P4, LOE P5).

For example, the 7 factors included as relevant quality items for randomized controlled trials (LOE 1) were the following:

- Was patient assignment to treatment randomized?
- Was hidden list randomization carried out?

Table 3 Levels of evidence (LOE) for the recommendations of 2010

C2010. Levels of evidence for treatment intervention studies

| |
|---|
| LOE 1: Randomized controlled trials (RCT) (or metaanalyses of RCT) |
| LOE 2: Studies using concurrent controls without true randomization (e.g., “pseudo-randomization”) |
| LOE 3: Studies with retrospective controls |
| LOE 4: Studies without a control group (e.g., case series) |
| LOE 5: Studies not directly related to the specific patient / population (e.g., different patient / population, animal models, mechanical models, etc.) |

C2010. Levels of evidence for prognostic studies

| |
|--|
| LOE P1: Prospective cohort studies (or metaanalyses of prospective cohort studies) or clinical decision rule validation (CDR) |
| LOE P2: Follow-up of untreated control groups in RCT (or metaanalyses of follow-up studies) or derivation of CDR or validated only in a split sample |
| LOE P3: Retrospective cohort studies |
| LOE P4: Case series |
| LOE P5: Studies not directly related to the specific patient / population (e.g., different patient / population, animal models, mechanical models, etc.) |

C2010. Levels of evidence for diagnostic studies

| |
|--|
| LOE D1: Validation studies with cohorts (or metaanalyses of validation studies with cohorts) or clinical decision rule validation (CDR) |
| LOE D2: Exploratory cohort studies (or metaanalyses of follow-up studies) or derivation of CDR or validated only in a split sample |
| LOE D3: Case-control diagnostic studies |
| LOE D4: Studies of diagnostic results (without reference standard) |
| LOE D5: Studies not directly related to the specific patient / population (e.g., different patient / population, animal models, mechanical models, etc.) |

- Were all the patients that entered the trial evaluated upon its conclusion?
- Were all the patients analyzed in the group to which they were randomized?
- Were the patients and physicians blinded to the treatment received?
- Apart from the experimental treatment, were the groups treated equally?
- Were the groups similar at the start of the trial?

If the studies complied with all or almost all the items, they were classified as having good quality. If a good number of the items were met, quality was considered regular, and if few of them were met the study was taken to have poor quality (though of sufficient value for inclusion in an ulterior review).

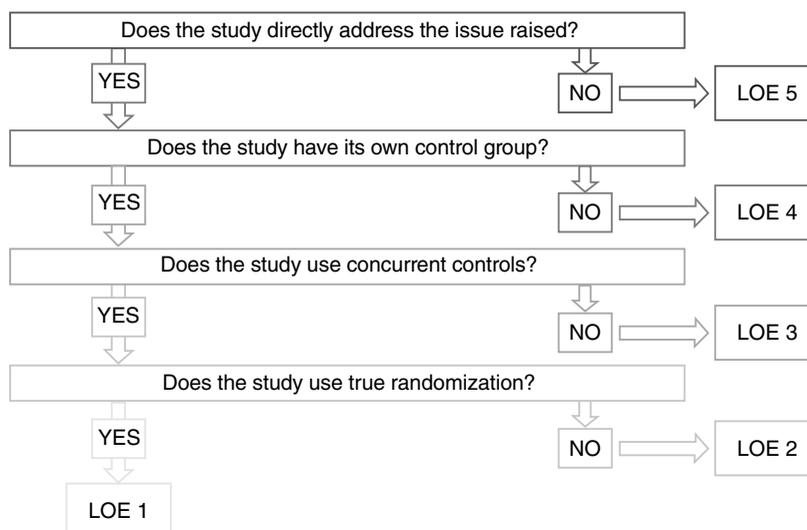


Figure 1 Algorithm used to assign LOE for the treatment intervention studies.

The four factors included as relevant quality items for prognostic studies (LOE P1, LOE P2 and LOE P3) were the following:

- Were the comparator groups clearly defined?
- Were the results measured in the same objective manner (preferably on a blind basis) in both groups?
- Were the known biases identified and adequately controlled?
- Was patient follow-up sufficiently prolonged and complete?

If the studies complied with all the items, they were classified as having good quality. Compliance with three items indicated regular quality, and compliance with only two items was indicative of poor quality. If a study complied with only one item, it was considered to be of insufficient quality for inclusion in the next review step.

The three factors included as relevant quality items for diagnostic studies (LOE D1, LOE D2 and LOE D3) were the following:

- Was the diagnostic test evaluated in an adequate population of patients (e.g., in those in which the test would be used in practice)? (minimizing population bias).
- Was there independent and blinded comparison with a reference standard (“diagnostic standard”)? (minimizing review bias).
- Was the reference standard applied regardless of the result? (minimizing verification bias).

If the studies complied with all the items, they were classified as having good quality. Compliance with two items indicated regular quality, and compliance with only one item was indicative of insufficient quality for inclusion in the next review step.

Tabulation of evidence in the worksheets

All the studies identified and evaluated for a concrete topic were reflected in standardized evidence tables that summarized the evidence found in relation to the topic addressed. Three tables were used:

- One reflecting all the studies meriting evaluation and which supported the topic addressed.
- Another table reflecting all the studies meriting evaluation and which were neutral in relation to the topic addressed.
- A third table reflecting all the studies meriting evaluation and which constituted evidence against the topic addressed.

Each of these tables clearly reflected the level of evidence (LOE), the methodological quality and the most relevant characteristics. As an example, Table 1 shows the table reflecting those studies offering evidence in support of therapeutic hypothermia in application to post-arrest syndrome.

The worksheet in Table 4 in turn shows the final comments of the reviewers, and evaluation of the evidence, and commented literature references to the reviewed articles.

Policy of conflicts of interest in the elaboration of the Consensus Document on the Science of Resuscitation and ECC with Treatment Recommendations (CoSTR) 2010

In the same way as in the elaboration of CoSTR 2005, the conflicts of interest (COI) policy during the development of the current recommendations has been rigorous and

Table 4 Example of the tabulation of the evidence supporting therapeutic hypothermia in a worksheet

| Summary of the evidence. Evidence supporting the clinical issue | | | | | |
|---|---|-----------------|---|---|---|
| Good | Arrich 2009 CD ^a Hypothermia After Cardiac Arrest Study Group, 2002 CD ^b Tainen, 2003 E ^b | | Bernard, 1997 C, D | Hovdenes, 2007 CD Wolff, 2009 DE | |
| Regular | Holzer, 2005 CD ^a | | Knafelj, 2007 CD Busch, 2006 C Belliard, 2007 CD Oddo, 2006 D Sunde, 2007 CD Storm, 2008 CDE Don, 2009 CD Bro-Jeppesen, 2009 D | Nielsen, 2009 CD Oksanen, 2007 C Sagalyn, 2009 ^a | |
| Poor | Hachimi-Idrissi, 2001 E Cheung, 2006 C | Arrich, 2007 CD | Castrejon, 2009 D | Williams, 1958 D | |
| Level of evidence | 1 | 2 | 3 | 4 | 5 |

A: recovery of spontaneous circulation; B: survival of the event; C: survival at hospital discharge; D: neurologically intact survival; E: other objectives.
^aMetaanalysis.
^bOverlapping patients.

transparent throughout –all participants, i.e., the authors of the worksheets, the members of the working groups, the participants in the Dallas 2010 meeting, and even the public contributing comments online during the process, being required to present their own COI declaration. A confidential telephone number was even habilitated to allow anonymous commenting of any potentially “forgotten” COI on the part of some participant. It should be noted that at no time during the process was any call received via this telephone “hotline”.

For a detailed description of the protocol used, and which may be taken to constitute a model for other works, the reader is referred to the original document of the ILCOR.¹¹

How to use the Consensus Document on the Science of Resuscitation and ECC with Treatment Recommendations (CoSTR) 2010

The CoSTR document of the ILCOR, which can be downloaded from the websites mentioned at the start of this article, constitutes the recommendations source of all the resuscitation guides of the different councils and organizations worldwide that conform the ILCOR, such as the Guides of the ERC and of the AHA. Throughout the document many links can be found allowing immediate access to the specific worksheet on the subject being dealt with, and where all the evidence available on each particular topic can be examined in an easy and comprehensible manner. As an example, under the heading “Therapeutic

hypothermia”,¹² we find the link ALS-PA-044. Clicking upon it with the left button immediately opens the webpage with the worksheet on this topic, and in a matter of minutes we can know the evidence in favor, the evidence against, and the neutral evidence, with the level of evidence and methodological quality of the reviewed studies, the comments of the authors and, where applicable, the proposed recommendation. Furthermore, we can examine the commented literature references on all the articles evaluated.

In sum, the Consensus Document on the Science of Cardiopulmonary Resuscitation and Emergency Cardiac Care of the ILCOR is an invaluable tool allowing us to quickly, simply and rigorously identify the evidence on which the Resuscitation Guides throughout the world are based. The way in which the Medicine based on evidence approach has been used for the review procedure may be regarded as a model to be followed for both individual and collective application in clinical practice –not only in the field of resuscitation, but also in other areas of Medicine.

From here we wish to express our gratitude to the hundreds of experts who have dedicated so much time and effort to make the CoSTR 2010 and the Resuscitation Guides 2010 a reality. We are sure that this effort will result in the improved care of patients at risk or who have suffered cardiac arrest –with the consequent benefits in terms of mortality and quality of life. The best way to honor the work of the experts is to apply the new knowledge gained as soon as possible, avoiding as far as we can the known delays (possibly several years) between the publication of new guides and their actual application to clinical practice.

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