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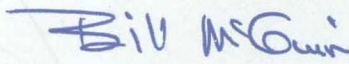

William W. McGuire, M.D.
United Health Foundation
www.unitedhealthfoundation.org

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SUMMER 2005

BMJ

clinical evidence concise

The international source of the best available evidence for effective health care

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The BMJ Publishing Group values the ongoing support it has received from the global medical community for *Clinical Evidence*. We are grateful to the clinicians and patients who have taken part in focus groups, which are crucial to the development of *Clinical Evidence*. Finally, we would like to acknowledge the readers who have taken the time to send us their comments and suggestions.

The BMJ Publishing Group wishes to thank United Health Foundation for its efforts in providing educational funding which has allowed the wide dissemination of this valuable resource to millions of physicians and health professionals in the USA.

United Health Foundation

9900 Bren Road East
Minnetonka MN 55343

June, 2005

Dear Colleague,

On behalf of United Health Foundation, it is my pleasure to provide you with the thirteenth edition of the BMJ Publishing Group's publication *Clinical Evidence Concise*. We remain committed to providing clinicians with each new update of this international source of the best available evidence for effective health care. It is our opinion that physicians should be supported in their best efforts to provide quality, safe and appropriate health care to their patients. From the many letters we receive from physicians across the nation, we know that *Clinical Evidence* is effective, not only in improving patient care, but also in enhancing patient-physician relationships and facilitating medical education.

As enthusiastic as we are about this thirteenth print version of *Clinical Evidence,* we are equally pleased to provide you with free access to the Internet version which is available at **www.clinicalevidence.com/uhf**. This website provides you with useful augmentations to the print version such as an efficient search tool, complete references, and monthly topic updates.

As a reader of *Clinical Evidence,* you demonstrate your commitment to the values of continuing professional development. On behalf of all of us at United Health Foundation, we thank you for your efforts to provide the best possible health care to all of your patients.

Sincerely,

William W. McGuire, M.D.
Chairman
United Health Foundation

Welcome to Issue 13

Welcome to Issue 13 of *Clinical Evidence*, the international source of the best available evidence on the effects of common clinical interventions. *Clinical Evidence* summarises the current state of knowledge and uncertainty about the prevention and treatment of clinical conditions, based on thorough searches and appraisal of the literature. It is neither a text book of medicine, nor a set of guidelines. It describes the best available evidence from systematic reviews, RCTs, and observational studies where appropriate, and if there is no good evidence it says so.

DEALING WITH UNCERTAINTY

Clinical Evidence and its sister product for patients, Best Treatments, aim to help people make informed decisions about which treatments to use. For clinicians and patients we wish to highlight treatments that work and for which the benefits outweigh the harms, especially those treatments that may currently be underused. We also wish to highlight treatments that do not work or for which the harms outweigh the benefits. Crucially, *Clinical Evidence* and Best Treatments can help people to distinguish between uncertainty due to gaps in the evidence or due to gaps in their own knowledge.

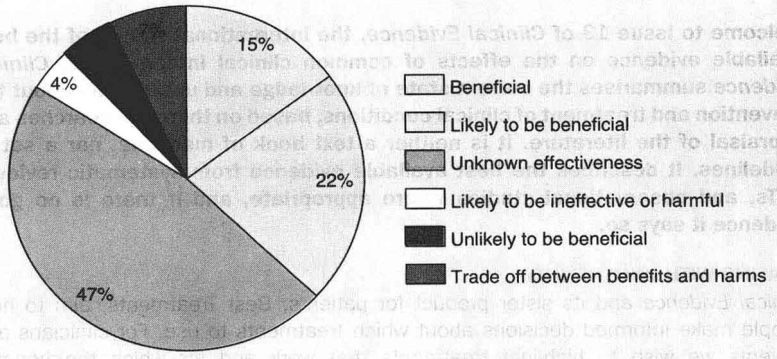
For the research community, *Clinical Evidence* and Best Treatments show where more research is needed—where there are currently no good RCTs or no RCTs that look at certain groups of people or important patient outcomes. We are pleased to be working closely with the James Lind Alliance, which is establishing partnerships between patients and clinicians to identify and prioritise current uncertainties about the effects of treatments. One important product of this initiative will be the free access Database of Uncertainties about the Effects of Treatments (DUET).

HOW MUCH DO WE KNOW?

So what can *Clinical Evidence* tell us about the state of our current knowledge? What proportion of commonly used treatments are supported by good evidence, what proportion should not be used or used only with caution, and how big are the gaps in our knowledge? Of the 2404 treatments covered in this issue, 360 (15%) are rated as beneficial, 538 (22%) likely to be beneficial, 180 (7%) as trade off between benefits and harms, 115 (5%) unlikely to be beneficial, 89 (4%) likely to be ineffective or harmful, and 1122 (47%), the largest proportion, as unknown effectiveness (see figure 1). Dividing treatments into categories is never easy. It always involves a degree of subjective judgement and is sometimes controversial. We do it because users tell us it is helpful, but judged by its own rules the categorisation is certainly of unknown effectiveness and may well have trade offs between benefits and harms. However, the figures above suggest that the research community has a large task ahead and that most decisions about treatments still rest on the individual judgements of clinicians and patients.

WHAT'S NEW

Clinical Evidence is continuously updated, with full literature searches on each topic every 12 months. Print copies containing the latest version of each topic are published every six months, and the website is refreshed, with new and updated content, every month. Before each topic is updated, we thoroughly review the structure of the topic, including the questions and the treatments covered, with the help of our expert authors and advisors in the field, to ensure maximum clinical relevance.



The content of *Clinical Evidence* Issue 13 is a snapshot of all content that was ready for publication in February 2005. Ten new topics have been added since Issue 12: Common cold, Angina (stable), Acne, Cervical cancer, Carbon monoxide poisoning, Non-Hodgkin's lymphoma, Glycaemic control in type 1 diabetes, End stage renal disease, Uncomplicated malaria and Kidney stones. In addition, 67 chapters have been updated, and by the time this reaches you more new and updated topics will have been posted on the website (www.clinicalevidence.com).

The regular updating of *Clinical Evidence* is now supplemented by BMJ Updates (www.bmjupdates.com), which provides readable summaries of the best and most relevant clinical research articles as they are published. You can ask the service to alert you to valid research in the areas that most interest you. BMJ Updates is a collaboration between the BMJ Publishing Group and McMaster University and can be accessed free via the *Clinical Evidence* website.

INTERNATIONAL REACH

Clinical Evidence has an international circulation, reaching more than a million clinicians worldwide in seven languages. In the USA, 500 000 clinicians receive copies of the concise edition thanks to the United Health Foundation. In the UK, the National Health Service distributes 50 000 copies of the concise edition to clinical staff in England, with free online access to everyone in England and Wales, and the BMA sends the concise edition to 10 500 UK medical students once a year. The governments of Norway and New Zealand now provide everyone in their countries with free online access, and thanks to the Italian Ministry of Health and the work of the Italian Cochrane Centre, 300 000 doctors in Italy receive a copy of the concise edition in Italian.

Clinical Evidence is available in other non-English language editions. The Spanish translation (published in collaboration with the Iberoamerican Cochrane Centre and Legis) now comes in all formats: full, concise and online. The full text is available in Japanese and Russian (seven broad speciality editions). The concise edition is also available in German and French.

Finally, *Clinical Evidence* continues to be available free online to people in developing countries as part of the HINARI initiative spearheaded by the World Health Organization and the BMJ Publishing Group. Details of those countries that qualify are available from the *Clinical Evidence* website (www.clinicalevidence.com).

FEEDBACK

Our web-site aims to encourage feedback, all of which we welcome. You can contact us at CEfeedback@bmjgroup.com, or use the Contact Us button on every page, or contact the editor on +44 (0)20 7383 6043. We are particularly interested to capture the clinical questions that first led you to use *Clinical Evidence* and to what extent your question was answered. If you have any comments on any of the material in *Clinical Evidence*, think that any important evidence has been missed, or have suggestions for new topics or questions please let us know.

Readers who would like to contribute either as authors or peer reviewers are also invited to send their CV to mmcneely@bmjgroup.com.

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A guide to Clinical Evidence Concise

SUMMARY PAGE

Clinical Evidence Concise is an index of the summary information from each chapter in *Clinical Evidence* Issue 13. It contains evidence relating to hundreds of therapeutic or preventative interventions, derived from thousands of original studies, and presents it in around 600 pages. For each condition, interventions are categorised according to whether they have been found to be effective or not. The full evidence detail behind these summaries, including clinical questions, figures, tables, and appendices, are featured online at www.clinicalevidence.com, along with quantified, referenced, and up to date information about each condition. The full evidence is also available by subscription to our full text paper version.

Making summaries involves discarding detail, and users of *Clinical Evidence Concise* need to be aware of the limitations of the evidence that is presented. It is not possible to make global statements that are both useful and apply to every patient or clinical context that occur in practice. For example, when stating that we found evidence that a drug is beneficial, we mean that there is evidence that the drug has been shown to deliver more benefits than harms when assessed in at least one subgroup of people, using at least one outcome at a particular point in time. It does not mean that the drug will be effective in all people given that treatment or that other outcomes will be improved, or even that the same outcome will be improved at a different time after the treatment.

MEASURE OF TREATMENT EFFECTS

The dilemma is how to present summaries that are useful but not misleading. We have experimented with providing statements with no numerical information at all, with NNTs only, with a batch of absolute and relative risks, or with just the odds ratio. Each measure has its advantages and disadvantages, and not all are available from the included studies. Quantitative results may be misleading in the absence of discussion of their precision, reliability, and applicability. In *Clinical Evidence Concise*, we present non-numerical information only. Detailed quantitative results are presented online, where we are able to discuss their interpretation in more detail. Your suggestions on improvements are welcome.

USING *CLINICAL EVIDENCE CONCISE* ONLINE

Clinical Evidence Concise is intended to be used as a first point of call when trying to decide what the options for treatment might be. A detailed exploration of the evidence will require looking up the detail in the full print version, or on *Clinical Evidence* online. The electronic versions link, whenever possible, to abstracts of the original research in PubMed or published online versions. In this way, *Clinical Evidence* is also designed to act as a pointer, connecting the clinician rapidly to the relevant original evidence.

INDEX PAGE

Each topic online contains an index page listing interventions within their assigned categories of whether they have been found to be effective or not. Key messages summarising the evidence for each intervention are listed below the categorisation table. The full evidence detail supporting the categorisation, consisting of the question, a summary statement, benefits, harms, and a comment can be accessed by a hyperlink from the categorisation table. We would value your feedback on the presentation of interventions in future issues.

CATEGORISATION

We have developed these categories of effectiveness from one of the Cochrane Collaboration's first and most popular products, *A guide to effective care in pregnancy and childbirth*.[1] The categories are explained in the table below.

TABLE **Categorisation of treatment effects in *Clinical Evidence***

Beneficial	Interventions for which effectiveness has been demonstrated by clear evidence from RCTs, and for which expectation of harms is small compared with the benefits.
Likely to be beneficial	Interventions for which effectiveness is less well established than for those listed under 'beneficial'.
Trade off between benefits and harms	Interventions for which clinicians and patients should weigh up the beneficial and harmful effects according to individual circumstances and priorities.
Unknown effectiveness	Interventions for which there are currently insufficient data or data of inadequate quality.
Unlikely to be beneficial	Interventions for which lack of effectiveness is less well established than for those listed under 'likely to be ineffective or harmful'.
Likely to be ineffective or harmful	Interventions for which ineffectiveness or harmfulness has been demonstrated by clear evidence.

Fitting interventions into these categories is not always straightforward. For one thing, the categories represent a mix of several hierarchies: the level of benefit (or harm), the level of evidence (RCT or observational data), and the level of certainty around the finding (represented by the confidence interval). Another problem is that much of the evidence that is most relevant to clinical decisions relates to comparisons between different interventions rather than to comparison with placebo or no intervention. Where necessary, we have indicated the comparisons. A third problem is that interventions may have been tested, or found to be effective, in only one group of people, such as those at high risk of an outcome. Again, we have indicated this where possible. But perhaps most difficult of all has been trying to maintain consistency across different topics. We are working on refining the criteria for putting interventions under each category.

REFERENCES

Full references to the individual studies cited in *Clinical Evidence Concise* are available online. References cited in the definition, incidence/prevalence, aetiology/risk factors, and prognosis sections are listed in the text but are available as hyperlinks from the equivalent section online.

TOPIC GLOSSARY

Topics may contain glossary listings; these are available in full online and can be accessed from the hyperlinks within the topic.

MAIN GLOSSARY

Words and terms that are used throughout *Clinical Evidence* are listed in the main glossary online.

TABLES AND FIGURES

The presence of figures and tables online are flagged up in a similar way to the glossary with the use of Ⓕ for figures and Ⓣ for tables.

FEEDBACK

The design of *Clinical Evidence Concise* will change progressively over the next few years. We will perform evaluation studies ourselves to measure the relevance of the material to the questions that are being asked in practice, the ease of use, and to check that the message extracted from the summary corresponds closely with that intended. If you have any comments, suggestions, or detect any errors, please let us know at CEfeedback@bmjgroup.com.

For more information on any of our products or processes, please visit our website at www.clinicalevidence.com.

REFERENCES

1. Enkin M, Keirse M, Renfrew M, et al. *A guide to effective care in pregnancy and childbirth*. Oxford: Oxford University Press, 1998.

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A Guide to *Clinical Evidence Concise*

Some topics listed here are not printed in this issue but are available on the website while awaiting update (www.clinicalevidence.com).

Non-Hodgkin's lymphoma (diffuse large B cell lymphoma)

Search date February 2004

Ellen Roxane Copson

What are the effects of first line treatments for aggressive non-Hodgkin's lymphoma (diffuse large B cell lymphoma)? New

BENEFICIAL

CHOP 21* New

CHOP 21 is the standard treatment for aggressive non-Hodgkin's lymphoma (not including Burkitt's lymphoma) and placebo or no treatment controlled trials would be considered unethical. Six RCTs identified by two systematic reviews found that no alternative regimen (MACOP-B, m-BACOD, ProMACE-CytaBOM, or PACEBOM) was shown to be consistently superior to CHOP 21 in terms of overall survival. Toxicity was generally similar with the different regimens.

LIKELY TO BE BENEFICIAL

CHOP 14 New

We found one RCT comparing CHOP 21 with CHOP 14 in people aged 18–60 years with good prognosis aggressive lymphoma and a second RCT comparing CHOP 21 with CHOP 14 in people aged 61–75 years with aggressive lymphoma. The RCT in younger people found no significant difference between CHOP 14 and CHOP 21 in complete response rates or 5 year event free survival. However, overall 5 year survival was higher with CHOP 14. The RCT in older people found that CHOP 14 improved complete response rate, 5 year event free survival, and overall survival compared with CHOP 21. Toxicity was similar with CHOP 14 and CHOP 21 in both studies.

CHOP 21 plus rituximab (increased survival compared with CHOP 21 alone) New

One RCT found that in people aged 60–80 years with stage II–IV disease, CHOP 21 plus rituximab reduced events and death compared with CHOP 21 alone at 2 years.

Short schedule CHOP 21 plus adjuvant radiotherapy (increased survival compared with longer schedule CHOP 21 alone) New

One RCT found that short schedule CHOP 21 plus adjuvant radiotherapy improved 5 year progression free survival and overall survival compared with longer schedule CHOP 21 alone. Longer schedule CHOP 21 alone increased the risk of congestive heart failure, and slightly increased the risk of myelosuppression, although this increase was not significant.

Non-Hodgkin's lymphoma (diffuse large B cell lymphoma)

What are the effects of treatments for relapsed aggressive non-Hodgkin's lymphoma (diffuse large B cell lymphoma)? New

LIKELY TO BE BENEFICIAL

Conventional dose salvage chemotherapy (consensus that treatment should be given but relative benefits of different regimens unclear)* New

We found no RCTs comparing different conventional dose salvage chemotherapy regimens (PACEBOM, ESHAP, RICE, IVAC) in people with relapsed aggressive non-Hodgkin's lymphoma. Consensus is that people with relapsed disease should be treated with salvage chemotherapy. One systematic review identified 22 phase II trials of various conventional dose salvage chemotherapy regimens. All regimens reported similar response rates and no single superior regimen could be identified.

High dose chemotherapy plus autologous transplant stem cell support (increased survival compared with conventional dose chemotherapy in people with chemosensitive disease) New

One systematic review identified one RCT comparing high dose chemotherapy plus autologous bone marrow transplantation with conventional dose chemotherapy in people with a chemosensitive relapse of aggressive non-Hodgkin's lymphoma. It found that high dose chemotherapy plus autologous bone marrow transplantation improved 5 year event free survival and overall survival compared with conventional chemotherapy. We found no RCTs in people in people with chemotherapy resistant disease.

*Based on consensus.

DEFINITION Non-Hodgkin's lymphoma (NHL) consists of a complex group of cancers arising mainly from B lymphocytes (85% of cases) and occasionally from T lymphocytes. NHL usually develops in lymph nodes (nodal lymphoma) but can arise in other tissues almost anywhere in the body (extranodal lymphoma). NHL is categorised according to its appearance under the microscope (histology) and the extent of the disease (stage). **Histology:** Since 1966, four major different methods of classifying NHLs according to their histological appearance have been published (see table 1)T;see table 2T;see table 3T;see table 4)T. At present, the World Health Organization (WHO)[1] system is accepted as the gold standard of classification. The WHO system is based on the underlying principles of the REAL classification system.[2] Historically, NHLs have been divided into slow growing "low grade" lymphomas and fast growing "aggressive" lymphomas. This chapter deals only with the most common aggressive NHL – diffuse B cell lymphoma (WHO classification; see table 1T). Interpretation of older studies is complicated by the fact that histological methods have changed and there is no direct correlation between lymphoma types in the WHO and other classification systems. Attempts to generalise results must therefore be treated with caution. We have however included some older studies referring to alternative classification methods if they included people with the following types of aggressive lymphomas, which overlap substantially with the WHO classification of interest: Working Formulation Classification – primarily intermediate grades (grades E–H; see table 2T);[3] Kiel classification – centroblastic, Immunoblastic, and anaplastic (see table 3T)[4] Rappaport classification – diffuse histiocytic, diffuse lymphocytic poorly differentiated, and diffuse mixed (lymphocytic and histiocytic; see table 4T).[5] **Stage:** NHL has traditionally been staged according to extent of disease spread using the Ann Arbor system (see table 5T).[6] The term "early disease" is used to describe disease that falls within Ann Arbor stage I or II while "advanced disease" refers to Ann Arbor stage III or IV disease. However, all people with bulky disease, usually defined as having a disease site larger