THE CHBG NEWSLETTER

The Cochrane Hepato-Biliary Group (CHBG)

Volume 7 Issue 2 October 2003

THE COCHRANE COLLABORATION®

Preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health-care interventions.

UPDATE ON ACHIEVEMENTS CHBG REVIEWS AND PROTOCOLS ON THE CLIB ISSUE 3 AND 4, 2003

New reviews (continuation)
None.

New protocols (continuation)
80. Methotrexate for primary biliary cirrhosis. Yan Gong et al., Denmark
81. Bile acids for liver transplanted patients. Wendong Chen* et al., Canada
82. Bicyclol for chronic hepatitis B. Taixiang Wu et al., China
83. Colchicine for primary biliary cirrhosis. Yan Gong et al., Denmark
84. Prostaglandin E1 analogues for chronic hepatitis B. Ruihong Luo et al., China

EXPECTED PROTOCOLS AND REVIEWS ON THE CLIB ISSUE 1, 2004

Medicinal herbs for acute hepatitis B. Yunxia Liu et al., China (P)
Beta-blockers for prevention of esophageal variceal rebleeding in cirrhotic patients. Wendong Chen* et al., Canada (P)
Beta-blockers for cirrhotic patients with esophageal varices that have never bled. Wendong Chen* et al., Canada (P)
Medicinal herbs for cholelithiasis. Tao Gan et al., China (P)
Glucocorticosteroids for viral hepatitis C. Jesper Brok et al., Denmark (R)
Antioxidants for preventing gastrointestinal cancers. Goran Bjelakovic* et al., Serbia and Montenegro (R)
Artificial and bioartificial support systems for liver failure. Jianping Liu* et al., UK (R)

* The authors performed the protocols and the reviews during their stay at The CHBG Editorial Base in Copenhagen, Denmark.

NEW REGISTERED TITLES

151. Antibiotics for hepatic encephalopathy. Tao Pan et al., China
152. Antibiotic prophylaxis in laparoscopic cholecystectomy. Alvaro Sanabria et al., Columbia
153. Hepatocyte growth factor for viral hepatitis. Xiaohong Zhang et al., China
154. Insulin and glucagon for alcoholic liver disease. Mariam Azizmohammadi et al., Denmark
155. Needle aspiration with or without metronidazole for amebic liver abscess. Eternity Labio et al., The Phillipines
156. Needle aspiration versus catheter drainage for amebic liver abscess. Eternity Labio et al., The Phillipines
157. Elective surgery for benign liver tumours. Dario Conte et al., Italy
158. Human recombinant factor VIIa for upper gastrointestinal bleeding in patients with liver diseases. Arturo Marti-Carvajal et al., Venezuela
159. Vitamin K for upper gastrointestinal bleeding in patients with liver diseases. Arturo Marti-Carvajal et al., Venezuela
160. Ursodeoxycholic acid for autoimmune hepatitis. Lise Lotte Gluud et al., Denmark

PAST EVENTS

2003 EASL MEETING – SWITZERLAND

The CHBG had its 15th meeting in Geneva on 2 July. Around thirty people attended the meeting. The CHBG, sponsored by EASL, had a stand at the exhibition. The list of members increased with about fifty new members.

2003 ANNUAL SCIENTIFIC MEETING – NEW ZEALAND

The annual meeting took place in Queenstown from 3 to 5 September 2003. There, Christian Gluud talked on 'Methodological quality of randomised clinical trials in hepato-gastroenterology: good or bad?'

TRAIN THE TRAINERS – NEW ZEALAND

The educational workshop for educators organised by the world association OMGE /OMED (Organisation Mondiale D'Endoscopie Digestive) took place in Queenstown from 6 to 9 September 2003. Christian Gluud, Denmark and James Toouli, Australia (CHBG editors) were among the tutors. They presented lectures on evidence-based medicine, critical appraisal, The Cochrane Collaboration, and how to design a clinical trial.

CHBG EDITORS MEETING – DENMARK

Owing to unforeseen circumstances, the planned CHBG editors meeting for 20 September 2003 in Copenhagen had to be moved to the afternoon of 19 September. A meeting took place with the editors Rosa Simonetti - Italy, Ronald Koretz - USA, Bodil Als-Nielsen - Denmark and the Group Coordinators Dimitrinka Nikolova and Sarah Frederiksen. The items discussed were how to shorten the peer reviewing process and how to improve the communication between the editors and the editorial base. Bodil Als-Nielsen was introduced as a new editor of The CHBG, and the decision that all associate editors become editors with effect of 19 September 2003 was announced and agreed upon. Broadening the team of editors is necessitated by the fact that the number of reviews undergoing peer review is constantly increasing. Luigi Pagliaro withdrew as editor of The CHBG. Torben Jørgensen withdrew as editor of The CHBG by letter dated 16 September because of lack of time. Presently The CHBG editors are:
Christian Gluud, Denmark (coordinating and criticism editor); Bodil Als-Nielsen (new), Denmark; Gennaro D'Amico (new), Italy; Saboor A. Khan, UK; Lise Lotte Gluud (change of family name), Denmark; Ronald Koretz, USA; Jianping Liu, UK; Alberto Morabito, Italy; Robert Myers, Canada; Thierry Poynard, France; Rosa Simonetti, Italy; Robert Sutton, UK; James Toouli, Australia.

WORKSHOP ON COCHRANE EDITING – DENMARK

A two-days' workshop on editing took place in Copenhagen on 18 and 19 September 2003. Editorial staff and reviewers of three review groups with editorial bases in Copenhagen participated. Enhancing the quality of Cochrane protocols and reviews and the means to achieve high quality was the topic. The items that were discussed ensued from a random sample of protocols and reviews prepared by the three groups and published on The Cochrane Library. These items were readability of the abstract and the whole text of the protocol or review, quality assessment of trials and getting rid of quality scales; heterogeneity of studies and hence when to lump and when to split a clinical question; reporting of benefits as well as harms; presentation of 'no effect'; how to deal with clinical relevant outcomes and the size of the effect; how to define the primary and the secondary outcome measures; how to distinguish between adverse effects and adverse events; setting confidence interval a priori; choice of summery statistics; symmetry of conclusions; update of reviews. Other problems are poor grammar, and typing errors (figures included).
Each one of the participants went back home with three items that were to be improved during the next twelve months. For The Hepato-Biliary Group these items are easy to read and well structured abstracts; shorter and clearer backgrounds; sufficient and consecutive information presented in the tables of each of the included and excluded trials.

FUTURE EVENTS

XI COCHRANE COLLOQUIUM – SPAIN

26 October to 31 October, Barcelona
This year the colloquium is divided into two parts. The first part is addressed to those who are currently working actively with Cochrane entities and/or wish to understand more about the methodology of systematic reviews. There will be again training workshops. The second part starting 29 October is for those outside the Collaboration who are interested in learning and participating in the discussions on the application of scientific evidence. We find Cochrane colloquia a useful forum for reviewers and their participation is encouraged.

2003 AASLD MEETING – USA

24 October to 28 October, Boston, MA

The 16th Cochrane Hepato-Biliary Group biannual meeting during the AASLD meeting will be held Monday, October 27 from 6:30 pm to 8:30 pm. During the meeting reviews not yet published on The Cochrane Library will be presented. Advocates or opponents of evidence-based medicine are kindly invited. There is no registration fee for the meeting and participation is free. The program is sent out with the present newsletter.

2004 EASL MEETING – GERMANY

14 April to 18 April 2004, Berlin

There is already information for the EASL meeting at
http://www.easl.ch/easl2004/call.htm
The deadline for submission of abstracts is 16 November 2003. The date for the 17th Cochrane Hepato-Biliary Group biannual meeting is still not fixed.

2004 IASL MEETING – BRAZIL

16 March to 20 March 2004,
Salvador da Bahia

The biennial scientific meeting of the international association for study of the liver (IASL) will be held together with the Latin American Association for the Study of the Liver (ALEH). For information visit http://www.eventussystem.com.br/liver/mensagem.html

2004 DIGESTIVE DISEASE WEEK – USA

15 to 20 May 2004, New Orleans

Jointly sponsored by four societies; the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA), the American Society for Gastrointestinal Surgery (ASGE), and the Society for Surgery of the Alimentary Tract (SSAT), the Digestive Disease Week (DDW) takes place every May in cities throughout the US. The 2004 meeting will be held in New Orleans, LA. For information visit http://www.ddw.org/

For the first time the four gastrointestinal Cochrane Groups have been invited to hold a meeting. The 2004 AGA meeting will be organised by The Upper Gastrointestinal and Pancreatic Diseases Group.

SEARCH STRATEGIES IN COCHRANE REVIEWS

Recently, the RevMan Advisory Group agreed that additional tables should be used for reporting the search strategies in the text of Cochrane Reviews. The proposal has now been passed to editors of the Cochrane Reviewers' Handbook so that the Handbook can be revised accordingly.

The search strategies should be described in sufficient detail in the review that the process could be replicated. It was agreed that using a separate table for individual search strategies (e.g., one for MEDLINE, another for EMBASE, etc.) would be the best option. However, in

The Cochrane Hepato-Biliary Group we prefer to have all strategies in one table but in separate rows, that is, one row per database. We suggest that as a minimum the table include three columns: one with the name of the database to be searched or already searched, one with the time span of the search and one with the search strategy. More columns can be added if necessary. The RevMan Advisory Group also suggested that pasting the whole strategy into one cell would work well, whereas pasting a line per row was both tedious and prone to error. However, in some cases the search strategy is saved in an "illegible" (coded) format and cannot be pasted directly into the table. In these cases the strategy must be typed in manually.

In 'Search strategy for identification of studies' the searches that were performed should be described without entering the exact strategies. The order of the databases should be The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials on The Cochrane Library, MEDLINE, EMBASE, and others. The time span of the search should be entered after each database (e.g., MEDLINE (1966 to October 2003)). If other methods were used for identifying further trials, e.g., handsearching of journals or contacting authors and companies etc., these should be described as well.

The RevMan Advisory Group also agreed that the next major version of RevMan (version 5) should support the inclusion of Appendices for Cochrane reviews. These Appendices might be a better place for search strategies in the future.

WILEY - THE NEW PUBLISHER OF THE COCHRANE LIBRARY

Since April 2003, Wiley is the new publishing partner for The Cochrane Collaboration's publishing activities. Wiley will deliver The Cochrane Library through Wiley InterScience (www.interscience.wiley.com). Wiley will also continue to make the product available on CD-ROM.
Reviewers of published Cochrane reviews are entitled to a 25 per cent discount on all Wiley books. For 'author discount cards' or to find out more about this offer and to register please access http://www.wiley.com or http://www.wileyeurope.com/go/authordiscount

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TRANSLATORS

We would like to acknowledge and thank Boris Rübner, USA and Yan Gong, Denmark, for their contribution to the review process as translators.

PEER REVIEWERS

We would like to acknowledge and thank the peer reviewers who reviewed the now published protocols on The Cochrane Library Issue 3 and 4, 2003. Marshall Kaplan - USA, Jean-Pierre Pignon - France, Luigi Pagliaro - Italy, Rosa Simonetti – Italy, Saboor A. Khan - UK, James Neuberger - UK, David S

Barnes - USA, Henry Ly Chan - China, Jianping Liu - UK, Christian Gluud - Denmark, M Malaguarnera - Italy, Lise Lotte Gluud - Denmark, Wendong Chen - Canada, Robert Flisiak - Poland.

GLOSSARY OF METHODOLOGICAL TERMS

Systematic review
An approach to reviewing literature or a research field that attempts to reduce biases by taking a systematic, replicable approach to the identification, selection and assessment of studies and the presentation of their findings.
Example: A systematic review that assesses the efficacy of S-adenosyl-L-methionine versus placebo or no intervention in patients with alcoholic steatosis, hepatitis, fibrosis, and/or cirrhosis on mortality (total and liver related), clinical symptoms and complications, liver biochemistry, and liver histology.

Heterogeneity (statistical heterogeneity)
The situation in which treatment effects being estimated by individual studies in a systematic review are not identical. This will manifest itself in greater variability in the estimates than would be expected by chance alone.
Example: Relative risks underlying the individual trials in a systematic review may differ because the trials are undertaken in populations with different responses to the drug.
There was an important heterogeneity between the two studies (Chi-square = 3.73, P = 0.05), probably accounted for by the different definitions used for the need of the transfusion of one blood unit.

Fixed effect meta-analysis
A meta-analysis that assumes every study is estimating the same unknown treatment effect – that is, that the underlying treatment effects are identical.
Example: A fixed effect meta-analysis of clinical trials comparing anabolic-androgenic steroids with placebo might assume that there is a single, unknown relative risk that all studies are trying to evaluate.

Random effects meta-analyses
A meta-analysis that assumes, that studies are estimating different, but related, unknown treatment effects, with the differences between these represented by random variation.
Example: A random effects meta-analysis of clinical trials comparing amantadine with placebo might assume that the underlying log relative risks follow a normal distribution across the studies.

The glossary terms are taken from Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002:7;1(51-61). Some of the examples are adapted for hepato-biliary reviews.

ASSESSING STATISTICAL HETEROGENEITY: CHI^2 OR I^2?

A generally desirable attribute of a meta-analysis is that the results of the studies *agree*. This may be important irrespective of how clinically or methodologically diverse the studies are. For example, consistent results across studies in different populations, with different methodologies and with slight variations on the outcome definition can add considerable weight to the generalizability of the findings. In statistical terms, we define consistency across studies in terms of *homogeneity*. We say there is homogeneity of effect across studies if every study is estimating the same magnitude of effect (for example, a common odds ratio or a common standardized mean difference). Whenever homogeneity does not exist, we say there

is *heterogeneity*. This article concerns how we should assess heterogeneity in a particular meta-analysis.

The traditional test: Chi^2

Meta-analyses in Cochrane Reviews, RevMan or MetaView include a statistical test that aims to answer the question of whether studies have homogenous effects. This is displayed below a meta-analysis, for example as:

'Test for heterogeneity chi-squared = 12.44 df = 7 p = 0.09'

In this case the test produces a chi-squared value of 12.44 on 7 degrees of freedom (df), the latter obtained as the number of studies minus one. (In the example there were eight studies). The resulting P value is 0.09, which would not be deemed statistically significant using the conventional cut-off of 0.05.

Is this a useful test? A well-known problem with the test is that it typically has low power, meaning that it is unlikely to yield a statistically significant result when there is genuinely some heterogeneity of effect. This is because it is difficult to demonstrate variation across studies when there aren't many of them. Thus a non-significant test result should not be taken as evidence of homogeneity. A more fundamental problem, however, concerns the whole notion of testing for heterogeneity. Since systematic reviews inevitably bring together studies in different populations, in different settings, using different methods, with different outcome definitions (and the list goes on...), we might reasonably always expect heterogeneity of underlying effects to be present. In that case we should not be interested in determining *whether* heterogeneity is present, but instead should focus attention on how large it is and how much it impacts on the conclusions of the review.

The new addition in RevMan 4.2: I^2

RevMan 4.2 supplements the test for heterogeneity with a new quantity that describes the impact of heterogeneity on the meta-analysis. The quantity is called I^2, and it is displayed thus:

'Test for heterogeneity: $Chi^2 = 12.44$ $df = 7$ $(p = 0.09)$ $I^2 = 44\%$'

I^2 measures the degree of *inconsistency* across studies. It is calculated as follows:

$$100\% \times (Chi^2 - df)/Chi^2.$$

Its lowest possible value is 0%, and its highest is 100%. It may be interpreted approximately as the proportion of total variation in the observed results of the studies that may be explained by heterogeneity rather than chance variation. Thus, if $I^2 = 0\%$, then there is no apparent heterogeneity, whereas in the example $I^2 = 44\%$ so almost half of the variability in effect estimates was due to genuine variation in the underlying effects. In practice, I^2 will never reach 100%, but values in excess of 70% would usually inspire particular caution in interpreting a meta-analysis.

Some useful properties of I^2 are:

- I^2 may be bigger than zero even if the test result is not statistically significant.
- I^2 will be bigger than zero if, and only if, a random effects meta-analysis differs from a fixed effect meta-analysis.
- Larger values of I^2 indicate greater heterogeneity, and less easily generalized conclusions.

To read more about I^2, see:
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency is preferable to testing for heterogeneity in meta-analysis. *BMJ* 2003; 327: 557-60

or

consult the following more technical paper:

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002; **21**: 1539-58

Julian Higgins
Co-convenor
Statistical Methods Group

PUBLICATIONS

Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials. A reflection of treatment effects or adverse events? *JAMA* 2003;290:921-8.

WORKSHOPS

Information about workshops is available from each centre site.

COCHRANE CENTRES

Australasian Cochrane Centre
http://www.cochrane.org.au
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Nordic Cochrane Centre
Cochrane information in Danish, details about the Nordic Centre and links to other Cochrane web sites.
http://www.cochrane.dk
South African Cochrane Centre
http://www.mrc.ac.za/cochrane/cochrane.htm
United States Cochrane Center
Information about the Cochrane Trials Register Development Group, handsearching of journals, and the staff of the United States Cochrane Center.
http://www.cochrane.us
United States Cochrane Center (San Francisco Branch)
http://www.ucsf.edu/sfcc/

The Cochrane Hepato-Biliary (CHBG) Newsletter is prepared, edited, and published in electronic and paper format by staff at the CHBG Editorial Base in Copenhagen, Denmark. It is issued twice a year and distributed free of charge by The CHBG worldwide to all people on The CHBG list who either have contributed, are contributing, or show interest in the work of the Group. The purpose is to inform CHBG members and other interested parties about activities within The CHBG and also to attract many more active members.

Editorial CHBG staff at the CHBG Editorial Base:
Christian Gluud, Co-ordinating & Criticism Editor, E-mail: cgluud@ctu.rh.dk; Dimitrinka Nikolova, Review Group Co-ordinator, E-mail: dnikolov@ctu.rh.dk; Sarah Louise Frederiksen, Trials Search Co-ordinator, E-mail: slf@ctu.rh.dk; Ninna Frydendal, Assistant, E-mail: ninna.f@ctu.rh.dk; Nader Salasshahri, IT advisor, E-mail: nader.s@ctu.rh.dk; Styrbjørn Birch, IT help and WEB master, E-mail: s.birch@ctu.rh.dk

Cochrane Hepato-Biliary Group,
Copenhagen Trial Unit,
Dept. 7102, H:S Rigshospitalet,
Blegdamsvej 9, DK-2100
Copenhagen Ø, Denmark,
Tel. +45 3545 7169 or + 45 3545 7175,
Fax +45 3545 7101,
E-mail: chbg@ctu.rh.dk
Website: http://inet.uni2.dk/~ctucph/chbg

The CHBG editors are: Christian Gluud, Denmark (coordinating and criticism editor); Bodil Als-Nielsen, Denmark; Lise Lotte Gluud, Denmark; Thierry Poynard, France; Alberto Morabito, Italy; Gennaro D'Amico, Italy; Rosa Simonetti, Italy; Jianping Liu, UK; Robert Sutton, UK; Saboor A. Khan, UK; Ronald Koretz, USA; Robert Myers, Canada; James Toouli, Australia.

PROGRAM
of

THE 16TH COCHRANE HEPATO-BILIARY GROUP BIANNUAL MEETING DURING THE 2003 AASLD MEETING BOSTON, MA, USA

Date: Monday, October 27, 2003
Time: 6:30 pm - 8:30 pm
Meeting room: Berkley
Meeting place: John B. Hynes Convention Center, Boston, Massachusetts, USA

Chairs: Christian Gluud and Ronald L. Koretz

6:30 pm – 6:35 pm	Welcome and presentation of the program.	Ronald L. Koretz
6:35 pm – 6:45 pm	The CHBG.	Christian Gluud
6:45 pm – 7:15 pm	Beta-blockers for primary and secondary prevention of esophageal variceal bleeding in cirrhotic patients. A Cochrane Systematic Review.	Wendong Chen, Dimitrinka Nikolova, Sarah Frederiksen, Christian Gluud
7:15 pm – 7:35 pm	Antioxidants for preventing gastrointestinal cancers. A Cochrane Systematic Review.	Goran Bjelakovic, Dimitrinka Nikolova, Rosa Simonetti, Christian Gluud
7:35 pm – 7:55 pm	Vasoactive drugs for hepatorenal syndrome. A Cochrane Systematic Review.	Mette S Kjaer, Annette Taastroem, Lise Lotte Gluud
7:55 pm – 8:15 pm	Immunsuppressive drugs for autoimmune hepatitis. A Cochrane Systematic Review	Eva Efsen, Lise Lotte Gluud, Mette Kjaer, Poul Schlichting
8:15 pm - 8:30 pm	Discussions and closing of the meeting	Ronald L. Koretz, Christian Gluud

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The Cochrane Hepato-Biliary Group (CHBG) meetings are run twice a year during the annual EASL and AASLD meetings.