



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

Clinical Pearls from The Cochrane Library

The Cochrane Collaboration, founded in 1993, is an international non-profit and independent organization, dedicated to making up-to-date, accurate information about the effects of healthcare interventions readily available worldwide. The Collaboration's main objectives are to conduct high quality systematic reviews of the effects of healthcare interventions and to publish them in The Cochrane Library. The Cochrane Library presently contains 2249 such reviews; the authors of these reviews are committed to updating them every 2 years. **Cochrane systematic reviews primarily summarize evidence from randomized controlled trials (RCTs).** The Cochrane Collaboration recognizes that many of its reviews can be improved, and thus encourages comments and criticisms. Submitted comments and criticisms may lead to improvements in the review and at the very least are published and appended to the review. **Cochrane systematic reviews have not only been demonstrated to be of comparable or better quality than systematic reviews published in paper journals, but they are more often updated.**¹

In this Letter we have chosen 5 Cochrane systematic reviews that provide clear clinical evidence to direct patient care.

Corticosteroids for acute traumatic brain injury

Originally published in 1997, the latest substantive update was completed in October 2004, and published in 2005 Issue 1.²

Findings: The update adds the recently published large CRASH RCT³ to the 17 existing RCTs and changes the conclusions. The CRASH trial randomized 10,008 adults within 8 hours of a head injury and with a Glasgow coma score of 14 or less to a 48 h infusion of methylprednisolone or placebo. Death from all causes within 2 weeks was higher in the steroid group, 21.1%, than the placebo group, 17.9%, RR 1.18 [1.09 – 1.27], ARI 3.2%, NNH 32 to cause 1 death.

Old conclusion: The conclusion before the update was based on a RR of death of 0.95 [0.84 – 1.07], and a RR of death or severe disability of 1.01 [0.91 – 1.11]; “Neither moderate benefits nor moderate harmful effects of steroids can be excluded.”



New conclusion: The updated conclusion is based entirely on the results of the large CRASH trial. **High dose corticosteroids for acute traumatic brain injury significantly increase short-term mortality.**

Clinical implications: “... steroids should no longer be routinely used in people with traumatic head injury.”²

Fixed dose subcutaneous low molecular weight heparins (LMWH) versus adjusted dose unfractionated heparin (UFH) for venous thromboembolism

Originally published in 1998, the latest substantive update was completed in August 2004 and published in 2004 Issue 4.⁴

Findings: In 22 RCTs of 8867 patients the following outcomes were reduced by LMWH as compared to UFH: thrombotic complications 3.6% versus 5.4%, RR 0.69 [0.56 – 0.85], ARR 1.8%, NNT 56, major hemorrhage 1.2% versus 2.0%, RR 0.58 [0.40 – 0.84], ARR 0.8%, NNT 125, and total mortality 4.5% versus 6.0%, RR 0.77 [0.64 – 0.93], ARR 1.5%, NNT 67.

Conclusions: “LMWH is more effective than UFH for the initial treatment of venous thromboembolism.”

Clinical implications: “LMWH treatment can safely be adopted as the standard therapy in people with deep venous thrombosis.”

RR – relative risk
ARR – absolute risk reduction
ARI – absolute risk increase
NNT – number needed to treat to prevent one event
NNH – number needed to treat to cause one harmful event



Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822•0700
Fax: 604 822•0701
E-mail: info@ti.ubc.ca
Web: www.ti.ubc.ca
(all Therapeutics Letters, Course Information)

Vaccines for preventing influenza in healthy adults

Originally published in 1999, the latest substantive update was completed in May 2004 and published in 2004 Issue 3.⁵

Findings: In 12 RCTs involving 12,145 people, the following outcomes were reduced by inactivated par-enteral vaccine as compared to placebo: clinically defined influenza cases RR 0.82 [0.77 – 0.87], ARR 6%, NNT 17; serologically confirmed influenza cases, RR 0.29 [0.20 – 0.44], ARR 6%, NNT 17; working days lost, weighted mean difference -0.12 [-0.24 – 0.00] days.

Conclusion: “The universal immunization of healthy adults should achieve a number of specific goals: reducing the spread of the disease, reducing the economic loss due to working days lost and reducing morbidity and hospitalization.” None of these goals have been demonstrated in the available RCT evidence.

Clinical implications: “Universal immunization of healthy adults is not supported by the results of this review.”

Antiplatelet agents and anticoagulants for hypertension

This review was completed in May 2004 and published in 2004 Issue 3.⁶

Findings: In 2 RCTs involving 20,128 people with elevated blood pressure, acetylsalicylic acid (ASA) as compared to placebo did not reduce total stroke, RR 0.94 [0.76 – 1.17] or total cardiovascular events, RR 0.92 [0.82 – 1.04] and increased major bleeds, RR 1.74 [1.32 – 2.30], ARI 0.6%, NNH 167 for 3.8 years. The ATC meta-analysis⁷ of a subgroup of patients with elevated blood pressure and established cardiovascular disease (secondary prevention) showed that ASA reduced major vascular events, ARR 4.1%. This 4.1% magnitude of benefit exceeds the magnitude of harm, (approximately 0.5% increase in major bleeds), which was similar in primary and secondary prevention RCTs.

Conclusion: For patients with elevated blood pressure and no cardiovascular disease the benefits of low-dose ASA do not outweigh the harms. For patients with elevated blood pressure and cardiovascular disease the benefits of ASA exceed the harms.

Clinical implications: The indications for low dose ASA (e.g. 80 mg.) to prevent cardiovascular events are the same for patients with normal and elevated blood pressure; **low dose ASA is recommended in patients with proven cardiovascular disease (secondary prevention), but not in those without cardiovascular disease (primary prevention).**⁷

This Therapeutics Letter was submitted for review to 45 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

Effect of longer-term modest salt reduction on blood pressure

This review was completed in October 2003 and published in 2004 Issue 1.⁸

Findings: In 17 RCTs involving 734 people with elevated blood pressure, an average reduction in salt intake of 78 mmol (4.6 g) per day for ≥ 4 weeks resulted in a lowering of blood pressure of 5.0 [4.2 – 5.8] / 2.7 [2.3 – 3.2] mmHg. In 11 RCTs of 2220 people with normal blood pressure an average reduction of salt intake of 74 mmol (4.4 g) per day for ≥ 4 weeks, resulted in a lowering of blood pressure of 2.0 [1.5 – 2.6] / 1.0 [0.6 – 1.4] mmHg.

Conclusion: “A modest reduction in salt intake for 4 or more weeks has a significant effect on blood pressure in individuals with normal and elevated blood pressure.”

Clinical implications: **Motivated individuals, who are able to lower and maintain a lower dietary salt intake, can be confident that this is a dietary strategy proven to lower blood pressure.**

How to access the Cochrane Library

UBC faculty, students and resident doctors can access the Cochrane Library through the UBC Library. Anyone else in BC who has access to the internet can access the abstracts at www.thecochranelibrary.com free of charge.

The full text of individual Cochrane reviews can be purchased on line (approx. \$30/review) or as part of a subscription to the Cochrane Library (approx. \$320/year).

Go to www.thecochranelibrary.com for more information.

Everyone in Australia, Denmark, England, Finland, Ireland, Norway, South Africa, Sweden and Wales, all the countries in the Caribbean and Latin and Central America, and the province of Saskatchewan has free access to The Cochrane Library. Efforts are currently under way to gain free access to The Cochrane Library for everyone in Canada.

References

- Jadad AR, Cook DJ, Jones A, et al. *Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals.* JAMA 1998;280:278-80.
- Alderson P, Roberts I. *Corticosteroids for acute traumatic brain injury.* The Cochrane Database of Systematic Reviews 2005, Issue 1.
- CRASH trial collaborators. *Effect of intravenous corticosteroids on death within 14 days in 10,008 adults with clinically significant head injury (MRC CRASH trial): randomized placebo-controlled trial.* Lancet 2004;364:1321-1328.
- Dongen CJJ, van den Belt AGM, Prins MH, et al. *Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism.* The Cochrane Database of Systematic Reviews 2004, Issue 4.
- Demicheli V, Rivetti D, Deeks JJ, et al. *Vaccines for preventing influenza in healthy adults.* The Cochrane Database of Systematic Reviews 2004, Issue 3.
- Lip GYH, Felmeden DC. *Antiplatelet agents and anticoagulants for hypertension.* The Cochrane Database of Systematic Reviews 2004, Issue 3.
- Antiplatelet Trialists' Collaboration. *Collaborative overview of randomised trials of antiplatelet therapy – I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients.* BMJ 1994;308:81-106.
- He FJ, MacGregor GA. *Effect of longer-term modest salt reduction on blood pressure.* The Cochrane Database of Systematic Reviews 2004, Issue 1.