Evidence-based nephrology

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Abstract. Systematic reviews and meta-analyses are the best approaches available for summarizing the available evidence concerning the efficacy of therapies. Although the renal field has been slow to use these techniques, they are being used increasingly. In March 1997, the Cochrane Renal Group was formed, and this group aims to produce and maintain up to date systematic reviews of the evidence on the effectiveness of therapies used to treat patients with renal diseases. This group is part of the Cochrane Collaboration which is an international structure grouping collaborators together, with the aim of preparing, maintaining and disseminating systematic reviews of the effects of health care in all areas of medicine.

Introduction

Many practising physicians rely on reviewing the published medical literature to keep themselves up to date with the latest clinical developments. However, the amount of medical literature that is published is forever increasing and, even if physicians use a substantial amount of their time for this activity, they cannot hope to find and read all the information on a given subject, even if they manage to overcome the problem of language. Therefore, increasingly, many physicians depend on general reviews and information provided by the pharmaceutical industry. The former are usually based on a selection of the evidence available and, in general, express the opinion of the author. The latter, although well presented since the pharmaceutical industry has many resources (both technical and financial), are generally far from complete and tend to provide ‘evidence’ for the particular firm’s products.

Here we will concentrate on information concerning therapies (in its broadest sense). This information, obtained in various ways, does not always have the same value. For example, the information or evidence on the efficacy of a given therapy provided by a large randomized controlled trial has more weight than that provided by a case–control study or a case report. Randomized clinical trials are considered to be the gold standard for the evaluation of the efficacy of a therapy. It is generally accepted that there is a hierarchy of the sources of evidence (Table 1).

Meta-analysis

Meta-analysis covers a group of techniques that enables data from different trials to be combined and analysed. When correctly performed, meta-analyses offer many advantages over traditional general reviews, and methods involving simple pooling of data or ‘vote-counting’. Traditional general reviews are descriptive summaries, and often no attempt is made to be exhaustive. If in a given situation, 10 clinical trials have been performed, with only five showing a positive effect for the tested treatment, this will not help prescribers in their therapeutic decision-making. Pooling of data and vote-counting (in which ‘positive’ trials are counted as votes in favour of a treatment effect, and ‘negative’ trials are counted as votes against) do not take into consideration the size of the trials and their variance. Thus, in the above example, if the five ‘positive’ trials included only a few patients, they will still contribute substantially to the combined result. Using meta-analytical techniques, these factors are taken into consideration and each trial has a weighting that is determined by its size (number of patients) and its variance.

The systematic reviews of the Cochrane Collaboration involve a structured process (Table 2) which may or may not include a meta-analysis of the data (this will depend on the nature of the data) [1].

Table 1. Hierarchy of the sources of evidence (from Sackett, 1989, ref. 8)

- Large randomized controlled trials
- Meta-analyses and small randomized controlled trials
- Prospective controlled trials
- Retrospective case–control studies
- Uncontrolled case report(s)
Table 2. Cochrane systematic reviews: steps in the process

- Pre-defined protocol with a well-formulated question
- Comprehensive data search
- Unbiased trial selection and data extraction process
- Critical appraisal of data
- Synthesis (meta-analysis) of data (where possible)
- Updating periodically

An important feature of the Cochrane systematic reviews is the periodical updating which differentiates them from usual meta-analyses. A meta-analysis can almost never be considered to be definitive since the data used is that available at the time the analysis was performed; if new data become available after this date, it is important to incorporate them into the analysis. The updating is facilitated by the diffusion medium for the reviews, i.e. a CD-ROM which is published every 3 months. Coupled with the commitment of the Cochrane Collaboration to provide up to date evidence [2], this means that as new evidence becomes available it can be incorporated into the review. This is important to improve patient care in a timely fashion for both ethical and financial reasons.

The Cochrane Collaboration uses a standardized approach to systematic reviewing aimed at guaranteeing quality. The first step involves writing a protocol which is then published (and can therefore be criticized by others). The published protocol prevents ad hoc analyses being presented as though they were planned initially, and minimizes potential biases. The completed review has a standardized form so that readers of the review can find the information readily once they have understood the format used.

Clinical trials and meta-analysis in nephrology

The treatment of renal diseases is changing rapidly due to development of more and more advanced techniques. However, clinical trials in the renal field often include small numbers of patients and, because of the high costs involved, often use intermediate outcomes rather than clinical outcomes. This situation is changing, but the availability of low power trials means meta-analysis can enable the current evidence to be synthesized, thus providing a means of prioritizing areas for research. The number of published meta-analyses in the renal field seems to have taken off, and we hope to see well over 100 systematic reviews in the year 2000 (Figure 1).

As an example of a meta-analysis in the renal field, we can look at the case of low-protein diets for patients with chronic renal failure to protect them against end-stage renal failure. In 1990, a literature overview described > 50 trials, but no conclusion was possible. In 1992, the first meta-analysis comparing low-protein vs normal diet in 890 patients was published [3]. The combined result for the primary outcome, i.e. renal death (defined as death or need for dialysis or transplantation), showed a reduction in favour of low-protein diets [odds ratio (OR) = 0.54, \( P < 0.001 \)]. In 1994, the results of the MDRD trial were published [4]. The primary outcome in this trial was the slope of the glomerular filtration rate decrease. The results showed an almost significant difference (\( P = 0.07 \)) in favour of low-protein diet in the 523 patients included. The updated meta-analysis in 1996 showed similar results to those obtained in 1992 for renal death (OR = 0.6, \( P < 0.001 \)) [5]. Therefore, based on two meta-analyses and one large randomized controlled trial, there is a good level of evidence for prescribing low-protein diets in chronic renal failure.

The Cochrane Collaboration

The Cochrane Collaboration was initiated by Iain Chalmers and his colleagues in Oxford, UK, with the financial support of the National Health Services Research and Development Programme. The Collaboration is named after Archie Cochrane, the British epidemiologist who in 1979 [6] criticized the medical profession when he wrote: ‘It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials.’

The collaboration is being built on a set of eight values: (i) collaboration; (ii) building on the enthusiasm of individuals; (iii) avoiding duplication; (iv) minimizing bias; (v) keeping up to date; (vi) ensuring relevance; (vii) ensuring access; and (viii) continually improving the quality of its work.

The principal production of the Collaboration is the Cochrane reviews which are prepared and maintained by the various international collaborative review groups. The established and planned review groups (> 40) cover most of the important areas of health care. Each collaborative review group has a plan which defines the scope of the group and the specific topics...
falling within this scope. The group’s work is planned, co-ordinated and monitored by a co-ordinating editor supported by an editorial team. Details of how the group will identify clinical trials and assemble these in a specialized trials register are also given in the plan. Each group also has an administrator who, based in the same place as the co-ordinating editor, is responsible for the day to day activities of the group.

The members of the groups, researchers, health care professionals, consumers and others, have access to training material and workshops developed by the Collaboration [1]. Other entities within the collaboration, such as Cochrane Centres, Methods Working Groups and Fields, contribute aid to the collaborative review groups, so that they can produce systematic reviews. The group thus produces a module of edited protocols and completed reviews which is then incorporated in the Cochrane Database of Systematic Reviews which is published quarterly in the electronic journal, the Cochrane Library (Figure 2) [7].

Consumer participation

Consumers participate throughout most of the Collaboration by giving input and feedback, which the Collaboration considers essential to fulfil its goals. To reflect the interests of these consumers, a Consumer Network has been established. Membership to this Network is open to all individuals and, as in all Collaboration entities, is free of charge.

The Cochrane Library

Several databases are included in the Cochrane Library [7]. In addition to the Cochrane Database of Systematic Reviews (Figure 2), there is a bibliographic database of controlled trials, the Cochrane Controlled Trials Register. Another bibliographic database gives details of articles on the science of research synthesis (The Cochrane Review Methodology Database). The fourth database, The Database of Abstracts of Reviews of Effectiveness (DARE), includes structured abstracts of systematic reviews which have been critically appraised. Also included in the Cochrane Library is a handbook on the science of reviewing research, and contact details for the various entities of the Collaboration. The electronic media used for the Cochrane Library offer many obvious advantages for updating and amending the systematic reviews as new evidence becomes available.

The Cochrane Renal Group

The Cochrane Renal Group officially came into being in March 1997. The editorial base is in Lyon, France, and the Co-ordinating Editor is Denis Fouque. The other members of the editorial board are: Ron Gansevoort, Groningen, The Netherlands, Alison MacLeod, Aberdeen, UK, Siu Ka Mak, Hong Kong, Netar Mallick, Manchester, UK, Giuseppe Remuzzi, Bergamo, Italy, Teut Risler, Tübingen, Germany and Charles Swainson, Edinburgh, UK. As of January 1, 1998, there are 48 collaborators in 16 countries.

The Cochrane Renal Group is concerned with the evaluation of the care relevant to those with renal disease. Evaluating the means of managing the problems associated with interventions for renal diseases, such as the side effects of medication, are also part of the scope of the group. The main topics covered by the group are: (i) acute renal failure; (ii) chronic renal failure; (iii) renal transplantation; (iv) renovascular hypertension; (v) the kidney in hypertension; (vi) glomerular diseases; (vii) tubular necrosis; (ix) urinary tract infection; and (x) nephrolithiasis.

The group has 15 titles for systematic reviews registered and eight protocols of reviews; three protocols have been published in volume 1 of the 1998 issue of the Cochrane Library. The process of review production is similar to that used by other collaborative review groups (Table 3).

How to participate

If you would like to participate, you can contact the Editorial Base directly, and state your intention. You

Table 3. How to perform a Cochrane Renal Group review

<table>
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<tr>
<th>Step</th>
<th>Description</th>
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<tr>
<td>1. Complete a pre-registration form</td>
<td>Provide all necessary information about the trial and intervention.</td>
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<td>2. Wait for Editorial Board approval (check for overlap)</td>
<td>Ensure that the trial does not overlap with other studies.</td>
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<tr>
<td>3. Prepare a draft protocol and submit for peer-review (first round)</td>
<td>Revise the protocol based on feedback and submit for peer-review.</td>
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<td>4. Publication of protocol (Cochrane Library)</td>
<td>Publish the protocol in the Cochrane Library.</td>
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<tr>
<td>5. Complete review and submit for peer-review (second round)</td>
<td>Revise the review based on feedback and submit for peer-review.</td>
</tr>
<tr>
<td>6. Corrections, if necessary; final peer-review</td>
<td>Make final corrections and submit for peer-review.</td>
</tr>
<tr>
<td>7. Publication in the CDSR (Cochrane Library)</td>
<td>Publish the review in the Cochrane Database of Systematic Reviews (CDSR).</td>
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<tr>
<td>8. Update the review periodically</td>
<td>Keep the review updated as new evidence becomes available.</td>
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need to decide what type of participation you are willing and able to offer. This could be to perform a review (or collaborate with others to do so) or to handsearch a renal journal. Alternatively, you might be able to provide or identify funding, offer your services as a peer-reviewer or simply want to be kept informed of our activities. Whichever level you choose, you will very welcome to join, and attend meetings.

References