Evidence-based medicine and its horizons: a useful tool for nephrologists?

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Abstract. Though the concept of ‘evidence-based medicine’ (EBM) nowadays has become very popular and even fashionable, its practice is far from being an established reality. There are many reasons why, despite its potential, EBM finds obstacles in expressing its full potential as a tool to better inform health care decisions. Broadly speaking, these obstacles fall into three categories: (i) inadequacy of available information with respect the complexities of health care delivery; (ii) poor quality of clinical research; and (iii) insufficient and inappropriate efforts to promote the uptake of effective interventions in clinical practice. In the first part of this paper, we will discuss: (i) what evidence-based medicine is; (ii) why systematic reviews are the fundamental tool of EBM and what is really special about them; (iii) what are the tools for the practice of EBM; (iv) what its limitations are; and (v) what are the hindrances to its implementation. In the second part, a brief assessment of the state of the art of systematic reviews in nephrology will be presented, with special reference to the activities of the recently launched Cochrane Collaborative Review Group in Renal Diseases.

Introduction

Evidence-based medicine (EBM) has become a fashionable concept nowadays, and the increasing number of editorials, articles, position papers and meetings devoted to it are there to confirm this new reality. Despite this popularity, critics are numerous, and some rightly complain that probably there has been too much enthusiasm for EBM before having seen what it really has contributed to the practice of medicine.

While it is fair to say that too many expectations have been generated regarding EBM as a ‘quick fix’ for many of the problems health care systems face, it is also true that critics not infrequently blame EBM not for what it is, but rather for characteristics that have never really been attributed to EBM even by its most ‘acritical’ supporters. Concerns stem mostly from the undue emphasis that some ‘EBM enthusiasts’ have put on the primacy of rigorous methodologies over the complexities of clinical and health care problems and the immediate applicability of scientific evidence to patient care and health care policy decisions.

In the first part of this paper, we will review conceptual and practical definitions of EBM and the innovations introduced by the ‘systematic review’ approach. We will then discuss tools, limitations and hindrances to the full implementation of EBM as a guiding tool for health care.

In the second part, a brief assessment of where we are with systematic reviews in nephrology will be made, introducing the Cochrane Collaboration, an international network of health professionals committed to prepare, maintain and disseminate systematic reviews of the effects of health care interventions, and the recently launched Cochrane Collaborative Review Group in Renal Diseases.

What is evidence-based medicine?

EBM recently was defined by D. L. Sackett as: ‘the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients’ [1]. Practising EBM thus means integrating individual clinical expertise with the best available external evidence from scientific research.

Individual clinical experience means the proficiency and judgement that individual clinicians acquire through clinical experience and clinical practice. Increased expertise is reflected in many ways, but especially in more effective and efficient diagnosis and in the more thoughtful identification and compassionate use of individual patient’s expectations, rights and preferences in making decisions about their care. The best available external clinical evidence means clinically relevant research, often from the basic science of

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Evidence-based medicine for nephrologists

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tionships. Assessments can be made of whether effects are in the same directions, and of the same general magnitudes, given the variation in study protocol. More specifically, systematic reviews can assess consistency among studies of the same interventions or even among studies of different interventions [16].

Conversely, a sixth reason for systematic reviews is to explore data inconsistencies and conflict in data. Whether a treatment strategy is effective in one setting and not in another or among some patients and not in others can be addressed [17].

Seventhly, an often cited advantage of quantitative systematic reviews in particular is increased power. Lastly, quantitative systematic reviews allow increased precision in estimates of effects [18].

**What is special about systematic reviews?**

An important reason to stress the concept of ‘systematic reviews’ is the consideration of how different they are from traditional ‘non-systematic’ reviews, still an important type of article reported in the medical literature [7]. Traditional reviews use a narrative format to summarize the proceedings and findings of studies on a coherent topic to attempt to draw conclusions or inform theories [7,11]. At their best, narrative reviews provide insights into the dynamics underlying the findings of individual studies [11].

As much as thoughtful narrative reviews have contributed to progress in many areas, even the best of them have suffered from several key limitations [7]. First, traditional reviews have rarely attempted to be exhaustive in their inclusion of studies that meet certain parameters. All too often, narrative reviews have emphasized easily available studies, such as those published in major journals or those written by the reviewer or their colleagues.

A constant problem in all research synthesis is ‘publication bias’: studies that fail to find expected effects of a treatment are less likely to be published than those that succeed [19]. Reliance on publication in major journals often overstates the effects of a treatment [20]. Another serious problem of traditional reviews is ‘reviewer bias’ in selecting studies to be included. Without a requirement that reviewers clearly specify inclusion criteria, and then exhaustively include all studies that fit these criteria, a reviewer may decide, consciously or unconsciously, to include studies that favour their own biases and ignore those that do not.

A third important problem of traditional reviews is that they rarely apply any systematic method to decide where the weight of the evidence lies. Often, authors of narrative reviews use the ‘count method’ where they count studies that found significantly positive, non-significantly positive, non-significantly negative and significantly negative results [11]. The reviewer may declare the treatment to be effective if positive outcomes substantially outnumber negative ones or if significant positive effects outnumber the sum of non-significant and negative effects. This procedure is inadequate in many ways; it gives too much weight to large studies, pays no attention to study quality and makes no distinction between large and small treatment effects [11].

**What are the tools for practicing EBM?**

Several tools today can assist doctors willing to practice EBM. As already discussed, systematic reviews are being produced at an increasing rate in the medical literature. According to a recent estimate, the number of systematic reviews published in medical journals has grown from 25 in 1987 to > 800 in 1996 [21].

A second important source of EBM information comes from the so-called ‘secondary publications’. Chronologically, the first such journal to appear was *ACP Journal Club*, a supplement to *Annals of Internal Medicine* [22]. Starting in late 1995, another similar journal called *Evidence-based Medicine* [23] appeared. Both journals survey a large number of general medical and surgical journals and select articles deemed to be most relevant for clinical practice. Structured abstracts of selected articles are published together with a short commentary prepared by an expert in the field discussing issues of internal validity and generalizability of findings. Increasing numbers of this type of journal are now already available or ready to start publication: *Evidence-based Health Policy, Evidence-based Nursing, Evidence-based Cardiovascular Disease* and *Evidence-based Mental Health*.

A third source of EBM information is represented by ‘practice guidelines’. It is important to remember here that they are broadly defined as ‘… systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific clinical circumstances …’ [24]. Two main types of practice guidelines currently exist (though a rigid distinction can rarely be made): (i) consensus-based guidelines; and (ii) evidence-based guidelines. The main distinction between these two types of guidelines lies in the extent to which the processes of panel identification and composition, information identification, retrieval and critical appraisal, and an explicit link of the strength of evidence to individual recommendations is documented explicitly [25]. Though the current balance still largely favours consensus-based guidelines, it is likely that EBM guidelines will become increasingly available and that they will eventually facilitate access to evidence-based information for practitioners.

**The limitations of EBM**

The limitations of EBM can be identified on two levels. The first is more conceptual and depends on the inherent reductionisms of much clinical research vis-à-vis the complexity of health care. Average clinical research looks at the ‘ideal’ patient, cared for by ‘ideal’ doctors under ‘ideal’ circumstances. In contrast, in
‘real’ life, ‘real’ patients meet with ‘real’ doctors in ‘real’ health care settings.

The second limitation is more practical and depends on the ‘relative poverty’ limitation of currently available research tools (i.e. methods) that have been developed and refined satisfactorily more for the investigation of the effects of intervention than for settling diagnostic or prognostic questions. It is fair to say, in fact, that despite the emphasis on EBM as a new general approach to the practice of medicine, its main contribution is especially important for therapy. Its more firm conclusions stem, in fact, from searching, critically appraising and using information about treatments proved to work through randomized control trials. There is much less evidence-based information on problems related to prognosis and diagnosis, the latter being essentially limited to the area of precision and accuracy. If we consider the two journals previously mentioned (i.e. *ACP Journal Club* and *Evidence-based Medicine*), 101 of 146 articles selected and summarized in the six issues of the latter published between September 1995 and February 1996 referred to randomized control trials or meta-analysis of new therapies, and only 11 related to diagnosis. Similarly, in the six issues of *ACP Journal Club* published in 1996, 83 of 123 articles were trials or meta-analyses on therapy and 12 on diagnosis. It should not thus come as a surprise that two recent articles that tried to assess how much of current in-patient [26] and out-patient [27] practice is ‘evidence-based’ concentrated exclusively on the analysis of the appropriateness of prescribing. In both cases, the thoroughness of diagnosis was taken a priori, without any attempt at scrutinizing it or assessing its correspondence to EBM standards.

Another way to understand where and how EBM is useful to practising clinicians is to look inside the usual clinical process. At least three distinct phases can be recognized [28]. The first has to do with recognizing the clinical problem. If the doctors is an expert, and the disease is familiar to him/her, the diagnosis is easily made by matching the characteristics of a previously seen patient to the knowledge of the disease. If the doctor is less experienced, or the case is more complex, the reasoning proceeds through a deductive process: several hypotheses are generated and then the more plausible one selected according to the presence/absence of certain symptoms/signs.

The second phase is ‘diagnosis verification and completion’. Especially if therapeutic decisions are complex, the diagnostic process must be completed taking into account disease severity, presence/absence of complications, etc. An integral part of this phase is a thorough assessment of a patient’s personal and social characteristics likely to influence his/her prognosis. The third phase deals with therapeutic decisions. What matters most here is knowledge of different treatment options, their effectiveness and the ‘natural history’ of the disease.

If this framework holds, it is then reasonable to conclude that EBM is of limited use for phase one (the recognition of a disease and the generalization of diagnostic hypotheses). It, in fact, depends on the amount of information memorized by individual clinicians and on their cognitive abilities. EBM is indeed more useful in phase two, when at issue is the refinement of a diagnosis from within a selected set of hypotheses or when laboratory or instrumental tests have to be selected. EBM is definitely more useful, though there are often ‘grey zones’ of uncertainty [29], when choices have to be made among different therapeutic approaches, including whether or not to treat a patient and, if yes, how.

**Hindrances to EBM**

Besides the limitations outlined above, there are also hindrances that prevent—even when good evidence is available—the easy translation of EBM information into health care policies. The first has to do with the difficulty of tailoring indications derived from scientific evidence to the local circumstances of a specific health care setting. The ‘old’ idea of a hierarchy between scientific evidence and clinical practice is no longer tenable as it implies that the former is ‘neutral’ and value-free: as it stems from a set of methodological criteria which are generally accepted, its findings are supposed to be generally acceptable and applicable.

Another important hindrance stems from the limited ability of health professionals, and even more so administrators, to critically appraise and interpret research results. Changes in the social contexts, on the other hand, have made the traditional paternalistic relationship between patients and doctors no longer tenable and call for a better way of communicating between a patient and their doctors and the medical community and consumers. This communication is, however, very difficult, and little effort generally is made by health care systems to ‘promote’ themselves.

Implementation of effective health care policies indeed requires proper incentives. A major limitation of efforts aimed at promoting the implementation of effective health care is indeed the inability to identify proper incentives. Despite small differences across different countries, health care systems have concentrated mostly on improving efficiency and controlling costs, and there are not many ideas around on how the delivery of effective health care can be promoted.

Finally, another hindrance to the implementation of evidence-based practices is the lack of credible and valid evaluation tools able to assess whether better processes of care do in fact lead to better outcome, especially at the population level.

**Systematic reviews in nephrology: where are we?**

A major force nowadays in the field of systematic review and EBM is the Cochrane Collaboration (CC), an international network of people (including both health professionals and lay consumers) devoted to the preparation, maintenance and dissemination of system-
matic reviews of the effects of health care interventions. Started in 1993 in Oxford (UK), the CC has evolved rapidly into an international organization with 15 Cochrane Centres in operation around the world and > 30 Collaborative Review Groups busy producing systematic reviews collected in the Cochrane Library, the quarterly electronic publication of the CC.

In 1997, the Renal Review Group was established [29] within the CC. Its main aims are performing and up-dating systematic reviews in the renal field. This new initiative clearly reflects the growing interest in clinical medicine, and health care more generally, towards accepting that better decisions can be made (both at the bedside and at the population level) if the totality of evidence in a given area is examined as a basis to conclude that a given intervention is effective, harmful or has no effect on people’s health. This is especially important in areas such as nephrology where studies are often under-sized due to the small numbers of patients enrolled. Indeed, since 1984, when only one systematic review on the role of immunosuppression in the management of lupus nephritis was available, > 30 articles on different renal topics reported results of systematic reviews and meta-analyses [30]. Table 1 displays a list of published reviews by year of publication. Although far from complete, this table nevertheless helps to identify controversial issues, such as, for example, the use of immunosuppressive agents in membranous nephropathy, which has always puzzled and challenged the nephrologists.

Interestingly, in little more than a few months, 15 potential systematic reviews already at a fairly advanced stage of completion have been registered with the Cochrane Collaborative Review Group, showing the enthusiasm of nephrologists in contributing to the CC. Not surprisingly, more than a half of the registered titles refer to the management of patients with end-stage renal disease. Other interesting topics are also covered, such as the use of antihypertensives in preventing or delaying the progression of kidney disease, as shown in Table 2.

There are several advantages to producing reviews under the supervision of the CC, but the single most important reason to bear in mind is probably the assurance that proper methodology is available and that methodological assistance can be sought if needed. All Cochrane reviews, in fact, are based on ‘hard’ endpoints (i.e. death, dialysis or renal

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**Table 1. Published meta-analyses in nephrology**

<table>
<thead>
<tr>
<th>Author</th>
<th>Short title</th>
<th>Source</th>
<th>Year of publication</th>
</tr>
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<tbody>
<tr>
<td>Naylor</td>
<td>Parenteral nutrition</td>
<td>Renal Failure</td>
<td>1988</td>
</tr>
<tr>
<td>Collins</td>
<td>Stroke, CHD and BP (short-term reduction)</td>
<td>Lancet</td>
<td>1990</td>
</tr>
<tr>
<td>MacMahon</td>
<td>Stroke, CHD and BP (prolonged reduction)</td>
<td>Lancet</td>
<td>1990</td>
</tr>
<tr>
<td>Schena</td>
<td>Steroid and immunosuppressants (IgA)</td>
<td>Nephrol Dial Transplant</td>
<td>1990</td>
</tr>
<tr>
<td>Cappuccio</td>
<td>Potassium supplementation</td>
<td>J Hypertension</td>
<td>1991</td>
</tr>
<tr>
<td>Glowaski</td>
<td>Immunoglobulin and CMV</td>
<td>J Am Soc Nephrol (Abs)</td>
<td>1991</td>
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<tr>
<td>Imperiale</td>
<td>Aspirin and pregnancy</td>
<td>J Am Med Assoc</td>
<td>1991</td>
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<tr>
<td>Leibovici</td>
<td>Single dose vs conventional antibiotics for UTI</td>
<td>Q J Med</td>
<td>1991</td>
</tr>
<tr>
<td>Denker</td>
<td>Fasting insulin and BP</td>
<td>Arch Intern Med</td>
<td>1992</td>
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<tr>
<td>Fouque</td>
<td>Low vs control protein diet in adult CRF</td>
<td>Br Med J</td>
<td>1992</td>
</tr>
<tr>
<td>Barrett</td>
<td>High vs low osmolar contrast media</td>
<td>Radiology</td>
<td>1993</td>
</tr>
<tr>
<td>Hricck</td>
<td>Steroid vs non-steroid immunosuppression</td>
<td>J Am Soc Nephrol</td>
<td>1993</td>
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<tr>
<td>Jernigan</td>
<td>Sepsin and central catheters</td>
<td>Ann Intern Med</td>
<td>1993</td>
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<tr>
<td>Kasiske</td>
<td>CA withdrawal</td>
<td>J Am Med Assoc</td>
<td>1993</td>
</tr>
<tr>
<td>Kasiske</td>
<td>Anti-HTN, treatment and diabetes mellitus</td>
<td>Ann Intern Med</td>
<td>1993</td>
</tr>
<tr>
<td>Keller</td>
<td>Netilmicin PK and renal function</td>
<td>Clin Pharmacokinet</td>
<td>1993</td>
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<tr>
<td>Morris</td>
<td>Fish-oil and BP</td>
<td>Circulation</td>
<td>1993</td>
</tr>
<tr>
<td>Pope</td>
<td>NSAIDs and BP</td>
<td>Arch Intern Med</td>
<td>1993</td>
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<tr>
<td>Couchoud</td>
<td>Membranous nephropathy</td>
<td>Nephrol Dial Transplant</td>
<td>1994</td>
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<tr>
<td>Bauer</td>
<td>Diabetic nephropathy and antihypertensive agents</td>
<td>South Med J</td>
<td>1994</td>
</tr>
<tr>
<td>Labrecque</td>
<td>NSAIDs and renal colic</td>
<td>Arch Intern Med</td>
<td>1994</td>
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<tr>
<td>Cappuccio</td>
<td>Calcium intake and BP</td>
<td>Am J Epidemiol</td>
<td>1995</td>
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<tr>
<td>Gansevoort</td>
<td>Proteinuria and ACEI</td>
<td>Nephrol Dial Transplant</td>
<td>1995</td>
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<tr>
<td>Hogan</td>
<td>Membranous nephropathy</td>
<td>Am J Kidney Dis</td>
<td>1995</td>
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<tr>
<td>Jones</td>
<td>Thiazides and fractures</td>
<td>J Bone Miner Res</td>
<td>1995</td>
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<tr>
<td>Kasiske</td>
<td>Lipids and anti-HTN drugs</td>
<td>Ann Intern Med</td>
<td>1995</td>
</tr>
<tr>
<td>Kasiske</td>
<td>Kidney donation/renal function</td>
<td>Kidney Int</td>
<td>1995</td>
</tr>
<tr>
<td>Maki</td>
<td>Anti-HTN, renal function and proteinuria</td>
<td>Arch Intern Med</td>
<td>1995</td>
</tr>
<tr>
<td>Massy</td>
<td>Antithromic treatment in renal disease</td>
<td>Kidney Int</td>
<td>1995</td>
</tr>
<tr>
<td>Rao</td>
<td>c-ANCA and Wegener granulomatosis</td>
<td>Ann Intern Med</td>
<td>1995</td>
</tr>
<tr>
<td>Weidmann</td>
<td>Anti-HTN,proteinuria in diabetes mellitus</td>
<td>ISN Madrid 1995</td>
<td>1995</td>
</tr>
<tr>
<td>Perna</td>
<td>Albuminuria and glomerular injury</td>
<td>Am J Kidney Dis</td>
<td>1996</td>
</tr>
<tr>
<td>Schieppati</td>
<td>Treatment of membranous nephropathy</td>
<td>Exp Opin Invest Drugs</td>
<td>1997</td>
</tr>
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</table>
transplantation), and include randomized controlled trials only.

In some respects, one may think that these high standards are too difficult to achieve. This is reflected by the fact that the number of controlled trials for some renal disorders is so small that only one or two single studies may fulfil the criteria for inclusion in a review. In the spirit of the CC, it is therefore crucial not just to produce the review but also to update it with new available evidence as soon as it becomes accessible. Another big advantage of the CC is that the risk of duplication of efforts is greatly reduced, because reviewers must submit their own protocol before starting their review and are encouraged to merge protocols whenever another person has expressed an interest in a similar topic.

Apart from the regular activities promoted by the Renal Review Group of systematically searching the available literature, including handsearching [31], another way to identify registries of clinical trials (RCTs) is to set up and maintain a prospective registration of RCTs in Nephrology. The need for this task was proposed by Tognoni and Mallick [32]. The Registry was formally created in 1994 by The Journal of Nephrology, owned by the Italian Society of Nephrology, enabling the whole trial protocol [33–38] or an abstract form to be submitted by interested investigators. In this way, unpublished and ongoing studies can be identified more easily, and the risk of publication bias [20] is at least partially reduced.

If, now and in the future, more nephrologists share the same perspectives as those mentioned above in approaching important therapeutic questions, we can realistically hope that ineffective/dangerous therapeutic manoeuvres can be eliminated from clinical practice more rapidly than they would otherwise.

### Conclusions

It is not news that the conditions under which health care is being delivered are changing. These changes are generated from several factors including ageing of the population, continuous technological advances, increasing expectations of people from health and health care, growing pressures for cost containment, regulation of clinical practices, and so on.

EBM has brought about great expectations of the possibility of coping with these challenges while still remaining able to provide health care to all those in need. While undoubtedly EBM has already made important cultural and practical contributions, its real potential will be exploited fully only in the years to come if it is used to improve the current situation characterized by too little and often poor quality health care research [39,40], and too limited, and often poorly directed, efforts to improve the uptake of results of clinical research into clinical practice.

The main challenge for the years to come is to build a better knowledge basis in order to make EBM a fully usable and applicable source of information for individual patients and community care.

### Table 2. Registered titles with the Cochrane Renal Group

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Short title</th>
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<tbody>
<tr>
<td>Feber</td>
<td>Early steroids in purpura nephropathy</td>
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<tr>
<td>Daly</td>
<td>CCPC vs CAPD in end-stage renal disease</td>
</tr>
<tr>
<td>Daly</td>
<td>Short vs long haemodialysis times</td>
</tr>
<tr>
<td>MacLeod</td>
<td>Type of haemodialysis membrane for ESRD</td>
</tr>
<tr>
<td>Daly</td>
<td>Bicarbonate-buffered dialysate in ESRD</td>
</tr>
<tr>
<td>Khan</td>
<td>CAPD delivery systems</td>
</tr>
<tr>
<td>Daly</td>
<td>Haemodialysis vs CAPD</td>
</tr>
<tr>
<td>Cody</td>
<td>RHu EPO in pre-dialysis chronic renal failure</td>
</tr>
<tr>
<td>MacLeod</td>
<td>SC vs IV erythropoietin in ESRD</td>
</tr>
<tr>
<td>Simon</td>
<td>Ca++ blockers in cyclosporin A toxicity prevention</td>
</tr>
<tr>
<td>Fouque</td>
<td>Low-protein diets and progression of renal failure</td>
</tr>
<tr>
<td>Koch</td>
<td>CsA in childhood idiopathic nephrotic syndrome</td>
</tr>
<tr>
<td>Gansevoort</td>
<td>Angiotensin-II antagonists and ACE-inhibitors</td>
</tr>
<tr>
<td>Schieppati*</td>
<td>Treatment of idiopathic membranous nephropathy</td>
</tr>
<tr>
<td>Braun*</td>
<td>Immunosuppression in membranous glomerulonephritis</td>
</tr>
</tbody>
</table>

*To be merged.

### References

37. The STOP investigators. A trial to evaluate the efficacy of picotamide in preventing thrombotic occlusion of the vascular access in hemodialysis patients.