

## Review Article

# An evidence based consultation in primary care dermatology: illustration with case management of atopic dermatitis

## 皮膚科基層醫療服務中的實証基礎諮詢：從異位性皮膚炎的治理個案作一淺談

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We make clinical decisions everyday. However, it is not uncommon to encounter difficulties in answering questions raised by our patients, particularly in the primary care setting. How can we solve these problems? In this article, the concept of evidence-based medicine (EBM) will be demonstrated through some interesting dermatology questions from our patients. Emphasis will be placed on how to select the most appropriate study designs, how to critically appraise a paper rapidly and how to apply the evidence.

作為醫者，每天均要作出不少臨床決策；與此同時，遇到病患提出令人為之結舌的艱深問題亦為數不少，尤常見於基層醫療服務。究竟我們可以怎樣去解決這些問題？以下內文，我們將引述病人對皮膚科的一些有趣提問，從而介紹實証醫學的概念；同時集中討論怎樣選取最合適的研究設計，對文章作出迅捷評析及實証應用的方法等等。

Keywords: Atopic dermatitis, evidence-based medicine

關鍵詞：異位性皮膚炎，實証醫學

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## Introduction

Evidence-based medicine (EBM) is not a new concept. It was first mentioned by a British epidemiologist called Archie Cochrane and is now generally accepted as the originator of the concept. His efforts in the mid-1950s to 1960s to categorise studies resulted in the pre-eminence of randomised, controlled trial studies as the gold standard for evaluating the validity and reliability of clinical research.<sup>1</sup> Later, David Sackett's definition is widely used as the basis for pedagogy in EBM. He defined EBM as "the conscientious,

explicit and judicious use of current best evidence in making decisions about the care of individual patients".<sup>2</sup> Muir Gray and his colleagues introduced a broader concept on EBM: "Evidence based clinical practice is an approach to decision making in which the clinician uses the best scientific evidence available, in consultation with the patient, to decide upon the option which suits the patient best."<sup>3</sup>

In this article, we will demonstrate how to apply the above concepts in our daily consultation. As atopic dermatitis is one of the most common skin diseases in primary care in Hong Kong, we have selected some interesting questions and try to answer them with support by the best available evidence.

## Searching strategies

The following reference databases were searched; namely the Pubmed and Cochrane Library as they are the most easily accessible resources for a busy family physician. The most obvious disadvantage is the lack of full text most of the time. The searching was performed between April and October in 2008. The average time spent for searching each question is less than 5 minutes, but the time to conclude from the evidence is more difficult to define because it depends on how vigorous you appraise the literature. However, if one follows some simple rules to search and read the abstract of an article, the time spent will be limited, e.g. for intervention studies, you can narrow down your search by limiting the study design to the highest hierarchy of evidence such as meta-analysis, instead of reading through every abstract of article. On the other hand, you may apply some quick appraisal skills for a meta-analysis (namely precise definitions of clinical variables and outcomes; appropriate and well-documented study identification and selection strategy; evaluation of bias; description and evaluation of heterogeneity; justification of data analysis techniques and use of sensitivity analysis)

or for a randomised controlled trial (RCT) (including randomised concealed assignment; group similarity in characteristic and treatment; loss in follow-up; use of intention-to-treat analysis and blindness of both investigators and patients in objective measurement). Even small violations of the above rules can lead to misleading conclusion.

Keywords and Medical Subject Headings terms were both searched for the following wordings: atopic dermatitis, atopic eczema, anti-histamine, traditional Chinese medicine, Chinese herbal medicine, probiotic, lactobacillus, topical corticosteroids, potent topical steroids, tacrolimus, pimecrolimus, evening primrose oil, diet restriction.

## Questions to be discussed

### *(i) Is oral antihistamine useful in my atopic dermatitis?*

Antihistamines are always prescribed to our patients with atopic dermatitis in our daily practice. Is it evidence-based? According to a systematic review that included 16 studies with a total of 803 subjects, large RCTs with definitive conclusions have not been performed. Instead, two small, better-performed randomised trials did not support the use of antihistamines in relieving pruritis. In the remaining trials which supported the use of antihistamines, they lacked placebo controls or randomisation, or contained less than 20 participants in each treatment group.<sup>4</sup> Hence, their results cannot be drawn into any conclusion. Similar conclusion was supported by another systematic review conducted later.<sup>5</sup>

The authors suggested that although antihistamines are often used in the treatment of atopic dermatitis, it seems that little evidence exists to support its use in relief of pruritis. Moreover, there is no good evidence to support the effectiveness of expensive non-sedating agents. More clinical trials examining the

therapeutic efficacy of the newer non-sedating anti-histamines are necessary to elucidate their role in the treatment of atopic dermatitis.

***(ii) Is Chinese herbal medicine helpful in my atopic dermatitis?***

Traditional Chinese herbal medicine has been used to treat atopic dermatitis for many years in Chinese society. Is it really beneficial to our patients? A recent Cochrane review may give us an answer. The authors performed a comprehensive search and only RCTs of Chinese herbal mixtures used in the treatment of atopic dermatitis were included. Four RCTs, with eight weeks for each phase, met the inclusion criteria. Nevertheless, the withdrawal rates ranged from 7.5% to 22.5% and no trial used intention to treat analysis. Though the authors concluded that Chinese herbal mixtures might be effective in the treatment of atopic dermatitis, further well-designed, larger scale trials are required to achieve a better conclusion.<sup>6</sup>

***(iii) Is Probiotic supplementation during my prenatal/postnatal period effective in the prevention and treatment of atopic dermatitis in my child?***

In a meta-analysis of RCTs, the authors concluded that prenatal probiotic supplementation significantly reduced the risk of developing paediatric atopic dermatitis (NNT=12; 8-25), but was not significantly superior to placebo for treating established diseases. On the other hand, postnatal supplementation alone did not significantly reduce the risk of paediatric atopic dermatitis.<sup>7</sup>

However, since the authors did not perform a formal procedure to exclude publication bias, negative studies are more likely to be unpublished and we must be aware that the true effect of the intervention may be deviated from what is reported.

***(iv) Is daily topical corticosteroids enough for atopic dermatitis?***

In a systematic review, the authors searched the

literature for RCTs comparing once-daily with more frequent dosing of topical corticosteroids for atopic dermatitis. The 2 primary outcomes consistent among most studies was "at least a good response or 50% improvement" and "dermatitis rated as cleared or controlled." It was well executed with a comprehensive search, a good description of inclusion/exclusion criteria, a careful abstracting of data, and an appropriate analysis. Of the 10 RCTs chosen (a total of 1,819 patient), 1 studied a very potent steroid, 8 studied potent steroids, and 1 studied a moderately potent steroid. Since the results among the studies were heterogeneous, it was impossible to combine the results. However, review of the individual studies showed little support for dosing more than once a day.<sup>8</sup>

The authors suggested that patients should start with once-daily dosing of topical corticosteroids for atopic dermatitis in order to avoid the side effects of topical steroids, but increasing to twice or 3 times per day only if symptoms are not well controlled.

***(v) Is either topical tacrolimus or topical pimecrolimus useful in atopic dermatitis?***

Nowadays, pimecrolimus and tacrolimus are two immunomodulating agents commonly used topically as alternatives to corticosteroids for the treatment of atopic dermatitis. The authors of a meta-analysis searched all RCTs comparing either drug with active treatment or placebo or with each other.<sup>9</sup> They also searched several databases, as well as reference lists of retrieved trials. Study selection and data extraction were performed independently by two authors. They included 25 trials with a total of 6897 patients. Both drugs were found to be significantly more effective than placebo. In moderate to severe atopic dermatitis, only topical tacrolimus was shown to be more effective than 1% hydrocortisone acetate in children and 0.1% hydrocortisone butyrate in adults. It may have a place for long-term use in patients with resistant atopic dermatitis on sites where side effects from topical corticosteroids might develop quickly. On the other hand, only a

single study has evaluated pimecrolimus 1% versus tacrolimus 0.03% in children with moderate to severe atopic dermatitis and found equivalent response rates over 6 weeks.<sup>9</sup> In another well conducted meta-analysis from the Cochrane database, topical pimecrolimus is less effective than moderate and potent corticosteroids and 0.1% tacrolimus. The therapeutic role of topical pimecrolimus is uncertain due to the absence of key comparisons with mild corticosteroids.<sup>10</sup> However, experience of long-term use of these agents is lacking so the risk of rare but serious adverse effects remains unknown. No conclusions can be confidently drawn about the cost-effectiveness of pimecrolimus or tacrolimus compared with active topical corticosteroids comparators.<sup>11</sup>

***(vi) Is evening primrose oil beneficial to patients suffering from atopic dermatitis?***

Evening primrose oil was initially proven efficacious in a poorly performed meta-analysis.<sup>12</sup> However, a better-performed meta-analysis has refuted the use of primrose oil in atopic dermatitis. The investigators performed a comprehensive database search and only RCTs of therapeutic agents used in the prevention and treatment of people with atopic dermatitis of any age were considered for inclusion. The quality assessment of retrieved RCTs included concealment of allocation of randomisation, blindness to the study interventions, and intention-to-treat analysis. Though a total of 1165 possible RCTs were retrieved in hard copy form for further scrutiny, only 272 RCTs of atopic dermatitis covering at least 47 different interventions were included. After vigorous analysis, the authors concluded there was insufficient evidence to make recommendations on evening primrose oil in established atopic dermatitis.<sup>13</sup> To further refute its usefulness, an ongoing Cochrane review may give us a clearer picture in the future.<sup>14</sup>

***(vii) Is diet restriction useful in atopic dermatitis?***

A recent Cochrane review has demonstrated the

limited role of diet restriction in atopic dermatitis. The reviewers performed a comprehensive literature search in different databases. They found 9 RCTs involving a total of 421 participants of which six were studies of egg and milk exclusion (N=288), one was a study of few-foods (N=85) and two were studies of an elemental diet (N=48). There appeared to be no benefit with egg and milk free diet, elemental or few-foods diet in unselected cases of atopic dermatitis. On the other hand, there may be some benefit in using an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs. One study found 51% of the children had a significant improvement in body surface area with the exclusion diet compared to normal diet (RR 1.51, 95% CI 1.07 to 2.11) and change in surface area and severity score was significantly improved in the exclusion diet compared to the normal diet at the end of 6 weeks (MD 5.50, 95% CI 0.19 to 10.81) and end of treatment (MD 6.10, 95% CI 0.06 to 12.14). However, methodological difficulties have made it difficult to interpret these studies. Poor concealment of randomisation allocation, lack of blinding and high dropout rates without an intention-to-treat analysis indicates that these studies should be interpreted with great caution.<sup>15</sup>

## **Limitation**

The opinions in this paper are only a preliminary search of evidences based on the best study designs. Moreover, search bias might be present as it was confined to Medline and Cochrane library. In addition, only literatures written in the English language were selected. Last but not least, as the articles in dermatology are growing rapidly, the information given in this paper may not be the most accurate and up-to-date.

## **Conclusion**

Clinical decision-making not only depends on the clinical evidence, but also the patients' benefits

and interests. However, there are always many unfounded beliefs among laymen and even health care professional. Therefore, we should always try our best to utilise the available and accessible electronic resources to get the most up-to-date information regarding different clinical situations and discuss pros and cons of each decision with our patients. Unlike in the old days, EBM skills are no longer confined to academics who have easy access to the medical libraries. EBM skills are easy to learn and to be mastered by all doctors. They are feasible for all determined front-lined clinicians nowadays, no matter whether you are in private or public practice.

Based on the appraised evidences, the following points can be summarised:

1. Evidence supported by meta-analysis/systematic review
  - Tacrolimus in atopic dermatitis
2. Evidence supported by RCT
  - Once daily dosage of topical steroids for atopic dermatitis
3. Inconclusive evidence
  - Antihistamine in atopic dermatitis
  - Chinese herbal medicine in atopic dermatitis
  - Probiotic supplementation in prevention or treatment of children with atopic dermatitis
  - Evening primrose oil
  - Diet restriction

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