Systematic Reviews and Meta-analysis in Dermatology

Suthee Rattanamongkolgul
MD, MPH, PhD
Department of Preventive and Social Medicine,
Faculty of Medicine,
Srinakharinwirot University

Outline

- What is a systematic review?
- What is the rationale for the systematic review?
- How can dermatology benefit from systematic review?
- Existing groups of dermatologists performing systematic reviews
- Experience in systematic reviews in dermatology

Meta-analysis of risk of the sudden infant death syndrome and infant sleeping position


Prophylactic corticosteroids for preterm birth.

BACKGROUND: Respiratory distress syndrome is a serious complication of prematurity causing significant immediate and long-term mortality and morbidity.

OBJECTIVES: The objective of this review was to assess the effects of corticosteroids administered to pregnant women to accelerate fetal lung maturity prior to preterm delivery.

SEARCH STRATEGY: The Cochrane Pregnancy and Childbirth Group trials register was searched.

SELECTION CRITERIA: Randomised and quasi-randomised trials of corticosteroid drugs capable of crossing the placenta compared with placebo or no treatment in women expected to deliver preterm as a result of either spontaneous preterm labour, prelabour rupture of the membranes preterm, or elective preterm delivery.

DATA COLLECTION AND ANALYSIS: Eligibility and trial quality were assessed by one reviewer.

MAIN RESULTS:

Eighteen trials including data on over 3700 babies were included.

- Antenatal administration of 24 milligrams of betamethasone, of 24 milligrams of dexamethasone, or two grams of hydrocortisone to women expected to give birth preterm was associated with a significant reduction in mortality (odds ratio 0.60, 95% confidence interval 0.48 to 0.75), respiratory distress syndrome (odds ratio 0.53, 95% confidence interval 0.44 to 0.63) and intraventricular haemorrhage in preterm infants.

- These benefits extended to a broad range of gestational ages and were not limited by gender or race.

- No adverse consequences of prophylactic corticosteroids for preterm birth have been identified.
Cumulative meta-analysis of therapeutic trials for myocardial infarction.

**BACKGROUND:** The large volume of published randomized, controlled trials has led to a need for meta-analyses to track therapeutic advances. Performing a new meta-analysis whenever the results of a new trial of a particular therapy are published permits the study of trends in efficacy and makes it possible to determine when a new treatment appears to be significantly effective or deleterious. We describe the use of such a procedure, cumulative meta-analysis, to assess therapeutic trials among patients with myocardial infarction.

**METHODS:** We performed cumulative meta-analyses of clinical trials that evaluated 15 treatments and preventive measures for acute myocardial infarction.

**RESULTS:**

An example of this method is its application to the use of intravenous streptokinase as thrombolytic therapy for acute infarction. Thirty-three trials evaluating this therapy were performed between 1959 and 1988. We found that a consistent, statistically significant reduction in total mortality (odds ratios, 0.74; 95 percent confidence interval, 0.59 to 0.92) was achieved in 1973, after only eight trials involving 2432 patients had been completed.

In particular, two very large trials, the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico trial in 1986 (11,712 patients) and the Second International Study of Infarct Survival trial in 1988 (17,187 patients) did not modify the already established evidence of efficacy.

We used a similar approach to study the accumulating evidence of efficacy (or lack of efficacy) of 14 other therapies and preventive measures for myocardial infarction.

**CONCLUSIONS:**

Cumulative meta-analysis of therapeutic trials facilitates the determination of clinical efficacy and harm and may be helpful in tracking trials, planning future trials, and making clinical recommendations for therapy.

**Importance of systematic reviews**

- The number of published systematic reviews is growing rapidly and receiving increased attention from scientists, editors, policy makers, and consumers compared to traditional review articles.
- Systematic reviews use an explicit and systematic predefined methodology to minimize bias and to increase the precision of measurements of treatment effects.
- Systematic reviews can reduce unnecessary duplication of clinical trials.
- Institutional review board panels and dermatology journals should consider requiring systematic reviews or reference to existing systematic reviews as a prerequisite for protocol approval and publication of clinical trials.
Importance of systematic reviews

- Systematic reviews are now required by some biomedical journals (for example, The Lancet) for clinical trial publication (Young and Horton, 2005).
- Expanding volume of published literature
- Different or controversial results from studies on the same topic
- Minimising possible biases
- Increased statistical power (meta-analysis)
- Improved generalisability

The Cochrane Collaboration make a commitment to update the review periodically with the goal of fine-tuning the research in light of any new studies that come along. If performed correctly, these reviews can provide complete, up-to-date, and unbiased measurements of treatment effectiveness.

High-quality systematic reviews may also indicate whether existing evidence is consistent and can be generalized across patient populations or variations in treatment (Collier et al., 2005; Parker et al., 2004).

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

Objectives To understand how frequently highly cited studies are contradicted or find effects that are stronger than in other similar studies.

Design All original clinical research studies published in 3 major general clinical journals or high-impact-factor specialty journals in 1990-2003 and cited more than 1000 times in the literature were examined.

Results: Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these:

- 7 (16%) were contradicted by subsequent studies,
- 7 (16%) had found effects that were stronger than those of subsequent studies,
- 20 (44%) were replicated, and
- 11 (24%) remained largely unchallenged.

7 of 6 highly cited nonrandomized studies vs 9 of 39 randomized controlled trials had been contradicted or had found stronger effects (P=.008).

Systematic versus narrative reviews

<table>
<thead>
<tr>
<th>Systematic review</th>
<th>Narrative review</th>
</tr>
</thead>
<tbody>
<tr>
<td>systematic methods used to control bias and imprecision</td>
<td>subjective and may be biased</td>
</tr>
<tr>
<td>uses rigorous scientific methodology to search literature</td>
<td>no explicit methods for searching literature or reporting and report results of results</td>
</tr>
<tr>
<td>can be replicated</td>
<td>cannot be replicated</td>
</tr>
</tbody>
</table>

Hierarchy of evidence

1. Randomized Controlled Trials
2. Nonrandomized Controlled Trials
3. Categorical Reviews
4. Systematic Reviews
5. Evidence-Based Guidelines
6. Clinical Guidelines
7. Subject Matter Expert
8. Public Opinion
**Systematic review - definition**

A review of a clearly formulated question that uses **systematic and explicit** methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review.

*Cochrane Reviewers’ Handbook 4.1.5*

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**Formulating review questions**

- State objectives of the review and define eligibility criteria.
- Comprehensively search for trials that seem to meet eligibility criteria.
- Identify characteristics of trials identified and assess their methodological quality.
- Apply eligibility criteria and reject any exclusions.
- Assemble the most comprehensive dataset feasible.

**Searching for studies**

- Electronic databases: MEDLINE, CINAHL, AMED, EMBASE, PsycInfo.
- Handsearching: Journals, conference proceedings.

**Publication bias**

The tendency to submit or accept studies for publication based on the direction or strength of the study findings.

*Publication and related biases. HTA 2000, 4(10)*

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**Review questions: “PICO”**

- People/patients/participants
- Interventions/controls
- Outcomes
- Study designs

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**Searching for studies**

- Electronic databases
  - e.g.: MEDLINE, CINAHL, AMED, EMBASE, PsycINFO
- Handsearching
  - e.g.: Journals, conference proceedings
- Checking reference lists
- Identifying unpublished studies
Approaches to data synthesis

* Evidence presentation
  - tables, graphs, narrative description

* Descriptive synthesis
  - the direction of effect
  - the size of effect
  - the consistency across studies
  - the strength of evidence

* Quantitative pooling (meta-analysis)

Data extraction form

<table>
<thead>
<tr>
<th>ID</th>
<th>Type of study</th>
<th>Year</th>
<th>Patients</th>
<th>Site (Facial?)</th>
<th>Interventions</th>
<th>Include</th>
<th>Exclude/Reason</th>
</tr>
</thead>
</table>

Assessing Publication Bias

Are studies with statistically significant or positive results, more likely to be published than those finding no difference between the study group?

<table>
<thead>
<tr>
<th>Publication</th>
<th>Risk of publication bias (folds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easterbrook et al. 1991</td>
<td>Statistically significant (n=134)</td>
</tr>
<tr>
<td></td>
<td>Non-significant (n=136)</td>
</tr>
<tr>
<td>Dickersin et al. 1992</td>
<td>Significant result (n=134)</td>
</tr>
<tr>
<td></td>
<td>Non-significant (n=136)</td>
</tr>
<tr>
<td>Dickersin &amp; Stun 1993</td>
<td>Significant result (n=134)</td>
</tr>
<tr>
<td></td>
<td>Non-significant (n=136)</td>
</tr>
<tr>
<td>Stern, 1997</td>
<td>p&lt;0.0001 (submission only)</td>
</tr>
<tr>
<td>Wormald, 1997</td>
<td>4.0, 95% CI; 0.6, 32</td>
</tr>
<tr>
<td>Cronin, 2004</td>
<td>0.53, 95% CI; 0.25, 1.1</td>
</tr>
<tr>
<td>Decullier, 20052</td>
<td>4.59, 95% CI; 2.21, 9.54</td>
</tr>
<tr>
<td>Decullier, 2006</td>
<td>1.58, 95% CI; 0.37, 6.71</td>
</tr>
</tbody>
</table>

Funnel plot

Antifungal vs. placebo in treatment of seborrheic dermatitis

Publication Bias

Statistically significant papers are more likely to be published than non-statistically significant papers
Assessing quality of research

Bias of research

**Sources of bias in trials**

- **Target population**
  - Allocation
    - Intervention group
    - Not exposed to intervention
  - Follow-up
    - Outcomes

- **Sources of bias**
  - **Selection bias**
  - **Performance bias**
  - **Attrition bias**
  - **Detection bias**

**Outcome Reporting Bias**

1. Primary outcome stated in protocol is the same as in the publication

2. Primary outcome stated in protocol is downgraded to secondary in the publication

3. Primary outcome stated in the protocol is omitted from the publication

4. A non primary outcome in the protocol is changed to primary in the publication

5. A new primary outcome that was not stated in the protocol (as primary or secondary) is included in the publication

6. Completeness of reporting

**CONSORT STATEMENT 2010**

- **Allocation and randomisation**
  - Methods
    - Random sequence generation
    - Allocation concealment

- **Participants**
  - Inclusion criteria
  - Exclusion criteria

- **Outcomes**
  - Primary outcomes
  - Secondary outcomes

- **Sample size**
  - Power calculations

- **Study quality**
  - **Methods**
    - **Random sequence generation**
    - **Allocation concealment**

- **Data synthesis**
  - **Analysis**
    - **Outcomes and estimation**
    - **Summary measures**

- **Conclusions**
  - **Limitations**
    - **Further research**
Assessment of study quality

Quality scales vs checklist

Validity assessment can be used:
- as a threshold for inclusion of studies
- as a possible explanation for heterogeneity
- in sensitivity analyses
- as weights in meta-analysis

Limitations of quality assessment

* Inadequate reporting of trials
* Lack of empirical evidence
* Subjectivity

Information from included studies

Bibliographic details
Study characteristics
- design/methods
- participants
- interventions
- outcome measures
Study results
- means, SD and/or SE
- no. of events and N

Meta-analysis
Meta-analysis

* Statistical combination of results, estimating the weighted average of treatment effect.

* Investigating heterogeneity across studies: subgroup analysis, meta-regression

Weight in meta-analysis

The contribution of the individual studies to the summary statistic

- The larger studies are given more weight than smaller studies
- Study quality assessment results as weight

An example of meta-analysis

Calcium supplementation in pregnancy for preventing preeclampsia

Atallah et al. The Cochrane Library. 2000

Variation in results across studies

What is Heterogeneity?

Statistical heterogeneity

Clinical heterogeneity

Methodological heterogeneity

Sources of heterogeneity

Chance

Variations in patients

Variations in interventions

Different outcome measures

Methodological quality

Dealing with heterogeneity

Assessing heterogeneity:

- Graphical methods
- Statistical testing

Investigating heterogeneity:

- Subgroup analysis
- Meta-regression
**$I^2$ statistic - quantifying heterogeneity**

$I^2$ is the percentage of total variation across studies that is due to heterogeneity rather than chance: $i^2/\left(\tau^2 + \sigma^2\right) \times 100$

- <25%: low heterogeneity
- 25% - 75%: moderate heterogeneity
- >75%: high heterogeneity

*Higgins et al. BMJ 2003; 327:557-60*

**Example – heterogeneity testing and subgroup analyses**

<table>
<thead>
<tr>
<th>Calcium supplementation meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled relative risk (95% CI), RE model</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>All studies</td>
</tr>
<tr>
<td><strong>Subgroup analysis</strong></td>
</tr>
<tr>
<td>Hypertension risk</td>
</tr>
<tr>
<td>Low (6 trials)</td>
</tr>
<tr>
<td>High (4 trials)</td>
</tr>
<tr>
<td>Diet c+ intake</td>
</tr>
<tr>
<td>Adeq (4 trials)</td>
</tr>
<tr>
<td>Inadeq (6 trials)</td>
</tr>
</tbody>
</table>

**Systematic review - limitations/pitfalls**

- Retrospective; bias may be introduced
- Inappropriate quantitative pooling
- Misleading subgroup analyses
- Depending on published literature
- Restricted by data reported in publications
- Ecological fallacy (aggregation bias)

**Organisation supporting systematic reviews**

The Cochrane Collaboration

*“The Cochrane Collaboration is an enterprise that rivals the Human Genome Project in its potential implications for modern medicine.”* — The Lancet

**Structure** — established as an international organisation in 1993, registered as a charity in the U.K.

**Aim** — to help people make well-informed decisions about health care.

**How** — by preparing and promoting access to systematic reviews of the effects of healthcare interventions.

[http://www.cochrane.org/](http://www.cochrane.org/)
The Cochrane Library

What is in The Cochrane Library?
- Cochrane Database of Systematic Reviews (Cochrane Reviews)
- Database of Abstracts of Reviews of Effects (Other Reviews)
- Central Register of Controlled Trials (Clinical Trials)
- Cochrane Methodology Register (Methods Studies)
- Health Technology Assessment Database (Technology Assessments)
- NHS Economic Evaluation Database (Economic Evaluations)

The Cochrane Database of Systematic Reviews

Cochrane Systematic Reviews investigate the effects of interventions for prevention, treatment and rehabilitation in a healthcare setting.

They are designed to facilitate the choices that doctors, patients, policy makers, and others face in health care.

Each review addresses a clearly formulated question; for example: can antibiotics help in alleviating the symptoms of a sore throat? The research is reviewed using stringent guidelines to establish whether or not there is conclusive evidence about a specific treatment.

Methodology reviews and protocols: Full-text reviews that examine the benefit of methodological studies e.g., Does editorial peer-review improve the quality of reports of biomedicale studies?

The impact of Cochrane Reviews

The Cochrane Library is used by a broad range of people interested in evidence-based health care, including consumers, clinicians, policy makers, researchers, educators, students and others.

- Each of these groups uses information in different ways, according to their different purposes.
- As Cochrane reviews have become known internationally as a source of high quality, reliable health information, many have also begun to interpret, adapt and disseminate Cochrane Reviews and information derived from them:
  - Clinical guidelines and health technology assessment organisations
  - Electronic databases
  - Journals
  - Health related websites

The Cochrane Library is evidence-based health care decision making.
Cochrane Reviews are known as the “gold standard” for systematic reviews in such key publications as The Lancet, New England Journal of Medicine, British Medical Journal, and the Journal of the American Medical Association and routinely appear there as well as in specialized medical journals for various specialty areas.

MeSH (Medical Subjects Heading Search)

Let us look at an example MeSH search.

**ABSTRACT**

**BACKGROUND**

Epidural analgesia is a common method of analgesia in labor. The benefits of epidural analgesia for labor pain are well documented. However, the effects on neonatal outcomes are less clear.

**OBJECTIVES**

The objective of this study was to assess the effects of epidural analgesia on neonatal outcomes.
Systematic review in dermatology

Cochrane Skin Group systematic reviews are more methodologically rigorous than other systematic reviews in dermatology

- Background The Cochrane collaboration aims to produce high-quality systematic reviews. It is not known whether the methods used in producing Cochrane Skin Group (CSG) reviews result in higher quality reviews than other systematic reviews in dermatology.
- Objectives The purpose of this study was to examine the quality of systematic reviews produced by CSG, and to compare them with other systematic reviews in the Cochrane Library.
- Methods Two reviewers independently assessed the quality of CSG reviews using the 10-item Oxman and Guyatt scale.
- Results Thirty-eight systematic reviews (17 CSG reviews published in The Cochrane Library, 11 CSG reviews published in peer-reviewed journals and 10 non-CSG reviews published in peer-reviewed journals) were included in the analysis. Cochrane reviews included quality of life (15/17 vs. 7/10, P = 0.04) and adverse outcomes (14/17 vs. 13/10, P = 0.04) more often than non-CSG reviews published in peer-reviewed journals.
- Conclusions The Cochrane Library systematic review methodology leads to higher quality reviews on dermatological topics.

Cochrane Reviews: Skin Diseases

- Antistreptococcal interventions for guttate and chronic plaque psoriasis
- Bacillus Calmette-Guerin (BCG) vaccine for preventing leprosy
- Balneophototherapy for chronic plaque psoriasis
- Biologics for chronic plaque psoriasis
- Chemoprophylaxis versus chemotherapy for metastatic malignant melanoma
- Chinese herbal medicine for atopic eczema
- Clinical diagnosis by primary care practitioner versus clinical diagnosis by dermatologist for skin cancer
- Complementary therapies for skin cancer
- Cox-2 inhibitors in the Prevention of Melanoma
- Dietary exclusions for established atopic eczema
- Dietary supplements for established atopic eczema
- Disposable nappies for preventing napkin dermatitis in infants
- Drugs for discoid lupus erythematosus
- Educational programmes for skin cancer prevention
- Emollients for eczema
- Fumaric acid esters for psoriasis
- H1 antihistamines for eczema
- H1 antihistamines for chronic urticaria
- Histamine H2-receptor antagonists for urticaria
- House dust mite reduction and avoidance measures for treating asthma
- Immunotherapy for insect sting allergy
- Interferon alpha for the adjuvant treatment of cutaneous melanoma
- Interventions for actinic keratoses
- Interventions for alopecia areata
- Interventions for American cutaneous and mucocutaneous leishmaniasis
- Interventions for androgenic alopecia in women
- Interventions for basal cell carcinoma of the skin
- Interventions for Bowen’s Disease
- Interventions for bullous pemphigoid
- Interventions for cellulitis and erysipelas
- Interventions for chronic palmoplantar pustulosis
- Interventions for cutaneous disease in systemic lupus erythematosus
- Experience in systematic reviews in dermatology
- Topical Medications for Seborrheic Dermatitis:
  Systematic Review & Meta-Analysis

Waraphorn Apasrawirote MD.
Suthee Rattanamongkolgul MD., MPH. Ph.D.
Montree Udompataikul MD.
METHODS

1. Search for all relevant studies
   1.1 Electronic databases (number of papers found)
   1.2 Citation tracking (number of papers found)
   1.3 Hand searching (number of papers found)
   1.4 Gray literatures (number of papers found)
   1.5 Abstract from meeting (number of papers found)
   1.6 Ongoing studies (number of papers found)
   1.7 Experts (number of papers found)
   1.8 Manufacturers (number of papers found)

2. Study inclusion/exclusion
   Inclusion criteria
   1. RCTs
   3. seborrheic dermatitis patients
   4. topical medications intervention
   5. No language limitation
   Exclusion criteria
   1. Immunocompromised patients such as HIV infection
   2. neurologic disorders such as Parkinson’s disease
   3. scalp lesions

3. Quality assessment
   The Cochrane Collaboration guidelines: 6 domains
   1. Randomization
   2. Allocation concealment
   3. Blinding of participants, investigators
   4. Incomplete outcome data
   5. Selective outcome reporting
   6. Other sources of bias

4. Data extraction
   - details of study :
     - methods
     - participants
     - outcome assessment
     - statistical analysis
     - results
   - entry in database

5. Statistical synthesis & analysis :
   Revman 5 program
   - Synthesis :
     Relative risk (RR) of treatment response with 95% CI
     (treatment response: clinical improvement ≥ 75%)
   - Analysis :
     Pooled relative risk: fixed effects model
     show by forest plot

METHODS

Data extraction form:
- Study ID
- Methods
- Participants
- Outcome assessment
- Statistical analysis
- Results
- Entry in database

METHODS

Forest plot

RR
- = 1 equally effective
> 1 favours treatment
< 1 favours control
If 95%CI included 1 = statistically not significant
6. Conclusion & Report

Follow QUOROM Guidelines

(The Quality Of Reporting Of Meta-analysis)

METHODS

RESULTS

Search results

Topical agents

No. of studies Total no. of patients

Antifungals: ketocnazole, metronidazole, ciclopiroxolamine, bifonazole

19 2861

Corticosteroids: hydrocortisone acetate, betamethasone dipropionate, betamethasone valerate, clobetasol 17-butyrate, hydrocortisone 17-butyrate

13 838

Immunomodulators: pimecrolimus

4 236

Others: ketocnazole+desonide, lithium, Aloe vera, septal®

5 537

RESULTS

Effectiveness of topical antifungals

Table: Topical antifungals vs. Vehicles

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Total (95% CI)</th>
<th>Total events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupuy P. 2001</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Green C.A. 1987</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Unholzer A. 2002</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Zienicke H. 1993</td>
<td>47</td>
<td>57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Total (95% CI)</th>
<th>Total events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.35, df = 3 (P = 0.50); I² = 0%

Test for overall effect: Z = 5.17 (P < 0.00001)

Pooled RR (95% CI)

Antifungals Vehicle

2.75 (1.87, 4.03)*

0.97 (0.75, 1.27)

1.15 (0.92, 1.45)

1.79 (1.32, 2.43)

* significant
**RESULTS**

### Effectiveness of topical corticosteroids

<table>
<thead>
<tr>
<th>Topical corticosteroids</th>
<th>No. of studies (total patients)</th>
<th>Pooled RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs. Vehicles</td>
<td>2 (323)</td>
<td>1.77 (1.25, 2.52)*</td>
</tr>
<tr>
<td>vs. Corticosteroids</td>
<td>3 (101)</td>
<td>1.15 (0.92, 1.42)</td>
</tr>
<tr>
<td>vs. Pimecrolimus</td>
<td>2 (118)</td>
<td>0.97 (0.70, 1.34)</td>
</tr>
</tbody>
</table>

* significant

### Effectiveness of topical pimecrolimus

<table>
<thead>
<tr>
<th>Topical pimecrolimus</th>
<th>No. of studies (total patients)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs. Vehicle</td>
<td>1 (94)</td>
<td>1.12 (0.88, 1.42)</td>
</tr>
</tbody>
</table>

**CONCLUSION**

- Conclusion from sufficient data for treating seborrheic dermatitis is "the antifungals were effective than vehicle".
- Other comparisons have less evidence for definite conclusion.

**LIMITATIONS**

1. Unavailable database sources such as EMBASE. But all relevant studies were retrieved via another sources.
2. The studies that published over 20 years are difficult to evaluate due to unclear methodology.
   - This may explain why the studies of corticosteroids were found less than antifungals.

**RECOMMENDATIONS**

- For practice: Topical antifungals have adequate evidence for the efficacy in treatment of seborrheic dermatitis
- For future research direction:
  - Evaluate seborrheic dermatitis in other views
  - Scalp lesions
  - Specific group of patients eg. HIV infection
  - Prevention of recurrence
  - Other route of administration eg. Oral
  - Economic evaluation

**THANK YOU**