Evidence-Based Medicine
Pharmacy, and Nursing
2010

林口長庚紀念醫院
實證醫學中心暨風濕過敏免疫科
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教學大綱

- 實證醫學介紹 (slide 1-42) 及教學應用
- 提出臨床問題 (PICO)
- 提升文獻搜尋技巧 (cite references)
- 嚴格文獻評讀
- 實例練習
  - 病歷紀錄引用參考文獻 (PubMed or UpToDate…)
Medical Education in the New Century

- Bioinformatics
- Ethics
- Humanities
- Patient-centered care
- Problem-based learning
- Evidence-based medicine
Evidence-Based Medicine

※ 定義: Use of current best evidence in making decisions about the care of individual patients.

※ EBM (EBN, EBP) is the integration of best research evidence with clinical expertise and patients’ unique biology, values and circumstances (patient’s expectation).

(Evidence-based Practice) (Sackett & Straus)
Decision Making in Health Care

- What you learned during your professional training
- Browse journals
- Textbooks
- Ask colleagues

- Searching bibliographic databases
- Clinical practice guideline (CPG)
- Evidence-based journal abstracts
- “Do no harm”

Chart record – cite reference
實證醫學的五大進行步驟

Five Steps to Practice EBM (5 As)

1. **Formulate an answerable question.** ~ **Ask (PI CO)**
   提問：由個案的臨床資料提出可回答的臨床問題

2. **Track down the best evidence.** ~ **Acquire (Cite paper)**
   尋找最佳的實證文獻〔各種文獻資料庫，包括發表及未發表的資料〕

3. **Critically appraise the evidence for validity, impact, and applicability.** ~ **Appraisal (VIP)**
   評估最佳實證醫學文獻的可信度、臨床重要性、以及可應用性

4. **Integrate with our clinical expertise and patient values.**
   整合並應用於實際患者的治療決策～〔臨床應用〕告知～**Apply (3 E)**

5. **Evaluate our effectiveness and efficacy.** 效果評估～**Audit**
   溝通用簡單且病人可以聽懂的語言，告知各種處置之可能利益與風險
臨床問題類型

診斷 (Diagnosis)
- Sensitivity, specificity 敏感度、特異度
- Predictive value (PPV, NPV) 陽性預測值、陰性預測值
- ROC curve, Likelihood ratio (LR+, LR-) 概似比

治療 (Therapy)
- Clinical trial (Randomized Controlled Trial, RCT, RR)

預後 (Prognosis)
- Prediction model (Survival analysis, HR 風險比)

危險因子探討 (Risk factor)
- Cohort study (Relative Risk, RR 相對風險比)
- Case-control study (Odds Ratio, OR 勝算比)
Five Steps to Practice EBM (5 As)

- **Step 1.** Converting the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc.) into an answerable question. *(Ask)* - PICO

- **Step 2.** Searching the best evidence with which to answer that question. *(Acquire)*

- **Step 3.** Critically appraising the evidence for its validity (closeness to the truth), impact (size of the effect), and applicability (usefulness in our clinical practice). *(Appraisal)* - VIP

- **Step 4.** Integrating the evidence with our clinical expertise and patients’ unique biology, values and circumstances. *(Apply)* - 3 E

- **Step 5.** Evaluating our effectiveness and efficiency in executing steps 1-4 and seeking ways to improve them for next time. *(Audit)*
The Evidence Pyramid
Level of Evidence I~V

Randomized Controlled Trials (RCT) ~ I

II 世代研究

III 病例對照研究

IV 病例報告及系列

V 個人意見、動物及試管研究

Animal, test tube research

研究設計與證據強度 (Bias, Robust)

Hierarchy of evidence: arranges study designs by their susceptibility to bias. (Robust)
<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Level of Evidence</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>[A]</td>
<td>1a</td>
<td>Systematic review (with homogeneity) of RCTs</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Single RCT (randomized controlled trial)</td>
</tr>
<tr>
<td></td>
<td>1c</td>
<td>‘All-or-none’</td>
</tr>
<tr>
<td>[B]</td>
<td>2a</td>
<td>Systematic review of cohort studies</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>Cohort study or poor RCT</td>
</tr>
<tr>
<td></td>
<td>2c</td>
<td>‘Outcomes’ research</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>Systematic review of case-control studies</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Case-control study</td>
</tr>
<tr>
<td>[C]</td>
<td>4</td>
<td>Case series</td>
</tr>
<tr>
<td>[D]</td>
<td>5</td>
<td>Expert opinion, physiology, bench research</td>
</tr>
</tbody>
</table>
US Preventive Services Task Force Rating System of Quality of Scientific Evidence

- **I**: Evidence obtained from at least 1 properly designed, randomized controlled trial

- **II-1**: Evidence obtained from well-designed controlled trials without randomization

- **II-2**: Evidence obtained from well-designed cohort or case-control analytic studies, preferentially from more than 1 center or group

- **II-3**: Evidence obtained from multiple time series with or without the intervention, or dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s)

- **III**: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
實證醫學沿革

1972年英國臨床流行病學者Archie Cochrane提出實證醫學的概念。
所有醫療行為都應有嚴謹研究且證實為有效的根據，才能將醫療資源做最有效的運用，並強調Randomized controlled trials 的重要性。〔*無效果之檢驗或治療不要做〕

1992英國國家衛生部成立實證醫學中心，並以Archie Cochrane之名命名，進而促使1993年Cochrane Collaboration的設立。 (Iain Chalmers, David Sackett)

Lancet 曾把Cochrane Collaboration比作臨床醫學的人類基因組計劃
Study Design

流行病学研究
(The Epidemiologic Study)

控制的分配
(Controlled Assignment)

實驗研究
(Experimental Studies)

社區研究
(Community Trials)

社區分配

個人隨機分配

隨機之臨床試驗
(Randomized Clinical Trials)

依結果取樣

病例對照研究
(Case-Control Studies)

依暴露因子取樣

世代研究
(Cohort Studies)

Observational Studies

観察研究
(Observational Studies)

控制的分配
(Controlled Assignment)

實驗性研究
(Experimental Studies)

社區研究
(Community Trials)

社區分配

個人隨機分配

隨機之臨床試驗
(Randomized Clinical Trials)

依結果取樣

病例對照研究
(Case-Control Studies)

依暴露因子取樣

世代研究
(Cohort Studies)

1. 分配：Experimental study 實驗性研究 vs. 觀察性研究 Observational study
2. 時間：Longitudinal (prospective or retrospective) vs. Cross-sectional study
Study research design The appropriate research design depends upon the question asked. A randomized, controlled trial is best for information on the effects of a therapeutic or preventive intervention, while a cross-sectional study is best for the evaluation of diagnostic test performance. Reproduced with permission from Fletcher, RH, Fletcher, SW. Principles of clinical epidemiology. In: Kelly, WN (Ed). Textbook of Internal Medicine. Philadelphia; JB Lippincott 1988.
# Study Design

<table>
<thead>
<tr>
<th>Study Design</th>
<th>研究種類</th>
<th>研究開始</th>
<th>問題（用途）</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>研究種類</td>
<td>時間性</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional (prevalence)</td>
<td>橫斷性</td>
<td>經過</td>
<td>▼收集資料▼Case &amp; non-Case</td>
</tr>
<tr>
<td>Cohort (longitudinal)</td>
<td>縱向性（前瞻）</td>
<td>定義世代並評估危險因子</td>
<td>觀察結果Y*N</td>
</tr>
<tr>
<td>Clinical Trial (experimental)</td>
<td>縱向性（前瞻）</td>
<td>作治療[治療組與對照組]</td>
<td>觀察結果Y*N</td>
</tr>
<tr>
<td>Case control (retrospective)</td>
<td>縱向性（回溯）</td>
<td>評估危險因子 Exposure: Y*N</td>
<td>限定病例組與非病例組</td>
</tr>
<tr>
<td>Repeated cross-sectional</td>
<td>橫斷性</td>
<td>收集資料▼</td>
<td>重複收集▼▼</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>研究種類</th>
<th>時間性</th>
<th>經過</th>
<th>現在</th>
<th>未來</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional (prevalence)</td>
<td>橫斷性</td>
<td>視診</td>
<td>定義世代並評估危險因子</td>
<td>觀察結果Y*N</td>
</tr>
<tr>
<td>Cohort (longitudinal)</td>
<td>縱向性</td>
<td>定義世代並評估危險因子</td>
<td>診斷</td>
<td></td>
</tr>
<tr>
<td>Clinical Trial (experimental)</td>
<td>縱向性</td>
<td>作治療[治療組與對照組]</td>
<td>藥物療效評估</td>
<td></td>
</tr>
<tr>
<td>Case control (retrospective)</td>
<td>縱向性</td>
<td>評估危險因子 Exposure: Y*N</td>
<td>限定病例組與非病例組</td>
<td>病因[尤其罕病]</td>
</tr>
<tr>
<td>Repeated cross-sectional</td>
<td>橫斷性</td>
<td>收集資料▼</td>
<td>重複收集▼▼</td>
<td>隨時間改變</td>
</tr>
</tbody>
</table>
Calculation of RR, OR

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Event (Disease)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Treatment)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Exposed</strong></td>
<td><strong>A = 1</strong></td>
<td><strong>B = 29</strong></td>
</tr>
<tr>
<td>(Experimental gr.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Not exposed</strong></td>
<td><strong>C = 9</strong></td>
<td><strong>D = 21</strong></td>
</tr>
<tr>
<td>(Control group)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EER**, experimental event rate $= \frac{a}{a+b} = 0.033$  \textbf{(Cohort study, RCT)}

**CER**, control event rate $= \frac{c}{c+d} = 0.30$

1. \textbf{Relative Risk} = Risk ratio = $\frac{EER}{CER} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} = 0.11$

2. \textbf{*Relative Odds} = *Odds Ratio = $\frac{a}{b} / \frac{c}{d} = \frac{ad}{bc} = 0.08$

*Experimental event Odds $= \frac{a}{b} = 0.034$  \textbf{(Case-control study)}

*Control event Odds $= \frac{c}{d} = 0.43$

In rare event (盛行率<10%), OR $\approx RR$  \textbf{Odds: a ratio of events to non-events} $= \frac{p}{1-p}$ vs. Probability = event / (event + non-event)
Treatment of diffuse proliferative lupus nephritis: A meta-analysis of randomized controlled trials


Fig 1. Flow chart indicating the number of citations retrieved by individual searches and final number of RCTs included in the systematic review. Reasons for exclusions are provided.
null hypothesis (虚無假設 RR, OR, or HR = 1, mean difference, effect size = 0): a vertical line at 1.0 representing equiva-

lence in risk for an outcome with experimental and control treatment. Values of RR less than 1 indicate a reduction in risk for the outcome with the experimental treatment. Conversely, values of RR more than 1 indicate an increase in risk.

3 Point estimate and 95% CI (點估計與區間估計): The RR for each outcome and its 95% CI are indicated by a solid square and a line. The 95% CIs are a measure of variability in the precision of the RR estimate and its statistical significance. The size of the solid square represents the contribution (weight) of the trial to the analysis.

4 Heterogeneity (‘non-combinability if p < 0.05’) of treatment effects between studies was investigated by visual examination of graphic meta-analysis plots and from the Cochran Q (heterogeneity chi-square) and I² statistic.
### Treatment of Proliferative lupus nephritis

严格評讀 ~ 研究方法的品質：如隨機產生方式、隱密性，盲性，ITT及失聯比率。

(評讀的 Checklist: Jadad score, Grade method, VIP, RAMbo, CAT, CASP…)

#### Table 3. Quality assessment of RCTs Included in This Systematic Review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Intention-to-Treat Analysis</th>
<th>Lost to Follow-Up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin et al(^{14})</td>
<td>1986</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>4/107 (3.7)</td>
</tr>
<tr>
<td>Balietta et al(^{16})</td>
<td>1992</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/10 (0.0)</td>
</tr>
<tr>
<td>Barron et al(^{12})</td>
<td>1982</td>
<td>Inadequate</td>
<td>No</td>
<td>No</td>
<td>0/22 (0.0)</td>
</tr>
<tr>
<td>Belmont et al(^{21})</td>
<td>1995</td>
<td>Unclear</td>
<td>Investigators, participants, outcome assessors</td>
<td>Yes</td>
<td>0/14 (0.0)</td>
</tr>
<tr>
<td>Boletis et al(^{25})</td>
<td>1999</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/14 (0.0)</td>
</tr>
<tr>
<td>Boumpas et al(^{17})</td>
<td>1992</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/65 (0.0)</td>
</tr>
<tr>
<td>Cade et al(^{6})</td>
<td>1973</td>
<td>Inadequate</td>
<td>No</td>
<td>No</td>
<td>4/54 (7.4)</td>
</tr>
<tr>
<td>Chan et al(^{24})</td>
<td>2000</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/42 (0.0)</td>
</tr>
<tr>
<td>Clark et al(^{11})</td>
<td>1981</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>0/12 (0.0)</td>
</tr>
<tr>
<td>Clark et al(^{13})</td>
<td>1983</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>3/39 (7.7)</td>
</tr>
<tr>
<td>Derksen et al(^{15})</td>
<td>1988</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/20 (0.0)</td>
</tr>
<tr>
<td>Donadio et al(^{11})</td>
<td>1974</td>
<td>Inadequate</td>
<td>No</td>
<td>No</td>
<td>1/19 (5.2)</td>
</tr>
<tr>
<td>Donadio et al(^{10})</td>
<td>1978</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/50 (0.0)</td>
</tr>
<tr>
<td>Doria et al(^{19})</td>
<td>1994</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/18 (0.0)</td>
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<tr>
<td>Fries et al(^{16})</td>
<td>1973</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/10 (0.0)</td>
</tr>
<tr>
<td>Fu et al(^{23})</td>
<td>1998</td>
<td>Adequate</td>
<td>No</td>
<td>No</td>
<td>0/40 (0.0)</td>
</tr>
<tr>
<td>Ginzler et al(^{9})</td>
<td>1976</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>0/14 (0.0)</td>
</tr>
<tr>
<td>Gourley et al(^{22})</td>
<td>1995</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>5/62 (6.1)</td>
</tr>
<tr>
<td>Hahn et al(^{9})</td>
<td>1975</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>2/24 (8.3)</td>
</tr>
<tr>
<td>Houssiau et al(^{27})</td>
<td>2002</td>
<td>Adequate</td>
<td>No</td>
<td>Yes</td>
<td>1/90 (1.1)</td>
</tr>
<tr>
<td>Lewis et al(^{18})</td>
<td>1992</td>
<td>Adequate</td>
<td>No</td>
<td>Yes</td>
<td>1/86 (1.2)</td>
</tr>
<tr>
<td>Nakamura et al(^{26})</td>
<td>2002</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/20 (0.0)</td>
</tr>
<tr>
<td>Sesso et al(^{20})</td>
<td>1994</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>2/29 (6.9)</td>
</tr>
<tr>
<td>Steinberg et al(^{4})</td>
<td>1971</td>
<td>Unclear</td>
<td>Investigators, participants, outcome assessors</td>
<td>No</td>
<td>2/15 (13.3)</td>
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<tr>
<td>Wallace et al(^{24})</td>
<td>1998</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>1/19 (5.2)</td>
</tr>
</tbody>
</table>

*Values expressed as number/total number (percent).*
進階學習與教學

目前國外推動實證醫學著名的單位

- 英國 Oxford University 的 Centre for Evidence-Based Medicine
  - [http://cemb.jr2.ox.ac.uk](http://cemb.jr2.ox.ac.uk) (CAT maker 計算器: 95% CI, CAT form)

- 加拿大 McMaster University 的 HI RU (Health Information Research Unit) 是 Cochrane Collaboration 重鎮
  - [http://hiru.mcmaster.ca/](http://hiru.mcmaster.ca/)

- 美國 American College of Physician (ACP)，出版 ACP Journal Club Online
  - [http://www.acpjc.org](http://www.acpjc.org)
Resource Centers for Guidelines

- **NGC** - National Guideline Clearinghouse  

- **AGREE** - appraisal of guideline research & evaluation  

- Guidelines International Network (GIN)  
  [http://www.g-i-n.net/](http://www.g-i-n.net/)

- **SIGN** - Scottish Intercollegiate Guidelines Network  
  [http://www.sign.ac.uk/](http://www.sign.ac.uk/)

- **NI CE** - National Institute for Health and Clinical Excellence  
Resource Centers for Guidelines

- National Library for Health (NLH) > 12,000
  http://www.library.nhs.uk/Default.aspx
- NZGG - New Zealand Guidelines Group
  http://www.nzgg.org.nz/
- National Health and Medical Research Council
- Center for Evidence-based Medicine, Oxford
  http://www.cebm.net/
- CMA Infobase (Canadian Medical Association)
  http://mdm.ca/cpgsnew/cpgs/index.asp
- 台灣實證臨床診療指引平台 (建置中)
  http://ebpg.nhri.org.tw/
學習目標
“Learning by Doing”

Five steps in practicing EBM
- Formulate clinical question ~ PICO principle
- Search database
  - Cochrane database, CCTR, DARE, ACP journal club
  - UpToDate
  - PubMed - Clinical queries (high quality filter) etc.
  - Micromedex, CINHAL...
- Judge level of evidence (研究設計), critical appraisal (VIP principle, RAMbo, Critical appraisal sheet, CASP...)
- Calculate NNT, NNH
  - number needed to treat (NNT = 1/ARR)
  - number needed to harm (NNH = 1/ARI)
  - Read forest plot (meta-analysis)
- Practice
  - 主動積極 自我學習 Attitude and behavior change
  - apply to patient care and chart record (cite reference!).
我家裡老大有氣喘，如果我吃益生菌，可以預防第2胎新生兒氣喘的發生嗎？
28歲懷孕三個月的母親，帶著2歲有氣喘的兒童，到婦兒科門診，問優酪乳可不可以預防或減少未來新生兒過敏病（氣喘）的發生？

Q&A: 益生菌 (probiotics)、優酪乳可不可以預防或減少過敏氣喘病發生或嚴重程度？

電視、報紙、PubMed上、許博士說：喝優酪乳增加腸道益生菌減少氣喘等效果。

『益生菌』(Probiotics) 就是對身體友好處的「好菌」，是一種可改善宿主腸內菌相平衡，有益宿主健康之活微生物體。例如一般人熟悉的A、B菌，被認爲具有保健效益，主要為乳酸菌和部分酵母菌。

『益菌生』(Prebiotics，又稱為益生源) 又是什麼？它是指可以刺激腸道裏的好菌生長的「食物」，這類的物質如我們常聽到的膳食纖維和果寡糖就是。『益菌生』物質能夠被有益菌利用而產生有機酸，刺激腸蠕動，並且能促進有益菌生長，抑制壞菌數量，使腸道更健康。

科學家發現，人體免疫樞紐部位的細胞T淋巴球，由所分泌的細胞素不同而分成二型（簡稱Th1，Th2），兩者間具有動態的平衡關係，影響免疫系統對抗原的反應，如Th2反應太強，就會出現過敏症狀。初生嬰兒的免疫機制偏向易造成過敏的Th2，益生菌有助新生兒建立平衡的Th1／Th2免疫機制。
實證醫學的五大進行步驟
Five Steps to Practice EBM (5 As)

1. **Formulate an answerable question.** *(Ask: PICO*)
   由個案的臨床資料形成可回答的臨床問題* (PI CO)

2. **Track down the best evidence.** *(Acquire: cite ref.)*
   尋找最佳的實證 [各種文獻及資料庫，包括發表及未發表的資料]

3. **Critically appraise the evidence for validity, impact, and applicability.** *(Appraisal: VI P)*
   評估各種醫學報告的可信度、臨床重要性，以及可應用性

4. **Integrate with our clinical expertise and patient values.** *(Apply: 3 E)*
   整合並應用於實際患者的治療決策 [臨床應用]

5. **Evaluate our effectiveness and efficacy.** *(Audit)* 效果評估
   告知以病人可以聽懂的語言，告知各種處置之可能利益與風險 (%)
1. Asking Answerable Clinical Questions (PI CO)

Well-built Clinical Question

- **“Background” question**
  - Ask general knowledge about a disorder
  - Have two essential components:
    - A question root (who, what, why, when, how, why, where) with a verb
    - A disorder, or an aspect of a disorder

- **“Foreground” question**
  - Ask for specific knowledge about managing patients with a disorder
  - Have four (or three) essential components (PI CO):
    1. **Patient/Problem**: Who is the patient or what is the problem being addressed? (病人族群與特徵)
    2. **Intervention**: What is the intervention (treatment)? (A 處置或檢驗)
    3. **Comparison intervention**: What are the alternatives? (B 處置或檢驗)
    4. **Outcomes**: What are the outcomes? (重要的臨床結果、指標)
There Are Four Elements of a Well-formulated Question
~ use PICO format ~

**Patient** ~ Who is the patient or what is the problem being addressed?

病人問題

**Intervention** ~ What is the intervention? (A)

介入處置 或 檢驗

**Comparison** ~ What are the alternatives? (B)

對照的處置 或 檢驗（其它的選擇）

**Outcome** ~ What are the outcomes?

重要的臨床結果、指標
1. Asking Answerable Clinical Question (PI CO)

<table>
<thead>
<tr>
<th>Patient/Problem</th>
<th>孕婦 (有氣喘家族史)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>吃益生菌 (probiotics)</td>
</tr>
<tr>
<td>Comparison</td>
<td>不吃益生菌</td>
</tr>
<tr>
<td>Outcomes</td>
<td>減少新生嬰兒氣喘的發生率</td>
</tr>
</tbody>
</table>

**Step 1. 提出問題的要點：** *As specific as possible!*
### Scenario 临床情境

: Ask ~ PI CO

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passenger</td>
<td>Stocking</td>
<td>No stocking</td>
<td>DVT</td>
</tr>
<tr>
<td>Population</td>
<td>Influenza vac.</td>
<td>No vaccine</td>
<td>URI %</td>
</tr>
<tr>
<td><strong>SLE nephritis</strong></td>
<td><strong>Endoxan</strong> / steroid</td>
<td>No hormone</td>
<td>Mortality/ESRD</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Hormone</td>
<td>Observation</td>
<td>Cancer</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>Anti-virus / Steroid</td>
<td>CPK-MB</td>
<td>Complication</td>
</tr>
<tr>
<td>Acute coronary</td>
<td>Troponin I</td>
<td>Low dose aspirin</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Kawasaki</td>
<td>High dose aspirin</td>
<td></td>
<td>aneurysm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intervention</th>
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<tr>
<td>Kawasaki</td>
<td>High dose aspirin</td>
<td></td>
<td>aneurysm</td>
</tr>
</tbody>
</table>
2. Searching The Best Evidence

尋找最佳實證資料

- 直接使用次級醫學資料庫 (secondary journals or databases) ~ ACP journal club, Cochrane database, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Micromedex…

- 同時尋找原始研究論文資料庫 (primary journals or databases) ~ 如 Medline, NEJM, Lancet…

- 原則：搜尋與病人問題相同或類似且證據等級 (level of evidence – 由上往下 top down) 較高之文獻，再謹慎嚴格評讀與評估此文章的證據在此問題的適用性。
Search the Best Evidence

1. Cochrane library, CCTR*, ACP journal club, DARE
2. UpToDate, MD consult
3. PubMed, Medline, CI NAHL
   - Meta-analysis
   - Systematic review
   - Cochrane (keyword 関鍵字)
   - Clinical queries* (高品質)

- Clinical evidence
- Best evidence
- Guidelines Clearinghouse
- (Evidence is never enough) …

一般醫學 Medicine

- Books@Ovid 電子書
- EBL (Ebook Library) 電子書
- Ebsco Electronic Journals Service (EJS) 電子期刊
- MEDLINE+OVID
- ProQuest Health 全文
- ProQuest Medical Library 電子期刊
- PubMed

證據醫學 Evidence Based Medicine

- Clinical Evidence
- Cochrane Controlled Trials Register
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effectiveness
- FBM Reviews - ACP Journal Club

書目管理軟體 Bibliography Tool

- Reference Manager 10版, 11版
- EndNote 7版, 8版, 9版

藥學 Pharmacology

- Micromedex(CCIS) 藥學、毒物、急診 全文

護理學 Nursing

- UpToDate Topic Review 全文資料庫
- 中國期刊全文數據庫 下載瀏覽器
5S EBM Resources

1. Systems
   連結個別病歴的臨床知識與支援決策系統

2. Summaries
   整合證據提供特定臨床問題之概述與建議
   ACP PIER
   BMJ Clinical Evidence
   DynaMed
   MDconsult
   UpToDate

3. Synopses
   對單篇研究或回顧性文獻作摘要評述
   ACP Journal Club, Evidence-Based Medicine
   (PubMed, Ovid Medline)

4. Syntheses
   特定臨床問題的系統性評論文獻
   Cochrane Database of Systematic Reviews
   Database of Abstracts of Reviews of Effects
   (PubMed, Ovid Medline): Systematic Reviews

5. Studies
   原始文獻 original studies
   (PubMed, Ovid Medline, CINAHL, EMBASE
   Cochrane CENTRAL, Google Scholar
   CEPS中文電子期刊, 中文期刊篇目索引)

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Browse by topic:

Related resources

Cochrane Colloquium
Freiburg, Germany, 3-7 October 2003
Past & future colloquiums here.
Level of Evidence I ~ V

Randomized Controlled Trials (RCT) ~ I

I 隨機控制對照研究
Double Blinded RCT

II 世代研究

III 病例對照研究

IV 病例報告及系列

V 個人意見、動物試管研究

研究設計與證據強度 (Bias, Robust)

Hierarchy of evidence: arranges study designs by their susceptibility to bias. (Robust)
## Current Best Evidence

### 證據等級 (修改自 Oxford Centre for Evidence-based Medicine, Level of Evidence)

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention</th>
<th>Diagnosis</th>
<th>Prognosis</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td>A SR of level II studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>RCT</td>
<td>Cross-sectional study among consecutive or random presenting patients</td>
<td>Prospective inception cohort study</td>
<td>Prospective cohort study</td>
</tr>
<tr>
<td>III</td>
<td>Pseudo-RCT or non-randomized experimental study</td>
<td>Cross-sectional study among non-consecutive patients</td>
<td>Untreated control patients in a RCT</td>
<td>A retrospective cohort study</td>
</tr>
<tr>
<td></td>
<td>Comparative observational study with concurrent control group (cohort study, case-control study)</td>
<td>Diagnostic case-control study</td>
<td>Retrospectively assembled cohort study</td>
<td>Case-control study</td>
</tr>
<tr>
<td>IV</td>
<td>Case series</td>
<td>Case series</td>
<td>Case series, or cohort study of patients at different stages of disease</td>
<td>Cross-sectional study</td>
</tr>
</tbody>
</table>

*SR = Systematic Review; RCT = randomized controlled trial*
<table>
<thead>
<tr>
<th>Level</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>Differential diagnosis/symptom prevalence study</th>
<th>Economic and decision analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>SR (with homogeneity*) of RCTs</td>
<td>SR (with homogeneity*) of inception cohort studies: CDRT validated in different populations</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; CDRT† with 1b studies from different clinical centres</td>
<td>SR (with homogeneity*) of prospective cohort studies</td>
<td>SR (with homogeneity*) of Level 1 economic studies</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCT (with narrow Confidence Interval‡)</td>
<td>Individual inception cohort study with &gt; 80% follow-up: CDRT validated in a single population</td>
<td>Validating** cohort study with good††† reference standards; or CDRT† tested within one clinical centre</td>
<td>Prospective cohort study with good follow-up****</td>
<td>Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>1c</td>
<td>All or none§</td>
<td>All or none case-series</td>
<td>Absolute SpPins and SnNouts‡‡</td>
<td>All or none case-series</td>
<td>Absolute better-value or worse-value analyses ††††</td>
</tr>
<tr>
<td>2a</td>
<td>SR (with homogeneity*) of cohort studies</td>
<td>SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs</td>
<td>SR (with homogeneity*) of Level &gt;2 diagnostic studies</td>
<td>SR (with homogeneity*) of Level &gt;2 economic studies</td>
<td>SR (with homogeneity*) of Level &gt;2 economic studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study (including low quality RCT, e.g., &lt;80% follow-up)</td>
<td>Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDRT† or validated on split-samples only</td>
<td>Exploratory** cohort study with good††† reference standards; CDRT† after derivation, or validated only on split-samples or databases</td>
<td>Retrospective cohort study, or poor follow-up****</td>
<td>Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>2c</td>
<td>“Outcomes” Research, Ecological studies</td>
<td>“Outcomes” Research</td>
<td>Ecological studies</td>
<td>Audit or outcomes research</td>
<td>Audit or outcomes research</td>
</tr>
<tr>
<td>3a</td>
<td>SR (with homogeneity*) of case-control studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual Case-Control Study</td>
<td>Non-consecutive study; or without consistently applied reference standards</td>
<td>Non-consecutive cohort study, or very limited population</td>
<td>Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.</td>
<td>Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.</td>
</tr>
<tr>
<td>4</td>
<td>Case-series (and poor quality cohort and case-control studies)***</td>
<td>Case-series (and poor quality prognostic cohort studies)***</td>
<td>Case-control study, poor or non-independent reference standard</td>
<td>Case-series or superseded reference standards</td>
<td>Analysis with no sensitivity analysis</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”</td>
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<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”</td>
</tr>
</tbody>
</table>

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.
The Best Evidence Depends on the Type of Question

- **What are the phenomena/problems?**
  - Observation

- **What is frequency of the problem?** \(\text{(Frequency)}\)
  - Random (or consecutive) sample

- **Does this person have the problem?** \(\text{(Diagnosis)}\)
  - Random (or consecutive) sample with gold standard

- **Who will get the problem?** \(\text{(Prognosis)}\)
  - Follow-up of inception cohort

- **How can we alleviate the problem?** \(\text{(Therapy)}\)
  - Randomized controlled trial \(\text{(RCT)}\)
Thank you!

- 以下 slide 43-79 爲參考附件

- Q & A
**Search Strategy**

- **Boolean** AND, OR, NOT
- **Truncation**: $ *$
- **Combine textwords/keywords/MeSH with OR**
  - Textwords/keywords 的部分，最好能善用 truncation 的功能
  - 要找有關 Salmonella 的資料，但論文中有時以 Salmonellosis 表示，這時你可以用 Salmonell$ or Salmonell*$ 代表所有 Salmonell 開頭的字串！
- **MeSH (Medical Subject Heading) in PubMed**
- **Free text searching, limit function**

- 將 P/ I/ C/ O 分別轉換成不同的字串／關鍵字／MeSH 再搜尋

<table>
<thead>
<tr>
<th>Primary Term</th>
<th>Synonym 1</th>
<th>Synonym 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (Kawasaki)</td>
<td>OR mucocutaneous lymph node syndrome OR</td>
<td>AND</td>
</tr>
<tr>
<td>I (Aspirin)</td>
<td>OR salicylic acid OR salicyl*</td>
<td>AND</td>
</tr>
<tr>
<td>C (Coronary aneurysm)</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>O (Coronary aneurysm)</td>
<td>OR</td>
<td>OR</td>
</tr>
</tbody>
</table>
**Scenario**

- **Patient and/or problem:**
  - A 3-y-o Kawasaki disease children with high fever for 5 days.

- **Intervention:**
  - IVIG and **High dose aspirin** (30-100 mg/kg/d) (treatment **A**) – anti-inflammation dose

- **Comparison intervention:**
  - IVIG and **Low dose aspirin** (3-5 mg/kg/d) (treatment **B**) – anti-platelet dose

- **Outcomes:**
  - Coronary artery aneurysm (%) 重要結果 outcome
Keywords: xxx and xxx and (Cochrane or meta-analysis or Systematic review) Dr.Yu

Extending the Pyramid

Assessing "Meta" skills like Professionalism

高品質過濾資料
Kawasaki disease and aspirin - PubMed Results - Microsoft Internet Explorer

A service of the National Library of Medicine and the National Institutes of Health

Search PubMed for "Kawasaki disease and aspirin"

Display: Summary

All: 423

Items 1 - 20 of 423

1: Credilla A.

2: Yamagata-Nakahashida MA, Ramirez-Vargas N, De Robens-Figueroa J.


4: Higashi K, Terai M, Hanada H, Honda T, Kansewa M, Kohno Y.

5: Uehara R, Yasutaka M, Oki I, Nakaizumi Y, Yanagawa H.
使用Clinical Queries來加速得到高等級實證醫學證據
使用Clinical Queries来加速得到高等级证据


5. Soga K.
<table>
<thead>
<tr>
<th>#</th>
<th>Search History</th>
<th>Results</th>
<th>Display</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Kawasaki and aspirin).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]</td>
<td>34</td>
<td>DISPLAY</td>
</tr>
</tbody>
</table>

Enter **Keyword** or phrase (use "$" for truncation):

[Search Strategy]

http://gateway.tx.ovid.com/gw2/ovidweb.cgi?Titles+Display=1&S=OLLHFFCFILDDGAIDMCILKE0KDDPPA00

(圖像) 開始 | 院區網路 | 財團法人... | Ovid: Search Form - Microsoft Internet Explorer | 未命名 - 小書家 | PM 12:15
EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2007> (3 records) | EBM Reviews - ACP Journal Club <1991 to September/October 2007> (0 records) | EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2007> (3 records) | EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2007> (28 records)

Results of your search: (Kawasaki and aspirin).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]

Viewing 1-10 of 34 Results
Go to #: 1

Q&A: 哪一篇是 Best evidence?

嚴格評讀文章 2009.06


5. 乳酸菌達人 氣喘過敏兒的實驗報告 ～台灣氣喘衛教學會理事長徐世達醫師 過敏氣喘照護的新觀念：益生菌的功能


3. 如何評讀論文

V-I-P principle
(RAMbo, CAT, CASP, Gate frame...)

- ✔ Yes
- ✗ No
- ☐ ? Unclear

How do I apply the results to the care of my patients? Both 1 & 2 (V-I-P)

1. ✔ Are the result Valid? (可信度：文章結果可信嗎? Truth?)
2. ✔ What is the Impact? (重要性：效果大小 Size of the effect NNT)
3. Practical in Practice?
3. Critically **Appraising** the Evidence

治療文獻 (RCT) 論文評讀 重點

☑ Yes  ☐ No  □ ? Unclear

評估文章的可信度 (**Validity**) 和實用性 （*注意研究選入病人的條件*）

1. 病人的分組是隨機分派的嗎？(random allocation)  ☑ Yes
2. 分派的方法是否保密？(concealment of allocation)  ☒ No
3. 追蹤是否完整？(follow-up duration) (> 80%) (失聯者少於20%)  ☑ Yes
4. 治療方法對病患、醫護人員、研究者是否 blinded？  ☑ Yes
5. 分析是否利用 Intention-to-Treat analysis (ITT)？☑ No vs. per protocol
6. 除了研究治療項目以外，其他的治療在各組間是否相同？  ☑ Yes
7. 兩組在治療開始時的 baseline 是否相似？(Table 1)  ☑ Yes

在閱讀每一篇文章時，要注意是否符合這些基本原則，如果沒有，是為什麼沒有，對於結果有沒有影響？(in Material & Method, Result section)

當有了一個可信的結果，還要考慮文章的結果對病人實際上的意義為何？重不重要 (**Impact** 重要性 **importance**: size of the effect, NNT, NNH)

文章常以 RRR (Relative risk reduction) 表示療效，但以 NNT (Number Needed to Treat), 及 NNH (Number needed to harm) 表達更為直接。
3. Critical Appraisal of the Evidence

(Critically appraising the evidence for its \textit{VIP})

\begin{itemize}
\item \textbf{Validity (closeness to the truth/可信度)} ~ 注意文章 inclusion criteria
  \begin{enumerate}
  \item Was the assignment of patients to treatment randomized?
  \item Was follow-up of patients sufficiently long and complete? (> 80%)
  \item Were all patients analyzed in the groups to which they were randomized? (ITT, Intension To Treat analysis) vs. per protocol
  \item Were patients and clinicians kept blind to treatment?
  \item Were groups treated equally, apart from the experimental therapy?
  \item Were the groups similar at the start of the trial?
  \begin{itemize}
    \item \textbf{Validity (truth)}: consider selection bias, information bias, confounding factor
    \item \textbf{Reliability} of measurement (Repeatability): intraobserver (similarity over time), interobserver, internal consistency
      \begin{itemize}
        \item SD, variance, point estimate - 95% CI (narrow or wide), p value (< 0.05)
      \end{itemize}
  \end{itemize}
\end{enumerate}
\item \textbf{Impact (size of the effect, importance)}: 臨床的重要性
  \begin{itemize}
    \item \textbf{NNT} (number needed to treat) = 1/ARR (absolute risk reduction)
    \item \textbf{NNH} (number needed to harm) = 1/ARI (absolute risk increase)
  \end{itemize}
\item \textbf{Practice Applicability (usefulness in our clinical practice)}
  \begin{itemize}
    \item Integrating the evidence with our clinical expertise and patients’ values and preferences (expectation). \textit{(3E)}
  \end{itemize}
\end{itemize}
### Asking an Answerable Question

**Impact:** NNT, NNH

<table>
<thead>
<tr>
<th><strong>Patient/Problem</strong></th>
<th>Insulin-dependent diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Intensive insulin regimen</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>Regular insulin regimen</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>1. Retinopathy</td>
</tr>
<tr>
<td></td>
<td>2. Symptomatic hypoglycemia</td>
</tr>
</tbody>
</table>
Treatment Effects

NNT 益一治療數

- Occurrence of diabetic retinopathy at 5 years among insulin-dependent diabetic in the DCCT trial
  - Usual insulin regimen (CER: control event rate): 38%
  - Intensive insulin regimen (EER: experimental event rate): 13%

Risk reduction (calculation): NNT

- Absolute risk reduction (ARR)
  \[ \text{ARR} = |\text{CER-EER}| = 38\% - 13\% = 25\% \]
- Relative risk reduction (RRR)
  \[ \text{RRR} = \frac{|\text{CER-EER}|}{\text{CER}} = \frac{25\%}{38\%} = 66\% \]
- Number needed to treat (NNT)
  \[ \text{NNT} = \frac{1}{\text{ARR}} = \frac{1}{25\%} = 4 \text{ patients} \]

NNT: The number of patients that need to be treated to prevent one bad outcome or get one good outcome.

增加一位病患得到某種處置好處所需的治療病人數 = 1/ ARR, 即與對照組療法相比而言，使一位病人達到實驗組治療之有利結果（或預防產生不利結果）所需治療的病人數目。(NNT 越少越好)
Harm: NNH

The proportion of patients with at least one episode of **symptomatic hypoglycemia**
- Usual insulin regimen (CER: control event rate): 23%
- Intensive insulin regimen (EER: experimental event rate): 57%

Risk increase (calculation): **NNH**

- Absolute risk increase (ARI) = | EER - CER | = 57% - 23% = 34%
- Relative risk increase (RRI) = | EER-CER | / CER = (57%-23%)/23% = 148%
- **Number needed to harm (NNH)** = 1/ ARI = 1/0.34 = 3 patients (整數)

- NNH: The number of patients that need to be treated to cause one bad outcome (being harmed).
- 增加一位受試者罹患某種醫源性傷害的治療病人數：即對多少病人進行實驗組治療〔與對照組療法做比較〕會有多一個病人產生不良副作用。
  (NNH 數目, 越大越好)
From **RRR** to **ARR** and **NNT**

Measures of the effects of treatment: **RRR**, **ARR**

<table>
<thead>
<tr>
<th></th>
<th>CER</th>
<th>EER</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A</td>
<td>50%</td>
<td>39%</td>
<td>22%</td>
<td>11%</td>
<td>9 人</td>
</tr>
<tr>
<td>Treatment B</td>
<td>5.0%</td>
<td>3.9%</td>
<td>22%</td>
<td>1.1%</td>
<td>90 人</td>
</tr>
<tr>
<td>Treatment C</td>
<td>0.5%</td>
<td>0.39%</td>
<td>22%</td>
<td>0.11%</td>
<td>900 人</td>
</tr>
</tbody>
</table>

*RRR (RR, OR) can not discriminate huge treatment effects from small ones!*  
(also consider Patient’s baseline/control event rate, and time factor)

指標 Relative Risk (risk ratio) = EER/CER vs. Absolute Risk reduction (risk difference) = | EER–CER | vs. NNT=1/ARR
<table>
<thead>
<tr>
<th>呈现的方式</th>
<th>代表的意義</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk (相對風險) (RR)</td>
<td>治療組發生風險相對於對照組的倍數。RR=1 兩組無差別，RR &lt; 1 治療可降低風險， RR &gt; 1 治療會增加風險</td>
</tr>
<tr>
<td>RR = 0.10 / 0.15 = 0.67</td>
<td>RR &lt; 1 表示治療可降低死亡的風險</td>
</tr>
<tr>
<td>Absolute Risk Reduction (ARR)</td>
<td>治療組與對照組發生風險的絕對差異</td>
</tr>
<tr>
<td>(絕對危險性降低)</td>
<td>治療的益處是降低 5%的死亡率</td>
</tr>
<tr>
<td>ARR = 0.15 – 0.10 = 0.05 or 5%</td>
<td></td>
</tr>
<tr>
<td>Relative Risk Reduction (RRR)</td>
<td>相對於對照組，治療組降低風險的比率 (最常見的呈現方式)</td>
</tr>
<tr>
<td>(相對風險性降低)</td>
<td>相對於對照組，治療可以降低死亡的的機率 33%</td>
</tr>
<tr>
<td>RRR = 0.05 / 0.15 = 0.33 or 33% or RRR = 1 – 0.67 = 0.33 or 33%</td>
<td></td>
</tr>
<tr>
<td>Number Needed to Treat (NNT)</td>
<td>要預防一位病人不良結果發生，所必需治療的病人數</td>
</tr>
<tr>
<td>(益一需治數)</td>
<td>治療20位病人2年，才能預防1人死亡</td>
</tr>
<tr>
<td>NNT = 1 / ARR = 1 / 0.05 = 20</td>
<td></td>
</tr>
</tbody>
</table>
Five Steps to Practice EBM

- **Step 1.** Converting the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc.) into an answerable question. *(PICO)*
- **Step 2.** **Searching** the best evidence with which to answer that question. *(cite reference)*
- **Step 3.** Critically **appraising** the evidence for its validity (closeness to the truth), impact (size of the effect), and applicability (usefulness in our clinical practice). *(VIP)*
- **Step 4.** **Integrating** the evidence with our clinical expertise and patients’ unique biology, values and circumstances *(expectation)*. *(3E)*
- **Step 5.** **Evaluating** our effectiveness and efficiency in executing steps 1-4 and seeking ways to improve them both for next time.

**重點:** 用簡單且病人可以聽懂的語言，對病患告知診療決策的利與弊
Appraising the evidence:

- **Applicability** 臨床可應用性

- Are the result Valid?
- Is it clinical important? (Impact: NNT..)
- Applicability to our patient? (臨床可應用性)
  - Is our patient so different from those in the study that its results cannot apply?
    - Data from Taiwan, China, or Asia (種族差異)? Cost-effectiveness analysis (效益分析)
    - Do I miss any data? 搜尋參考文獻 詢問專家 有沒有其他處置方式?
  - What’re our Pt’s potential **benefits** from CCRT?
  - What’re our Pt’s potential **harms** from CCRT?
  - What’re our Pt’s values & preferences for the outcomes & side effect? (3 E)

- Discussion, apply and Audit
  - Plain language summary (absolute % difference, NNT, NNH)
Evidence-Based Practice

Clinical Scenario

- **Patient’s Clinical Problem**
  - raise clinical question

- **Perform Five Steps in EBM (5 As)**
  - **Ask (PI CO):** ask a clinical question (P-I-C-O)
  - **Acquire:** search database (cite reference)
  - **Appraisal (VIP):** Valid? Important? Practical?
  - **Apply:** to patient’s problem (3E evidence, experience, expectation)
    - **Plain language summary**
  - **Audit:** effectiveness (Explain treatment options to you patient)
1. 目前醫學上的證據並不支持孕婦服用益生菌預防氣喘的發生（文獻等級1a）。而您本身第一胎有氣喘，屬於高危險族群，雖然益生菌對於過敏疾病高危險嬰兒可能減少濕疹的機率，但對氣喘預防並沒有效果（文獻等級1a）。New Meta-analyss RR 1.47 (1.04-2.09)

2. 2008年有一篇研究，甚至發現孕婦生產前4-6周及嬰兒服用益生菌(LGG)6個月反而會增加二歲時氣喘的危險百分之16.9%，服用益生菌者中每六位( NNH = 6)會多增加一位得到氣喘的危險（文獻等級1b）。
Two Fundamental Principles of EBM

- **EBM posits a hierarchy of evidence to guide clinical decision making.** (Level of evidence)

- **Evidence** alone is never sufficient to make a clinical decision. **3E:**
  - Consider the patient’s value (Expectation of the Patient) 告知 同意：用病人可以聽得懂的語言 (explain)
  - Integrate clinical expertise (Expert opinion)
    - Trade the benefits and risks (NNT, NNH)
    - Costs ($)
    - Inconvenience
      - 研究效果需要因應個別病人做調整
      - 如治療 Patient NNT = 1/ (RRR × PEER)
      - PEER = patient expected event rate (your case)
Critical appraisal Checklist

CAT
- Oxford CEBM Critical Appraisal Sheets (include RAMBo sheet)
    - Report: CAT (Critical Appraisal Topic) form

CASP
- Critical Appraisal Skills Programme (CASP) appraisal tool
  - [http://www.phru.nhs.uk/pages/PHD/resources.htm](http://www.phru.nhs.uk/pages/PHD/resources.htm)

GATE frame (critical appraisal with picture)
診斷檢驗
Diagnostic test
Sensitivity. Specificity, PPV, NPV, LR, ROC curve

<table>
<thead>
<tr>
<th>檢查 (Test)</th>
<th>疾病 (Disease)</th>
<th>有 (Present)</th>
<th>無 (Absent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>陽性 (Positive)</td>
<td>真陽性</td>
<td>TP</td>
<td>a</td>
</tr>
<tr>
<td></td>
<td>僞陽性</td>
<td>b</td>
<td>FP</td>
</tr>
<tr>
<td>陰性 (Negative)</td>
<td>僞陰性</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>真陰性</td>
<td>d</td>
<td>TN</td>
</tr>
</tbody>
</table>
### Diagnosis

<table>
<thead>
<tr>
<th>Diagnostic test (ferritin)</th>
<th>Disease (IDA)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Positive (陽性)</td>
<td>731 <strong>TP a</strong></td>
<td>b <strong>FP 270</strong></td>
</tr>
<tr>
<td>Negative (陰性)</td>
<td>78 <strong>FN c</strong></td>
<td>d <strong>TN 1500</strong></td>
</tr>
</tbody>
</table>

Sensitivity (Sn) = \( \frac{a}{a+c} = \frac{731}{809} = 90\% \)

Specificity (Sp) = \( \frac{d}{b+d} = \frac{1500}{1770} = 85\% \)  
(敏感度會受疾病嚴重程度影響)

Positive predictive value (PPV) = \( \frac{a}{a+b} = \frac{731}{1001} = 73\% \) (=post-test probability)

Negative predictive value (NPV) = \( \frac{d}{c+d} = \frac{1500}{1578} = 95\% \)

*但在不同的疾病盛行率下，预测值会有所不同。～LR 概似比

**Positive predictive value (PPV)** 用贝叶斯定理表达为：
\[
PPV = \frac{Sen \cdot P}{Sen \cdot P + (1-Sp) \cdot (1-P)}
\]

<table>
<thead>
<tr>
<th>P</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>80.0%</td>
</tr>
<tr>
<td>0.05</td>
<td>17.4%</td>
</tr>
<tr>
<td>0.005</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

例：卵巢癌 CA-125: PPV ~ 2% in screen vs. 97% in pelvic mass cases
**Prevalence (different clinical situations) affect predictive value**

例：Ovarian cancer CA-125: PPV ~ 2% in screen vs. 97% in pelvic mass cases

- **Increasing the Prevalence of Disease Before Testing**: When the prevalence of disease in the population tested is relatively high — more than several percent — the test performs well.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Disease (HIV)</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (陽性)</td>
<td>9</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Negative (陰性)</td>
<td>1</td>
<td>9890</td>
<td></td>
</tr>
</tbody>
</table>

Note: spectrum of patients, age, gender, risk factors, clinical findings (prevalence)
Increasing the Prevalence of Disease Before Testing

~ Prevalence affect the PPV

**Community-wide HIV screening**

- Test: 90% sensitivity, 99% specificity
- Population: 10,000

| Prevalence: 0.1% | = 10/10,000 |
| PPV = 9/(9+100) = 0.08 = 8% |
| NPV = 9890/(1+9890) = 0.9999 = 100% |

Population = 10,000

| Prevalence = 10% | = 1000/10,000 |
| Sensitivity = 900/1000 = 90% |
| Specificity = 8910/9000 = 99% |
| PPV = 900/990 = 0.91 = 91% |
| NPV = 8910/9010 = 0.99 = 99% |

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Disease (HIV)</th>
<th></th>
<th>Disease (DM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Positive</td>
<td>9 TP</td>
<td>100 FP</td>
<td>900 TP</td>
</tr>
<tr>
<td>Negative</td>
<td>1 FN</td>
<td>9890 TN</td>
<td>100 FN</td>
</tr>
</tbody>
</table>
### Diagnosis

**LR**: likelihood ratio (multi-levels odds)

<table>
<thead>
<tr>
<th>Diagnostic test (ferritin)</th>
<th>Disease (IDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td><strong>Positive</strong> (陽性)</td>
<td>731 TP a</td>
</tr>
<tr>
<td><strong>Negative</strong> (陰性)</td>
<td>78 FN(II) c</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{TP}{TP+FN} = \frac{a}{a+c} = 731/809 = 90\% \)  
Sn  
Sp  
SNout, SpPin

Specificity = \( \frac{TN}{FP+TN} = \frac{d}{b+d} = 1500/1770 = 85\% \)

Positive predictive value (PPV) = \( \frac{a}{a+b} = 731/1001 = 73\% \) (=post-test probability)

Negative predictive value (NPV) = \( \frac{TN}{FN+TN} = \frac{d}{c+d} = 1500/1578 = 95\% \)

**LR**+ for a positive result = \( \frac{Sens}{1-Spec} = \frac{a}{a+c} / \frac{b}{b+d} = 90\%/15\% = 6 \)

**LR**- for a negative result = \( \frac{(1-sens)}{spec} = \frac{c}{a+c} / \frac{d}{b+d} = 10\%/85\% = 0.12 \)

Pre-test probability (prevalence) = \( \frac{a+c}{a+b+c+d} = 31\% \)

Pre-test odds = prevalence / (1-prevalence) = \( \frac{31\%}{69\%} = 0.45 \)

* Post-test odds = Pre-test odds \( \times \) LR = \( 0.45 \times 6 = 2.7 \)

Posttest probability = Posttest odds / (odds + 1) = \( 2.7/(2.7+1) = 73\% \) (= PPV 73\%)
Diagnosis

**Use of Sensitivity Test** (高敏感度檢查的運用)
- Treatable disease **Screening**: maximize sensitivity while optimizing specificity
- 未被檢查出來會有嚴重後果者 treatable or transmissible
  - e.g. screen donated blood for HIV, Pap smear, mammograms
- Rule out disease ~ \((SNout)\) e.g. ANA

**Use of Specificity Test** (高特定度檢查的運用)
- 當假陽性結果會傷害患者身體、情緒、財物時
  - e.g. cancer chemotherapy
- Rule in disease ~ \((SPin)\) **Diagnosis**: maximize specificity while optimizing sensitivity. e.g. anti-ds DNA

**ROC (receiver operating characteristic) curve**
- 以真陽性\((TP, \text{ 優敏度})\)為縱軸，假陽性\((FP, \text{ 1-特異度})\)為橫軸，即將有病及無病者檢驗結果呈陽性的機率做一比較。ROC curve下方的面積越大，診斷工具的準確度越好
  - Optimum **cutoff point** correlated with the best **Youden index** = \((\text{sensitivity} + \text{specificity} - 1)\)
  - \(\text{c.f. } LR^+\) for a positive result = \(\frac{\text{sensitivity}}{1 - \text{specificity}}\): The probability of that test result in people with the disease divided by the probability of the result in people without disease
  - Accuracy: proportion of correct results = \(\frac{a+d}{a+b+c+d} = \text{prevalence} \times \text{sensitivity} + (1-\text{prevalence}) \times \text{specificity} = \frac{TP+TN}{(TP+TN+FP+FN)}\)
Diagnosis Strategies
Serial vs. parallel test

- **Serial Test** (高特定度)
  - The result of test 1 are considered before test 2, and so on
  - In order to be considered positive, all test in the series must be positive
    - **Highly specific but insensitive**
  - **Useful when false positive are undesirable**
    - Such as treatment is highly invasive or toxic e.g. cancer chemotherapy

- **Parallel Test** (高敏感度)
  - Any positive is considered a positive
    - **Sensitive but not specific**
  - **Useful when rapid diagnosis is necessary and a missed diagnosis in undesirable**
EBM步驟一：形成一個可以回答的臨床問題 (Ask)

試著將您的問題分成下列四個部分 (PICO)：

- **Patient or Problem** 病人或問題
- **Intervention or Indicator** 介入或指標
  - 某種治療、檢查、危險因子等
- **Comparator** 比較－該治療和甚麼相比？
- **Outcome** 結果－您想要達成或避免甚麼？

EBM 步驟二：搜尋最佳證據 (Acquire)

- 利用問題的 PI CO結構（如上述 Ask）設定搜尋策略。
- 回想問題中各PI CO部份的每一個辭彙及同義詞。一次就單一PI CO元素進行搜尋。如，從介入（Intervention）開始，但必須確定你已聯集（OR）所有的同義詞。
- 可以使用截斷字（truncation），並加上”*”，如以 child*取代children搜尋文件：請試著從Cochrane開始；其他問題型態則建議試試PubMed: Clinical Queries 或 National Library for Health (NLH)。

- Dr. Yu KH ~ PubMed 快速搜尋技巧：(P) and (I) and (Cochrane or meta-analysis or systematic review)
步驟三 Appraisal ：嚴格評讀證據之
(a) 效度 與 (b) 重要性 (效益大小)

(a) 效度 (Validity) 各種形式的問題都含以下三個共同項目 (RAM-bo)
- 研究族群是否具有代表性 (Representative)？
  - 隨機選擇 (random selection)／連貫性／起始點病人群，或者如果是比較性的研究，組別間是否可以比較？隨機分派 (random allocation) ／調整
- 是否有足夠的確認和追蹤 (Ascertainment/ follow-up)？
  - 反應率／追蹤／確認 > 80%
- 結果的估計值測量 (Measurement) 是否公正無偏？恰當？
  - 結果以盲法 (blinded) 或客觀的 (objective) 估計
  - 以上這些答案，通常可以在文章中的方法學 (Method) 部分和結果 (Result) 的第一、二段中找到。這樣的評價，一開始可能會令您覺得困難重重（就像騎腳踏車一樣），但是，累積了一些經驗之後，您只要幾分鐘就能完成

(b) 重要性－效益大小
- 看結果段 (Results section) 中描述的主要結果。效果有多大？多重要？統計意義要看信賴區間及P值；相對危險 (relative risk)、相對危險性降低度 (relative risk reduction)、勝算比 (odds ratio) 代表生物學上的影響。效果的絕對估計值：絕對危險性降低 (absolute risk reduction)、益一需治數 (NNT, number needed to treat) 則代表在臨床上對病人的影響。
EBM 步驟四：將證據與臨床專業經驗及病人期望結合（Apply）

□ 您的病人是否與研究中的病人差別很大，以至於無法適用該研究結果？
□ 您期望您的病人從研究結果中獲得多大的好處？
□ 還有哪些替代方案？
□ 研究結果適用於您的病人嗎？
□ 病人的想法為何？

研究效果需要因應個別病人做調整，如治療

Patient NNT = 1/ (RRR × PEER)
EBM 步驟五：評估執行效果及效用－勤做紀錄，改善過程

最後一個步驟，看在執行過程中，您的表現如何？您可能要問自己下列幾個問題：

□ 您正在紀錄您的問題嗎？
□ 您是否正在廣大的資源中尋找有用的外部證據？
□ 您有能力將這些證據應用在適當的病人身上嗎？
□ 您是否依循這些新證據來改變您的診療習慣？