實證醫學病例討論報告

Evidence-Based Medicine

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Outline

- Clinical scenario-臨床場景
- Asking-提出問題
- Acquire- 搜尋資料
- Appraisal-嚴格評讀
- Apply-臨床應用
- Audit-自我評估

Clinical scenario(1)-General data

- Name:黃0康
- Gender: Male
- Age: 62 year-old
- Chart number: 22696535

Clinical scenario(2)

- This 62 year-old male presented with sudden onset blurred vision (od) for 2 days.
- Ophthalmic examination:
  - Vod: 0.1(NC), Vos: 0.6(0.8x-1.0xcyl-0.5x90)
  - Fundus: Branched retinal vein occlusion (od)
- Past history:
  - Hypertension (+)
  - Diabetes mellitus (+)
  - Hyperlipidemia (+)

Clinical scenario(3)

- Impression:
  - Branch retinal vein occlusion (od)

- Treatment
  - Intravitreal injection of Lucentis (od)

ASKING-提出臨床問題

1.Background questions

2.Foreground questions

Background Questions

- Q1:What is the etiology of branch retinal vein occlusion(BRVO)?
- Q2:How to treat branch retinal vein occlusion(BRVO)?

Q1:What is the etiology of BRVO?

- Retinal-vein occlusion is a common cause of vision loss in older persons, and the second most common retinal vascular disease after diabetic retinopathy.
- There are two distinct types, classified according to the site of occlusion.
  - **Branch retinal vein occlusion(BRVO)** - a vein in the distal retinal venous system is occluded, leading to hemorrhage along the distribution of a small vessel of the retina.
  - **Central retinal vein occlusion(CRVO)** - thrombus within the central retinal vein at the level of the lamina cribrosa of the optic nerve, leading to involvement of the entire retina.

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- **Risk factors**
  - Age
  - Hypertension
  - Diabetes mellitus
  - Smoking
  - Obesity
  - Hypercoagulable state
  - Glaucoma, which prevents retinal vein outflow and leads to stasis
  - Retinal arteriolar abnormalities

Q2: How to treat BRVO?

- Treatment options for retinal vein occlusion
  - **Laser photocoagulation** - an established therapy for patients with BRVO and either macular edema with visual impairment or with neovascularization.
  - Medical therapy
    - **Vascular endothelial growth factor (VEGF) inhibitors** - The choice of initial therapy is undergoing reassessment as familiarity with VEGF inhibitors is increasing and data from randomized trials are emerging
    - **Intravitreal glucocorticoids**
- Duration of treatment for BRVO and CRVO varies based on the treatment modality and response to treatment, but can last several weeks to months. The main goals of treatment include improvement or stabilization of visual acuity.

Apply to the patient

- The patient
  - 62 y/o
  - Diabetes mellitus (+), Hypertension(+)
- Treatment
  - Intravitreal injection of Lucentis (od)

Foreground Questions

- Is Intravitreal injection of Ranibizumab (Lucentis) effective in patients with BRVO?

PICOT

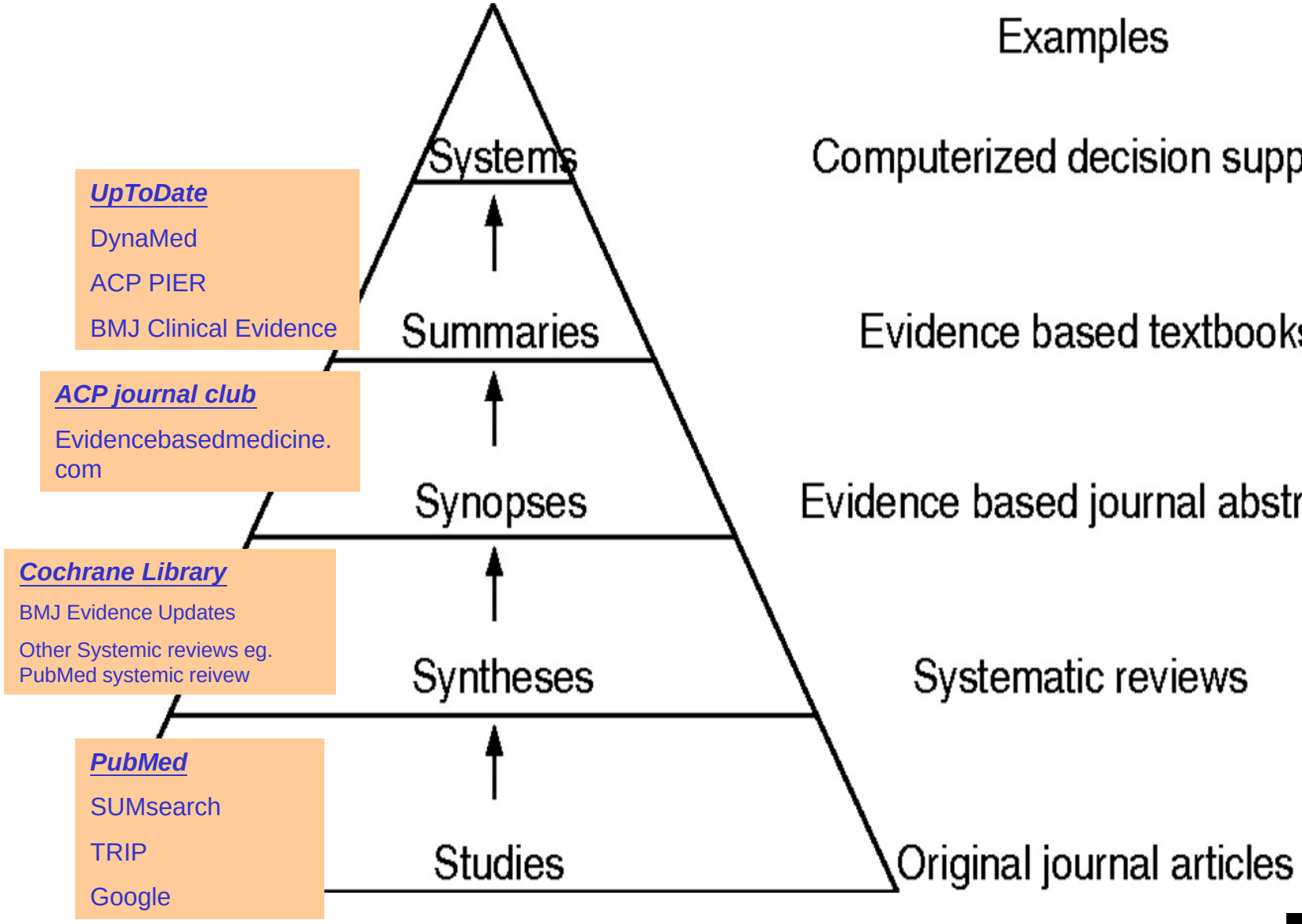
- Patient/Problem
  - Patients with branch retinal vein occlusion (BRVO)
- Intervention
  - Intravitreal injection of Ranibizumab (Lucentis)
- Comparison
  - Placebo
- Outcome
  - Improvement in visual acuity or visual function
- Time
  - Not confined

Acquire-搜尋最有用的資料

- 先從已經過評讀的database開始找起 (systems, summaries, synopses, synthesis)
- 最後再找尚未經過嚴格評讀的study

The "5S" levels of organisation of evidence from healthcare research

Brian Haynes, R Evid Based Med 2006;11:162-164



Summaries

- UpToDate
  - Key words:
    - Branch retinal vein occlusion
  - Article title:
    - Retinal vein occlusion: Treatment

Contents- Retinal vein occlusion: Treatment

- **Vascular endothelial growth factor inhibitors** — In RVO, they have been hypothesized to limit macular edema and improve vision by decreasing vascular permeability. Four anti-VEGF intravitreal agents available for clinical use are pegaptanib, bevacizumab, ranibizumab, and aflibercept. Only ranibizumab and aflibercept are approved for the indication of RVO by the US Food and Drug A dministration, the latter only for central RVO.
- Branch RVO — In the six-month BRAVO trial in which 397 patients with macular edema from BRVO were randomly assigned to ranibizumab (0.3 or 0.5 mg intraocularly) or sham, more patients receiving low- and high-dose ranibizumab had improvements in visual acuity of at least 15 letters (55 and 61 versus 29 percent) and achieved visual acuity of 20/40 or better (68 and 65 versus 42 percent).

- A 12-month update of the BRAVO trial has confirmed longer-term benefits, as more patients receiving low- and high-dose ranibizumab had improvements in visual acuity of at least 15 letters compared to sham (56 and 60 versus 44 percent, respectively) and achieved visual acuity of 20/40 or better (68 and 66 versus 57 percent, respectively)
- Given the improvement in visual acuity observed in the BRAVO trial, intravitreal ranibizumab is considered a reasonable alternative to grid laser photocoagulation in patients with BRVO and macular edema, particularly in whom retinal hemorrhage precludes laser treatment or in those who have not responded to laser treatment.

- Ranibizumab's advantage over laser treatment
  - Not associated with the risk of permanent paracentral scotoma induced by laser therapy, it could be given at the onset of significant visual loss at a time during which laser therapy is usually withheld.

- However, the long-term superiority of VEGF inhibitors over laser therapy as primary treatment has not been established.

Apply the Summary to the Patient

- In Our patient:
  - Branch retinal vein occlusion with macular edema
  - Significant visual loss
  - Onset: 2 days ago
  - Intravitreal ranibizumab is considered a reasonable alternative to grid laser photocoagulation

Synopses

- ACP Journal Club
  - Key words:
    - Branch retinal vein occlusion
  - Article title:
    - No match

Syntheses

- Cochrane Library
  - Key words:
    - Branch retinal vein occlusion
  - Article title:
    - Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion (Review)

Search methods

- We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 7), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 toAugust 2012), EMBASE (January 1980 to August 2012), LatinAmerican andCaribbean Literature onHealth Sciences(LILACS) (January 1982 to August 2012, the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com),ClinicalTrials.gov(www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en).
- We did not use any date or language restrictions in the electronic searches for trials.
- We last searched the electronic databases on 7 August 2012 and the clinical trials registers on 10 September 2012.

- Selection criteria
  - We included randomised controlled trials (RCTs) and quasi-RCTS of at least six months duration where anti-VEGF treatment was compared with another treatment, no treatment, or placebo. We excluded trials where combination treatments (anti-VEGF plus other treatments) were used and trials that investigated the dose and duration of treatment without a comparison group (other treatment/no treatment/sham).
- Data collection and analysis
  - Two review authors independently extracted the data. The primary outcome was the proportion of participants with an improvement from baseline in best-corrected visual acuity (BCVA) of greater than or equal to 15 letters (3 lines) on the Early Treatment in Diabetic Retinopathy Study (ETDRS) Chart at six months and at 12 months of follow-up.
- .

- The secondary outcomes we report are the proportion of participants who lost greater than or equal to 15 ETDRS letters (3 lines) and the mean VA change at six months and any additional follow-up intervals as well as the change in central retinal thickness on optical coherence tomography (OCT) from baseline and final reported follow-up, the number and type of complications, the number of additional interventions administered and any adverse outcomes. Where available, the cost benefit and quality of life data reported in the primary studies is presented

- Main results
  - We found one RCT and one quasi-RCT that met the inclusion criteria after independent and duplicate review of the search results.
  - The studies used different anti-VEGF agents and different study groups which were not directly comparable.
  - One multi-centre RCT (BRAVO) conducted in the USA randomised 397 individuals and compared monthly intravitreal ranibizumab (0.3mg and 0.5mg) injections with sham injection. The study only included individuals with non-ischaemic BRVO. Although repeated injections of ranibizumab appeared to have a favourable effect on the primary outcome, approximately 50% of the ranibizumab 0.3 mg group and 45% of the ranibizumab 0.5 mg group received rescue laser treatment which may have an important effect on the primary outcome. In addition, during the six-month observation period 93.5% of individuals in the sham group received intravitreal ranibizumab (0.5 mg). This cross-over design limits the ability to compare the long-term impact of ranibizumab versus a pure control group.

- The second trial was a small study (n = 30) from Italy with limitations in study design that reported a benefit of as-required intravitreal bevacizumab (1.25 mg) over laser photocoagulation in MO secondary to BRVO. We present the evidence from these trials and other interventional case series.

- Authors' conclusions
  - The available RCT evidence suggests that repeated treatment of non-ischaemic MO secondary to BRVO with the anti-VEGF agent ranibizumab may improve clinical and visual outcomes at six and 12 months.
  - However, the frequency of re-treatment has not yet been determined and the impact of prior or combined treatment with laser photocoagulation on the primary outcome is unclear.
  - Results from ongoing studies should assess not only treatment efficacy but also, the number of injections needed for maintenance and long-term safety and the effect of any prior treatment.

Studies

- PubMed
  - Keyword
    - Retinal vein occlusion, macular edema, ranibizumab
- Filters
  - Clinical trial, full-text available, recent 3 years, human
- Search results
  - Total 13 articles found
  - 5 articles excluded due to not relative

PubMed

- Search results (continued)
  - Improved vision-related function after ranibizumab for macular edema after retinal vein occlusion: results from the BRAVO and CRUISE trials
  - Varma R, Bressler NM, Suñer I, Lee P, Dolan CM, Ward J, Colman S, Rubio RG; BRAVO and CRUISE Study Groups.
  - **Ophthalmology**. **2012 Oct**;119(10):2108-18. doi: 10.1016/j.ophtha.2012.05.017. Epub 2012 Jul 18.
  - PMID: 22817833 [PubMed - indexed for MEDLINE]

Improved Vision-Related Function after Ranibizumab for Macular Edema after Retinal Vein Occlusion : Results from the BRAVO and CRUISE trials

- **Purpose:**
  - To examine the impact of intravitreal ranibizumab on patient-reported visual function using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) through 6 months in patients with macular edema (ME) secondary to branch or central retinal vein occlusion (RVO).
- **Design:**
  - Two multicenter, double-masked trials, which enrolled participants with ME secondary to branch or central RVO: the Ranibizumab for the Treatment of Macular Edema following BRAnch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) trial or the Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety (CRUISE) trial.

- **Participants:**
  - 397 BRAVO and 392 CRUISE patients.
- **Methods:**
  - Patients were randomized 1:1:1 to monthly sham, 0.3-mg, or 0.5-mg injections of ranibizumab for 6 months.
- **Main Outcome Measures:**
  - Although visual acuity was the **main outcome** measure for the trials, mean change from baseline in NEI VFQ-25 scores at month 6 was a **secondary outcome** measure.
- **Results(1):**
  - **In BRAVO**, among the 132, 134, and 131 patients randomized, respectively, to sham, 0.3 mg ranibizumab, or 0.5 mg ranibizumab, the study eye was the worse-seeing eye in 121 (91.7%), 118 (88.1%), and 125 (95.4%) patients and 123 (93.2%), 128 (95.5%), and 125 (95.4%), respectively, had a 6-month follow-up visit.

- Results(2):
  - In CRUISE, among the 130, 132, and 130 patients randomized, respectively, to sham, 0.3 mg ranibizumab, and 0.5 mg ranibizumab, the study eye was the worse-seeing eye in 117 (90.0%), 123 (93.2%), and 120 (92.3%) patients and 115 (88.5%), 129 (97.7%), and 119 (91.5%), respectively, had a 6-month follow-up visit.
  - In both trials, patients treated with ranibizumab reported greater mean improvements in visual function, with substantial differences observed as early as month 1, including the NEI VFQ-25 composite score and near and distance activities subscales, compared with sham patients. P values for comparisons with sham for the composite score and these 2 subscales were 0.05.

- **Outcomes during the Follow-up Phase (Month 6 to Month 12)**
  - During the 6- to 12-month follow-up phase, all patients were eligible to receive monthly injections of ranibizumab if they met prespecified criteria (sham group became sham/0.5-mg group)
  - Generally, improvements in NEI VFQ-25 scores from baseline achieved at month 6 were maintained through month 12 in both BRAVO and CRUISE trials.

- **Conclusions:**
  - These results from the BRAVO and CRUISE trials indicate that patients with ME from RVOs treated with monthly ranibizumab report greater improvements in vision-related function compared with sham-treated patients through 6 months, even when a majority of patients present with RVOs in the worse-seeing eye.

Apply the Study to the Patient

- In our patient:
  - Branch retinal vein occlusion with macular edema (od)

- The treatment with intravitreal ranibizumab should be appropriate.

Appraisal -嚴格評讀

對找到的文章
進行critical appraisal

AAMPICOT

- **A**:
  - Does this paper answer your question?

    Yes.

- **A**:
  - Is the author an expert of the field?

    Yes.
  - Is there any conflict of interest

    Yes. 由Genentech公司出資的study.

Method

- 證據等級: 1B
  - 針對PubMed這篇Improved vision-related function after ranibizumab for macular edema after retinal vein occlusion: results from the BRAVO and CRUISE trials

證據等級

Level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT所做成的綜合性分析(SR of RCTs)
1b	單篇RCT(有較窄的信賴區間)
1c	All or none
2a	用多篇世代研究所做成的綜合性分析
2b	單篇cohort及低品質的RCT
2c	Outcome research / ecological studies
3a	SR of case-control studies
3b	Individual case-control studies
4	Case-series(poor quality :cohort / case-control studies)
5	沒有經過完整評讀醫學文獻的專家意見

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

Population

- Population 取樣是否為隨機取樣？

  - 是

- 取的樣本是否具代表性？其特性是否接近我的病人？

  - 是

- 分組是否是隨機分組？

  - 是, Patients were randomized 1:1:1 to monthly sham, 0.3-mg, or 0.5-mg injections of ranibizumab for 6 months.

- 分組是否採用盲法？

  - 是

Intervention

- 給予實驗組的處置是否描述清楚，並且是臨床可行的？
  - 是

Comparison

- 給予對照組的處置是否描述清楚，並且是臨床可行的？各種可能比較皆有了？
  - 是

Outcome

- 測量了那些結果？是否用客觀的方式測量？

  - Visual acuity and patient-reported visual function using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25)

- 這些結果是否有統計學上的重要性？

  - 是

- 這些結果是否有臨床上的重要性？

  - 是

Time

- 測量結果的時間點是否合宜？
  - 是
- 追蹤時間是否夠長？
  - 不夠,目前僅一年的追蹤時間
- 文獻發表時間？
  - 2012年10月

Apply-臨床應用

結合醫學倫理方法

將study的結果應用在病人身上

醫療現況	病人意願
對於BRVO 併黃斑部水腫的病人目前健保並不給付Ranibizumab(Lucentis)的治療, 病人需自費一劑40000元	許多病人無法負擔此高額藥價
生活品質	**社會脈絡**
玻璃體內藥物注射後病人不會感覺不適, 且若視力改善對生活品質有相當大的影響	雖然玻璃體內注射Ranibizumab(Lucentis)對BRVO併黃斑部水腫的治療有效, 但目前無健保給付,僅少數人能負擔此治療

總結與討論

- 根據目前的研究,BRVO 併黃斑部水腫的病人接受玻璃體內注射Ranibizumab(Lucentis)視力會有改善, 相對於傳統的視網膜雷射, 是可採行的治療方式, 且在急性期就可以接受治療
- 缺點是Ranibizumab(Lucentis)藥價昂貴且目前健保不給付, 且非注射一次即可, 對病人經濟負擔大, 僅部分病人有能力接受治療
- 目前追蹤時間僅12個月, 長期的outcome還待進一步的研究結果

Audit-自我評估

在「提出臨床問題」方面的自我評估

- 我提出的問題是否具有臨床重要性？有
- 我是否明確的陳述了我的問題？
  - 我的foreground question 是否可以清楚的寫成PICO？可
  - 我的background question是否包括what, when, how, who等字根？是
- 我是否清楚的知道自己問題的定位？（亦即可以定位自己的問題是屬於診斷上的、治療上的、預後上的或流行病學上的），並據以提出問題？知道，屬於治療範疇
- 對於無法立刻回答的問題，我是否有任何方式將問題紀錄起來以備將來有空時再找答案？有

在「搜尋最佳證據」方面的自我評估

- 我是否已盡全力搜尋？是
- 我是否知道我的問題的最佳證據來源？是
- 我是否從大量的資料庫來搜尋答案？是
- 我工作環境的軟硬體設備是否能支援我在遇到問題時進行立即的搜尋？是
- 我是否在搜尋上愈來愈熟練了？是
- 我會使用「斷字」、布林邏輯、同義詞、MeSH term，限制(limiters)等方法來搜尋？會
- 我的搜尋比起圖書館人員或其他對於提供病人最新最好醫療有熱情的同事如何？希望能再更積極些

關於「嚴格評讀文獻」方面的自我評估

- 我是否盡全力做評讀了？是
- 我是否了解Number need to treat 的意義？了解
- 我是否了解Likelihood Ratios的意義？了解
- 我是否了解Worksheet每一項的意義？了解
- 評讀後，我是否做出了結論？是

關於「應用到病人身上」的自我評估

- 我是否將搜尋到的最佳證據應用到我的臨床工作中？是
- 我是否能將搜尋到的結論如NNT,LR用病人聽得懂的方式解釋給病人聽？是
- 當搜尋到的最佳證據與實際臨床作為不同時，我如何解釋？實證醫學是以目前的研究為基礎，分析統計後得到可能較佳的作法，並不一定適於每位病人，在臨床運用上，仍需評估實際症狀及療效

改變「醫療行為」的自我評估

- 當最佳證據顯示目前臨床策略需改變時，我是否遭遇任何阻止改變的阻力？否
- 我是否因此搜尋結果而改變了原來的治療策略？做了那些改變？否

效率評估

- 這篇報告，我總共花了多少時間？共約8小時
- 我是否覺得這個進行實證醫學的過程是值得的？尚可
- 我還有那些問題或建議？對統計分析方法不熟悉，需多加強

Thank you for your attention!