實證醫學病例討論報告

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臨床場景(clinical scenario)

1~病人基本資料及主訴
2~診斷（包含理學檢查、實驗室檢查、影像學檢查）
3~治療方式及對治療的反應
4~後續治療計畫

Patient profile

- Name：林O滿
- Age: 69 y/o
- Gender：male

clinical scenario-基本資料及主訴

- CC: progressive general weakness for about one month
- General data:
  - **69-year-old man**
    - 1.Rheumatic arthritis for 10 years with oral medicine control at 高雄長庚醫院
    - 2.Chronic kidney disease, stage 3
    - 3.Hypertension
- Finding:
  - Physical Examination finding:
    - No specific finding
  - Lab data:
    - Elevated CRP

clinical scenario

- Diagnosis: Multiple tuberculosis infection,suspect miliary tuberculosis
- Treatment :

Rifater	10/15-10/27			11/10-11/17	
EMB	10/15-10/27	10/29-			
Avelox		10/29-			
Streptomycin		10/29-11/6			11/18-11/22
Rifampin			11/6-11/9		

- Rifater (rifampicin 120mg, isoniazid 80mg, pyrazinamide 250mg)
- EMB (ethambutol) 400mg
- Avelox(moxifloxacin) 400mg

- 對治療的反應: Acute hepatic injury, related to anti-TB drugs
- 後續治療計畫: 將antituberculosis drug停藥，之後再使用沒有hepatotoxicity的anti-TB drug

提出 background questions

Question 1: Who often gets TB?

- **Risk factors**:
  - **Immunocompromise :** HIV infection, *Glucocorticoids*, *TNF inhibitors*, Malignancy, Celiac disease
- **Apply:**
  - The American Thoracic Society and the CDC list a daily dose of >15 mg of prednisone for ≥1 month as a risk factor for TB.
  - The use of corticosteroids was associated with TB as follows:
    - Current use of glucocorticoids, adjusted odds ratio [OR] 4.9, (95% CI, 2.9-8.3)
    - The risk of TB increased with increasing daily doses (adjusted ORs for use of <15 mg and ≥15 mg of prednisone were 2.8; 95% CI, 1.0-7.9 and 7.7; 95% CI, 2.8-21.4, respectively)

Question 2: How to treat TB ?

- **General principles of the treatment of tuberculosis** :
  - **Initial phase —**
    - Four drugs are used in the initial phase of treatment when the total duration of treatment is six months, because of the high incidence of isoniazid-resistant organisms in most communities.
    - Thus, the treatment regimen for most adults with previously untreated tuberculosis should consist of a ***two month initial phase*** of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB).
  - **Continuation phase —**
    - The continuation phase of treatment is given for either four or seven months and consists, in most cases, of INH and RIF alone. Most patients will be treated with the ***four month continuation*** phase (total duration of treatment six months).

TABLE 2. DRUG REGIMENS FOR CULTURE-POSITIVE PULMONARY TUBERCULOSIS CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS

Initial Phase			Continuation Phase				Rating* (Evidence)†	
Regimen	Drugs	Interval and Doses‡ (*minimal duration*)	Regimen	Drugs	Interval and Doses‡,§ (*minimal duration*)	Range of Total Doses (*minimal duration*)	HIV⁻	HIV⁺
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) *or* 5 d/wk for 40 doses (8 wk)‖	1a	INH/RIF	Seven days per week for 126 doses (18 wk) *or* 5 d/wk for 90 doses (18 wk)‖	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II)#
			1c**	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), *then* twice weekly for 12 doses (6 wk) *or* 5 d/wk for 10 doses (2 wk),‖ *then* twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II)#
			2b**	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	Seven days per week for 56 doses (8 wk) *or* 5 d/wk for 40 doses (8 wk)‖	4a	INH/RIF	Seven days per week for 217 doses (31 wk) *or* 5 d/wk for 155 doses (31 wk)‖	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

- Title :An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy. AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 174 2006.
- Jussi J. Saukkonen, David L. Cohn, Robert M. Jasmer, Steven Schenker, John A. Jereb, Charles M. Nolan, Charles A. Peloquin, Fred M. Gordin, David Nunes, Dorothy B. Strader, John Bernardo, Raman Venkataramanan, and Timothy R. Sterling, on behalf of the ATS Hepatotoxicity of Antituberculosis Therapy Subcommittee.
- **Level of evidence:**

8.8.1. Treatment without INH. As described in Section 5.2 (ALTERNATIVE REGIMENS), analysis of data from several studies conducted by the BMRC in patients with smear-positive pulmonary tuberculosis demonstrated high levels of efficacy with 6-month regimens despite *in vitro* resistance to INH so long as the initial phase contained four drugs and RIF was used throughout the 6 months (1). Subsequent studies by the Hong Kong Chest Service and the BMRC suggested that results were improved when PZA was used throughout the 6 months (2). Thus, it is reasonable to employ an initial phase regimen of RIF, PZA, and EMB followed by a continuation phase of RIF, EMB, and PZA (Rating BII). Although this regimen has two potentially hepatotoxic medications, it has the advantage of retaining the 6-month duration.

8.8.2. Treatment without PZA. Although the frequency of PZA-induced hepatitis is slightly less than occurs with INH or RIF, the liver injury induced by this drug may be severe and prolonged (3). Therefore, one might elect to employ a regimen with an initial phase of INH, RIF, and EMB for 2 months followed by a continuation phase of INH and RIF for 7 months, for a total of 9 months (Table 2, Regimen 4).

8.8.3. Regimens with only one potentially hepatotoxic drug. For patients with advanced liver disease, a regimen with only one potential hepatotoxic drug might be selected. Generally, RIF should be retained. Additional agents in such regimens could include EMB, a fluoroquinolone, cycloserine, and injectable agents. The duration of treatment with such regimens should be 12–18 months, depending on the extent of the disease and the response (Rating CIII). Consultation is advised in such situations.

8.8.4. Regimens with no potentially hepatotoxic drugs. In the setting of severe unstable liver disease, a regimen with no hepatotoxic agents might be necessary. Such a regimen might include SM, EMB, a fluoroquinolone, and another second-line oral drug. There are no data that provide guidance as to the choice of agents or the duration of treatment or that indicate the effectiveness of such a regimen. Expert opinion suggests that a regimen of this sort should be given for 18–24 months (Rating CIII). Consultation should always be obtained before embarking on such a treatment plan.

TABLE 3. DOSES* OF ANTITUBERCULOSIS DRUGS FOR ADULTS AND CHILDREN†

Drug	Preparation	Adults/Children	Doses: Daily	1×/wk	2×/wk	3×/wk
			First-Line Drugs			
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5ml); aqueous solution (100 mg/ml) for intravenous or intramuscular injection	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mk/kg (900 mg)	15 mg/kg (900 mg)
		Children (max.)	10–15 mg/kg (300 mg)	—	20–30 mg/kg (900 mg)	—
Rifampin	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults‡ (max.)	10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children (max.)	10–20 mg/kg (600 mg)	—	10–20 mg/kg (600 mg)	—
Rifabutin	Capsule (150 mg)	Adults‡ (max.)	5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)
		Children	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film coated)	Adults	—	10 mg/kg (continuation phase) (600 mg)	—	—
		Children	The drug is not approved for use in children	The drug is not approved for use in children	The drug is not approved for use in children	The drug is not approved for use in children
Pyrazinamide	Tablet (500 mg, scored)	Adults	*See* Table 4	—	*See* Table 4	*See* Table 4
		Children (max.)	15–30 mg/kg (2.0 g)	—	50 mg/kg (4 g)	—
Ethambutol§	Tablet (100 mg; 400 mg)	Adults	*See* Table 5	—	*See* Table 5	*See* Table 5
		Children‡ (max.)	15–20 mg/kg daily (1.0 g)	—	50 mg/kg (4 g)	—
			Second-Line Drugs			
Cycloserine	Capsule (250 mg)	Adults (max.)	10–15 mg/kg/d (1.0 g in two doses), usually 500–750 mg/d in two doses‖	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children (max.)	10–15 mg/kg/d (1.0 g/d)	—	—	—
Ethionamide	Tablet (250 mg)	Adults# (max.)	15–20 mg/kg/d (1.0 g/d), usually 500–750 mg/d in a single daily dose or two divided doses#	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children (max.)	15–20 mg/kg/d (1.0 g/d)	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration

Streptomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max.)	**	**	**	**
		Children (max.)	20–40 mg/kg/d (1 g)	—	20 mg/kg	—
Amikacin/ kanamycin	Aqueous solution (500 mg and 1-g vials) for intravenous or intramuscular administration	Adults (max.)	**	**	**	**
		Children (max.)	15–30 mg/kg/d (1 g) intravenous or intramuscular as a single daily dose	—	15–30 mg/kg	—
Capreomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max.)	**	**	**	**
		Children (max.)	15–30 mg/kg/d (1 g) as a single daily dose	—	15–30 mg/kg	—
p-Aminosalicylic acid (PAS)	Granules (4-g packets) can be mixed with food; tablets (500 mg) are still available in some countries, but not in the United States; a solution for intravenous administration is available in Europe	Adults	8–12 g/d in two or three doses	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	200–300 mg/kg/d in two to four divided doses (10 g)	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
Levofloxacin	Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500-mg vials) for intravenous injection	Adults	500–1,000 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	††	††	††	††
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 ml) for intravenous injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	‡‡	‡‡	‡‡	‡‡
Gatifloxacin	Tablets (400 mg); aqueous solution (200/20 ml; 400 mg/40 ml) for intravenous injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	§§	§§	§§	§§

- Fluoroquinolones — None of the quinolones is approved by the Food and Drug Administration for use against tuberculosis, but some authors attribute the improved prognosis of MDR-TB over the past decade largely to the administration of these agents. Quinolone antibiotics have considerable in vitro activity against M. tuberculosis and have become widely used in the treatment of MDR-TB. However, there are few useful data from controlled trials to define the exact role of these drugs in the treatment of tuberculosis.
- Among the newer quinolones, moxifloxacin has the most in vitro activity against M. tuberculosis, followed by levofloxacin, ofloxacin, and ciprofloxacin. Moxifloxacin also demonstrates bactericidal activity in animal models. Data are limited on the clinical efficacy of this drug, but several studies on sputum concentrations of M. tuberculosis document early bactericidal effects in humans.

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提出 foreground questions

因爲hepatotoxicity，而使用了second-line的抗結核藥streptomycin (SM), ethambutol (EMB), moxifloxicin - fluoroquinolone，想要了解fluoroquinolone還有其他方面用藥，其效果較moxifloxicin好，所需的療程時間較少，complication比較少?

將問題寫成PICOT

P	Tuberculosis (TB) infection, hepatotoxicity cause by Antituberculosis Therapy
I	Second-line therapy: *streptomycin (SM), ethambutol (EMB), moxifloxicin*
C	Other regimen： *streptomycin (SM), ethambutol (EMB), other quinolone*
O	Better effect
Time	No defined

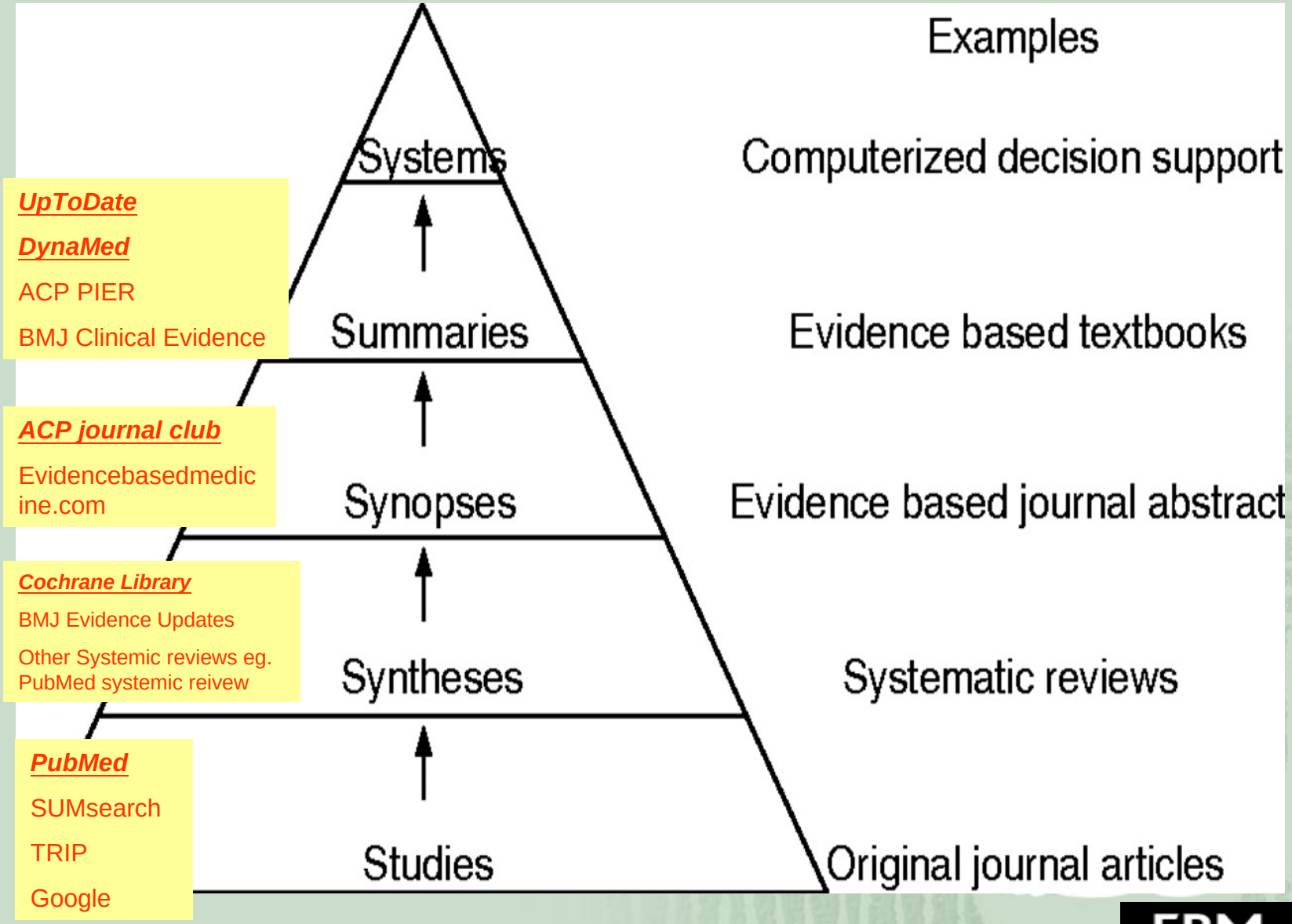
搜尋最有用的資料

先從已經過評讀的database開始找起
(system,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



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搜尋到的文章內容 (1)

- The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis.
  - Gosling RD; Uiso LO; Sam NE; Bongard E; Kanduma EG; Nyindo M; Morris RW; Gillespie SH
  - Am J Respir Crit Care Med 2003 Dec 1;168(11):1342-5. Epub 2003 Aug 13.
- Level of evidence: level 2B

- Patients in whom acid-fast bacilli smear-positive pulmonary tuberculosis was newly diagnosed were randomized to receive 400 mg moxifloxacin, 300 mg isonaizid, or 600 mg rifampin daily for 5 days.
- Bactericidal activity was estimated by the time taken to kill 50% of viable bacilli (vt50) and the fall in sputum viable count during the first 2 days designated as the early bactericidal activity (EBA).
- The mean vt50 of moxifloxacin was 0.88 days (95% confidence interval [CI], 0.43-1.33 days) and the mean EBA was 0.53 (95% CI 0.28-0.79).
- For the isoniazid group, the mean vt50 was 0.46 days (95% CI, 0.31-0.61 days) and the mean EBA was 0.77 (95% CI, 0.54-1.00).
- For rifampin, the mean vt50 was 0.71 days (95% CI, 0.48-0.95 days) and the mean EBA was 0.28 (95% CI, 0.15-0.41).

- Using the EBA method, isoniazid was significantly more active than rifampin ($p < 0.01$) but not moxifloxacin.
- Using the vt50 method, isoniazid was more active than both rifampin and moxifloxacin ($p = 0.03$).
- Moxifloxacin has an activity similar to rifampin in human subjects with pulmonary tuberculosis, suggesting that it should undergo further assessment as part of a short course regimen for the treatment of drug-susceptible tuberculosis.

搜尋到的文章內容 (2)

- Sterilizing activities of fluoroquinolones against rifampin-tolerant populations of Mycobacterium tuberculosis.
  - Hu Y; Coates AR; Mitchison DA
  - Antimicrob Agents Chemother 2003 Feb;47(2):653-7.
- Level of evidence: level 2C

- The bactericidal activities of ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, and gatifloxacin were tested in three models of rifampin-tolerant Mycobacterium tuberculosis persisters.

- Model 1 was a 100-day-old, unshaken, anaerobically adapted culture in which serial dilutions of the quinolones were incubated for 5 days and CFU counts were then done In models 2 and 3, 100 mg of rifampin/liter was added to the 100-day culture for 5 or 7 days to produce tolerant organisms that did not grow on plates; the rifampin was then washed off, fresh medium was added to allow recovery of growth on plates, and the culture was incubated for 7 days before CFU counts.
- In model 2, the quinolones were added after rifampin had been washed off, whereas in model 3 the quinolones were added to the cultures containing rifampin. In models 1 and 2, ciprofloxacin had the least bactericidal activity, ofloxacin and levofloxacin had greater activities, and moxifloxacin and gatifloxacin had the greatest activities.
- In model 3, ofloxacin had no detectable activity whereas moxifloxacin killed about log(10) 0.279 CFU of the persisters per ml at concentrations attainable in lesions; isoniazid had virtually no activity.

- These findings predict that ofloxacin will not be found to have effective sterilizing activity in clinical studies now planned whereas moxifloxacin will be able to shorten treatment.

搜尋到的文章內容 (3)

- Fluoroquinolone-containing third-line regimen against Mycobacterium tuberculosis in vivo.
  - Veziris N; Truffot-Pernot C; Aubry A; Jarlier V; Lounis N
  - Antimicrob Agents Chemother 2003 Oct;47(10):3117-22.
- Level of evidence:

- The WHO regimen combines ofloxacin (OFX), ethionamide, amikacin, and pyrazinamide; in the two derivatives of this regimen, OFX was replaced by levofloxacin (LVX) or moxifloxacin (MXF).
- The four drugs, a fluoroquinolone (either OFX, LVX, or MXF), ethionamide, pyrazinamide, and amikacin, were administered for the first 2 months (initial phase); and two drugs, a fluoroquinolone (either OFX, LVX, or MXF) and ethionamide, were administered for the following 10 months (continuation phase).

- The results for mice treated with the LVX-containing regimen fell between those for the groups receiving the MXF- and OFX-containing regimens.
- In conclusion, the MXF-containing third-line regimen seems to be a powerful alternative for the treatment of tuberculosis (TB) when isoniazid and rifampin cannot be used, which is the main feature of multidrug-resistant TB.

Method

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

使用work sheet嚴格評讀

Should these valid, potentially important results of a critical appraisal about a harmful treatment change the treatment of your patient?	
Can the study results be extrapolated to your patient?	可以。
What are your patient's preferences, concerns and expectations from this treatment?(病人的期望、喜好、關心)	病人希望能完成療程出院。
What alternative treatments are available?	使用無hepatotoxicity的antituberculosis drug

Apply

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
使用無hepatotoxicity副作用的抗結核用藥，但需要服用更長的時間。	患者願意接受治療，尋求能改善症狀。
生活品質	**社會脈絡**
此次因general weakness, fever而住院，因為感染的關係身體虛弱，入院治療後，症狀有改善。	一般的抗結核用藥都有健保給付，故用藥並無社會脈絡之顧慮。

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？是，可以作為治療參考。
- 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？未能全部包括
- 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？學校資源便利。
- 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？部份會。
- 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？需要加強。

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？沒有，目前證據未改變臨床策略
- 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？沒有改變。

效率評估

- 這篇報告，我總共花了多少時間？一至兩天晚上。
- 我是否覺得這個進行實證醫學的過程是值得的？值得。
- 我還有那些問題或建議？尋找paper的時間很長，效率不佳。

End & thank you