實證醫學病例討論

- 職級：PGY洪慈穗
- 姓名：洪慈穗
- 職編：970387

臨床場景(clinical scenario)

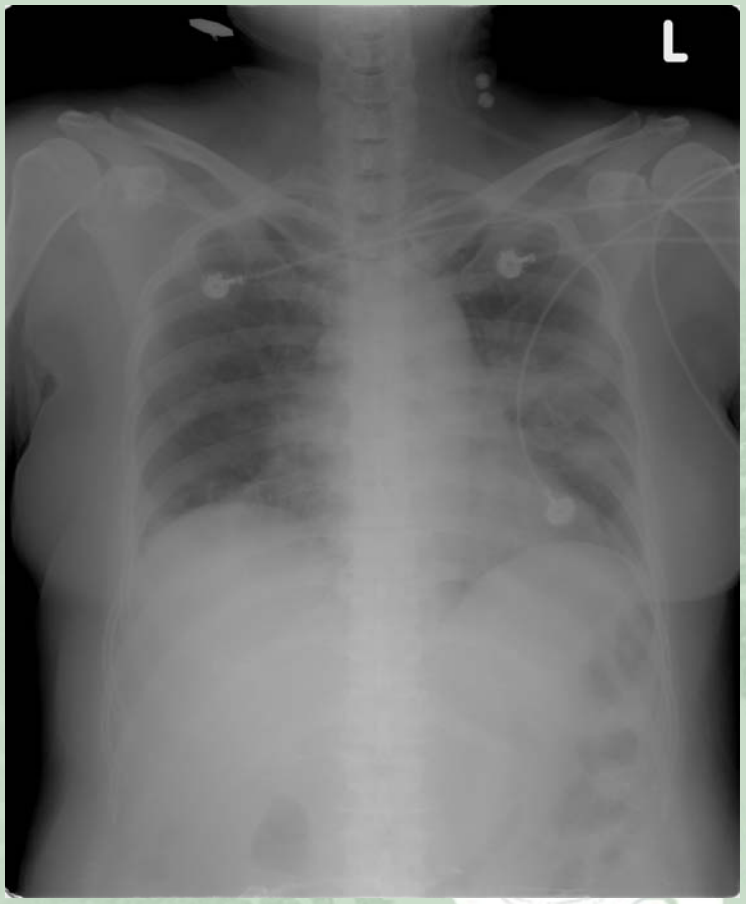
1~病人基本資料及主訴
2~診斷（包含理學檢查、實驗室檢查、影像學檢查）
3~治療方式及對治療的反應
4~後續治療計畫

clinical scenario-基本資料及主訴

- CC: intermittent fever for 3 days
- General data:
  - 55-year woman
  - Underlying :Diabetes mellitus ,Gout
- s/s: cough with yellowish sputum
- Finding:

  Lab : 17000 CRP: 344.08

  CXR:



clinical scenario

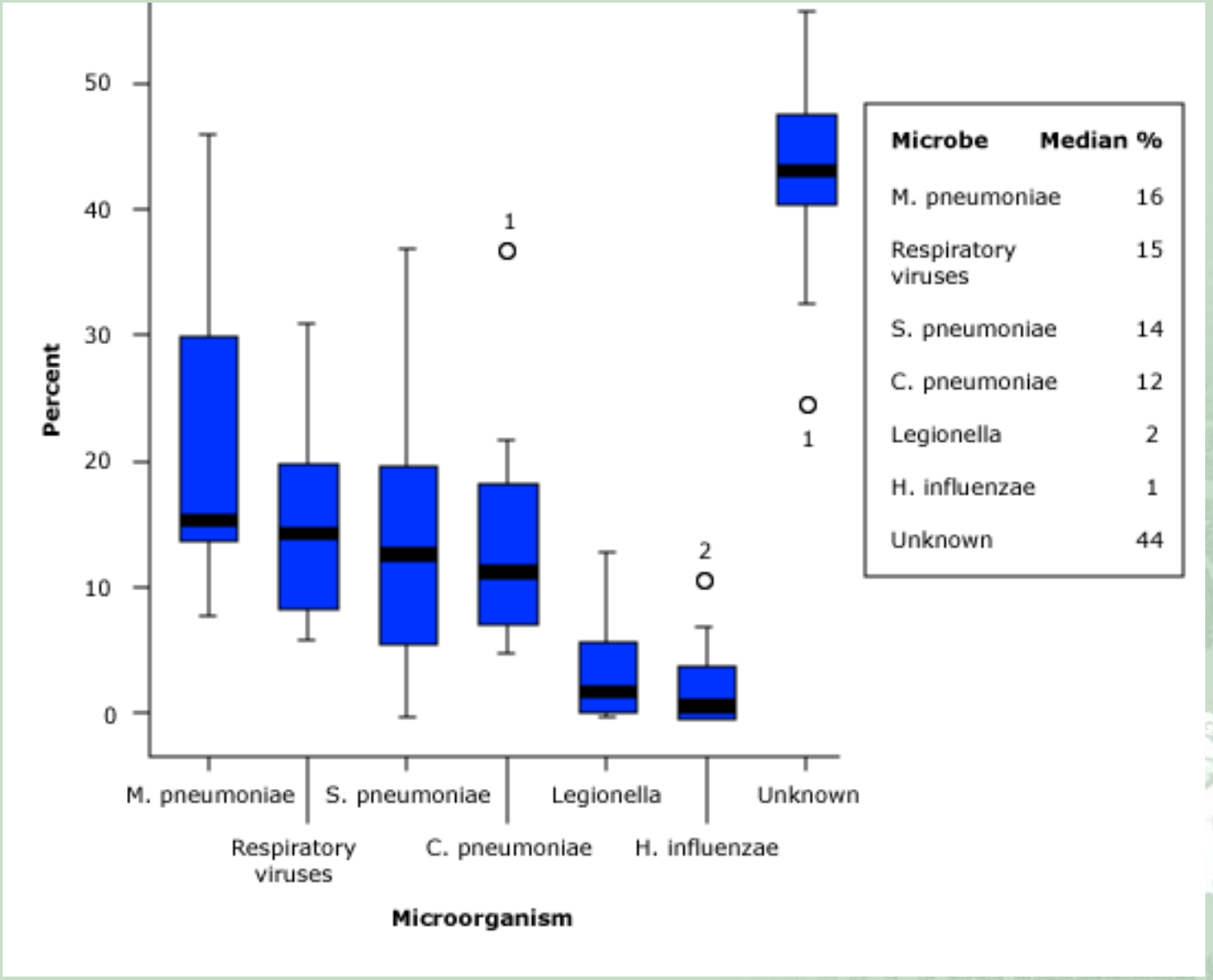
- Diagnosis: community acquired pneumonia
- Treatment : cefuroxime 1.5g Q8H
  zithromax 2# 3 days
- 對治療的反應:responsive
- 後續治療計畫: keep current treatment

提出 background questions

Question

- What are the common pathogens?
- What are the empirical regimen ?
- How long is the duration of the treatment ?

common pathogens



Microbe	Median %
M. pneumoniae	16
Respiratory viruses	15
S. pneumoniae	14
C. pneumoniae	12
Legionella	2
H. influenzae	1
Unknown	44

Empirical empiric antibiotics in inpatients

for patients not in ICU

- **respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)**
- **macrolide plus beta-lactam**
  - **doxycyline is alternative to macrolide**
  - **preferred beta-lactams include cefotaxime, ceftriaxone, ampicillin**
  - **alternative beta-lactam is ertapenem for selected patients**

for ICU patients

- **beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or fluoroquinolone**
- **respiratory fluoroquinolone plus aztreonam recommended for penicillin-allergic patients**

Empirical empiric antibiotics in inpatients

for *Pseudomonas* infection

- **antipneumococcal, antipseudomonal beta-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus one of the following**
  - **ciprofloxacin**
  - **levofloxacin [750 mg dose]**
  - **aminoglycoside plus azithromycin**
  - **aminoglycoside plus antipneumococcal fluoroquinolone**
- **replace beta-lactam with aztreonam for penicillin-allergic patients**

Duration

- **duration of antibiotics 7 days or less is as effective as longer antibiotic courses for adults with mild-to-moderate community-acquired pneumonia (level 1 [likely reliable] evidence)**

提出 foreground questions

Empirical antibiotics是否一定要cover atypical pathogens ?

將問題寫成PICO

P	Adult , community-acquired pneumonia, hospitalized
I	Cover atypical pathogens: **beta-lactam plus macrolide** **respiratory fluoroquinolone**
C	Not cover atypical pathogens: **beta-lactam**
O	Mortality ,treatment failure

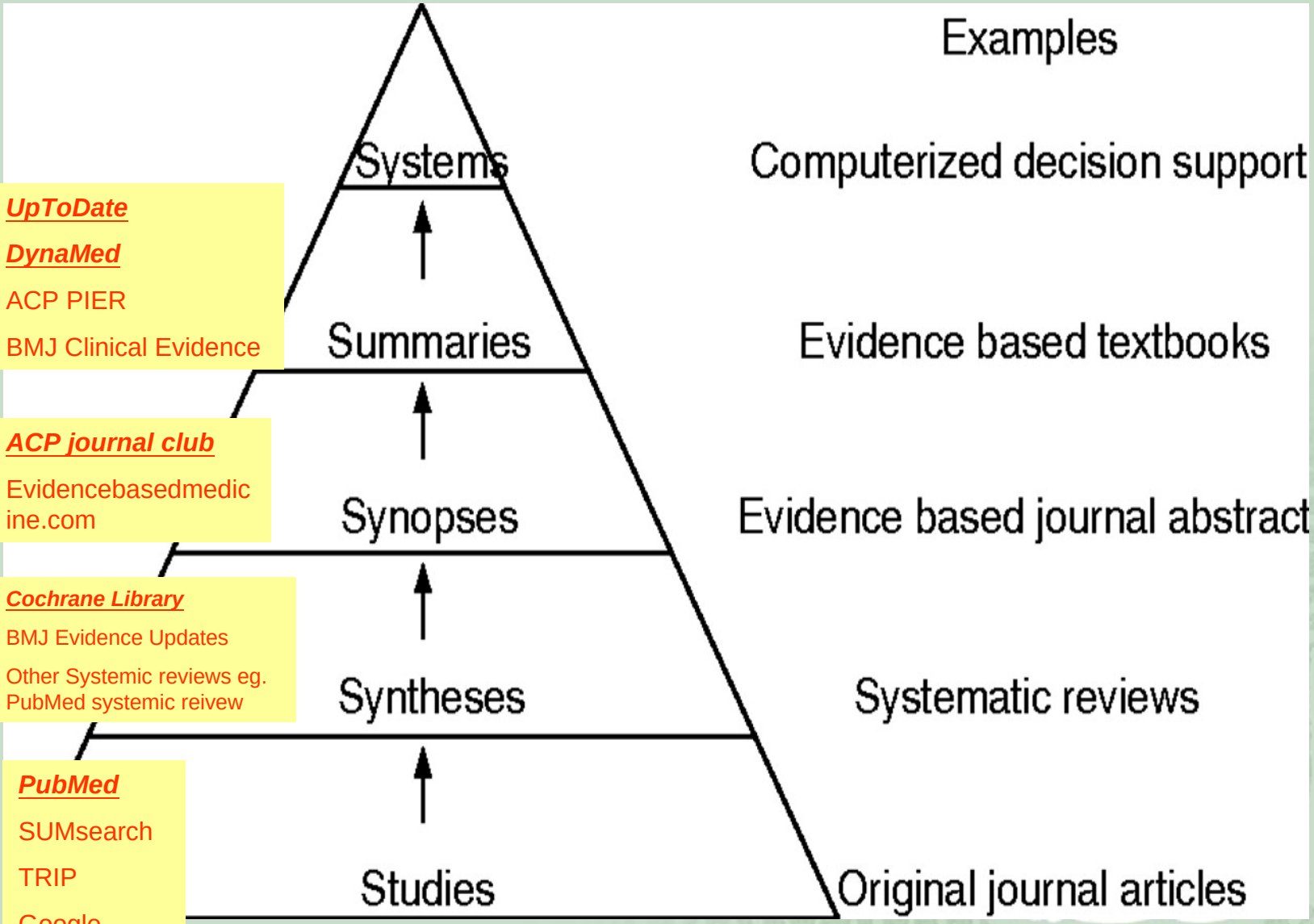
搜尋最有用的資料

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



搜尋Summaries

- Key word: community-acquired pneumonia
- 搜尋到的文章標題:
- **Topic : pneumonia –treatment**

搜尋到的文章內容

- **Empiric coverage of atypical organisms does not appear to improve outcomes in hospitalized patients (level 2 [mid-level] evidence)**
- **Empiric antibiotic regimens with and without atypical coverage appear to have similar efficacy in hospitalized patients with community-acquired pneumonia (level 2 [mid-level] evidence)**
  - **Reference - systematic review last updated 2007 Nov 1 (Cochrane Library 2008 Issue 1:CD004418), earlier version published in Arch Intern Med 2005 Sep 26;165(17):1992, commentary on earlier version can be found in Evidence-Based Medicine 2006 May-Jun;11(3):74**

Main results

- 25 trials were included, encompassing 5244 randomized patients. There was no difference in mortality between the atypical arm and the non-atypical arm (RR 1.15; 95% CI 0.85 to 1.56).
- The atypical arm:an insignificant trend toward clinical success and a significant advantage to bacteriological eradication, which disappeared when evaluating methodologically high-quality studies alone.
- Clinical success for the atypical arm : significantly higher for *Legionella pneumophilae* (*L. pneumophilae*) and non-significantly lower for pneumococcal pneumonia.
- There was no significant difference between the groups in the frequency of (total) adverse events, or those requiring discontinuation of treatment. However, gastrointestinal events were more common in the non-atypical arm (RR 0.73, 95% CI 0.54 to 0.99).
- All but two included trials compared a single atypical antibiotic to a beta-lactam, while no trials assessing the addition of an atypical antibiotic to a beta-lactam were identified.

Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults

Objectives

- To assess the efficacy and need of adding antibiotic coverage for atypical pathogens in hospitalized patients with CAP, in terms of mortality and successful treatment.

Search strategy

- We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, issue 1) which includes the Acute Respiratory Infection Group's specialized register; MEDLINE (January 1966 to March 2007); and EMBASE (January 1980 to January 2007).

Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults

- **Selection criteria**
- Randomized trials of adult patients hospitalized due to CAP, comparing antibiotic regimens with atypical antibiotic coverage to a regimen without atypical antibiotic coverage.

Data collection and analysis

- Two review authors independently appraised the quality of each trial and extracted the data from included trials. Relative risks (RR) with 95% confidence intervals (CI) were estimated, assuming an intention-to-treat (ITT) basis for the outcome measures.

Main results

- 25 trials were included, encompassing 5244 randomized patients. There was no difference in mortality between the atypical arm and the non-atypical arm (RR 1.15; 95% CI 0.85 to 1.56).
- The atypical arm showed an insignificant trend toward clinical success and a significant advantage to bacteriological eradication, which disappeared when evaluating methodologically high-quality studies alone.
- Clinical success for the atypical arm was significantly higher for *Legionella pneumophilae* (*L. pneumophilae*) and non-significantly lower for pneumococcal pneumonia.
- There was no significant difference between the groups in the frequency of (total) adverse events, or those requiring discontinuation of treatment. However, gastrointestinal events were more common in the non-atypical arm (RR 0.73, 95% CI 0.54 to 0.99).
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Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults

Authors' conclusions

- No benefit of survival or clinical efficacy was shown to empirical atypical coverage in hospitalized patients with CAP.
- This conclusion relates mostly to the comparison of quinolone monotherapy to beta-lactams (BL) or cephalosporins.
- Further trials, comparing BL or cephalosporins therapy to BL or cephalosporins combined with a macrolide in this population, using mortality as its primary outcome, should be performed.

搜尋Synopses ，ACP Journal Club

- Key word: pneumonia
- 搜尋到的文章標題:
- **Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials.**
  2005**Shefet D**, **Robenshtok E**, **Paul M**, **Leibovici L**.
  Department of Medicine E, Beilinson Campus, Rabin Medical Center, Petah-Tiqva, Israel.
  dshefet@yahoo.com

- Robenshtok E, Shefet D, Gafter-Gvili A, Paul M, Vidal L, Leibovici L. **Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults.** Cochrane Database Syst Rev. 2008 ;CD004418. [PubMed ID: 18254049]

搜尋 syntheses, Cochrane Central Register of Controlled Trials

- Key : community-acquired pneumonia
- 搜尋到的文章標題:
- **Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults**

1Department of Medicine E, Beilinson Campus, Rabin Medical Center, Petah-Tiqva, Israel. 2Infectious Diseases Unit and Department of Medicine E, Rabin Medical Center, Petah-Tikva, Israel. 3Department of Internal Medicine E, Beilinson Campus, Rabin Medical Center, Petah-Tiqva, Israel

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搜尋Studies, Pubmed

- Key word:

  ("Pneumonia, Bacterial/drug therapy"[Mesh] AND "beta-Lactams"[Mesh]) AND "Macrolides"[Mesh]

Limit: human ,adult ,time: since 2007

Pubmed

- **The need for macrolides in hospitalised community-acquired pneumonia: propensity analysis.**
- Paul M, Nielsen AD, Gafter-Gvili A, Tacconelli E, Andreassen S, Almanasreh N, Goldberg E, Cauda R, Frank U, Leibovici L.
- Department of Medicine E, Rabin Medical Center, Beilinson Hospital, 49100 Petah-Tiqva, Israel.
- Epub 2007 May 30.
- A prospective multinational observational study

Abstract

- The present study compared beta-lactam macrolide ("combination") therapy versus beta-lactam alone ("monotherapy") for hospitalised community-acquired pneumonia, using propensity scores to adjust for the differences between patients. A prospective multinational observational study was carried out. Baseline patient and infection characteristics were used to develop a propensity score for combination therapy. Patients were matched by the propensity score (three decimal point precision) and compared with 30-day mortality and hospital stay. The propensity score was used as a covariate in a logistic model for mortality. Patients treated with monotherapy (n = 169) were older (mean+/-sd age 70.6+/-17.3 versus 65.0+/-19.6 yrs), had a higher chronic diseases score and a different clinical presentation compared with patients treated with combination therapy (n = 282). Unadjusted mortality was significantly higher with monotherapy (37 (22%) out of 169 versus 21 (7%) out of 282). Only 27 patients in the monotherapy group could be matched to 27 patients in the combination group using the propensity score. The mortality in these groups was identical, with three (11%) demises each. The multivariable odds ratio for mortality associated with combination therapy, adjusted for the propensity score and the Pneumonia Severity Index, was 0.69 (95% confidence interval 0.32-1.48). The benefit of combination therapy versus monotherapy cannot be reliably assessed in observational studies, since the propensity to prescribe these regimens differs markedly.

Appraisal (嚴格評讀）

對找到的文章
進行critical appraisal

Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults

證據等級(針對PubMed這篇)

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

將文獻寫成PICO

P	**Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults**
I	Cover atypical agent : **Monotherapy Respiratory Quinolone ,** **Macrolide /or plus bata-lactams**
C	Non-atypical regimen: **beta-lactam,BL/BLI, cephasporin,carbapenems,penicilline**
O	Overall Mortality , Number of pt with treatment failure

使用work sheet嚴格評讀

THERAPY WORKSHEET

來自系統性的證據是有效的嘛?

- 這是一個隨機試驗的系統性的回顧嘛? 是
  - ***Types of studies***
  - Any randomized or quasi-randomized controlled trial, assessing empirical antibiotic treatment of CAP in hospitalized adults. Trials with a drop out rate of over 30% were excluded.

來自系統性的證據是有效的嘛?

- 有關相關試驗搜尋是否完整描述?
  - 是
  - **Search methods for identification of studies**
  - ***Electronic searches***
  - We searched **the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, issue 2) which includes the Acute Respiratory Infection Group's specialized register; MEDLINE (January 1966 to June 2007); and EMBASE (January 1980 to June 2007).**

    Searching other resources

    In addition we searched **Clinical Trials.Gov and FDA** new drug approval documents for ongoing or unpublished trials.
  - 語言:English :19,French:2 ,Japanese :2,Spanish:1,German:1

來自系統性的證據是有效的嘛?

- 個別研究是否做過效度評估?
  - 是
  - **Risk of bias in included studies**

IIT verse per-protocol analsis

Mortality was not a primary outcome and was usually reported in the safety analysis.

13 studies recounted information regarding overall mortality by ITT ,while 11 provided data per-protocol. 1 study does not specifically mention or rule out deaths (Kobayashi 1984).

Follow up

Follow up duration was specified in 22 studies (88%), of which 16 studies defined a specific time for outcome measurement (64%). Follow up ranged from immediately after completion of treatment to three months after.

Allocation

- **Adequate allocation concealment : in one quarter of the studies (6 out of 25). No sufficient information was available for the other studies.**
- **Adequate Allocation generation: in 9 out of 25 studies.**

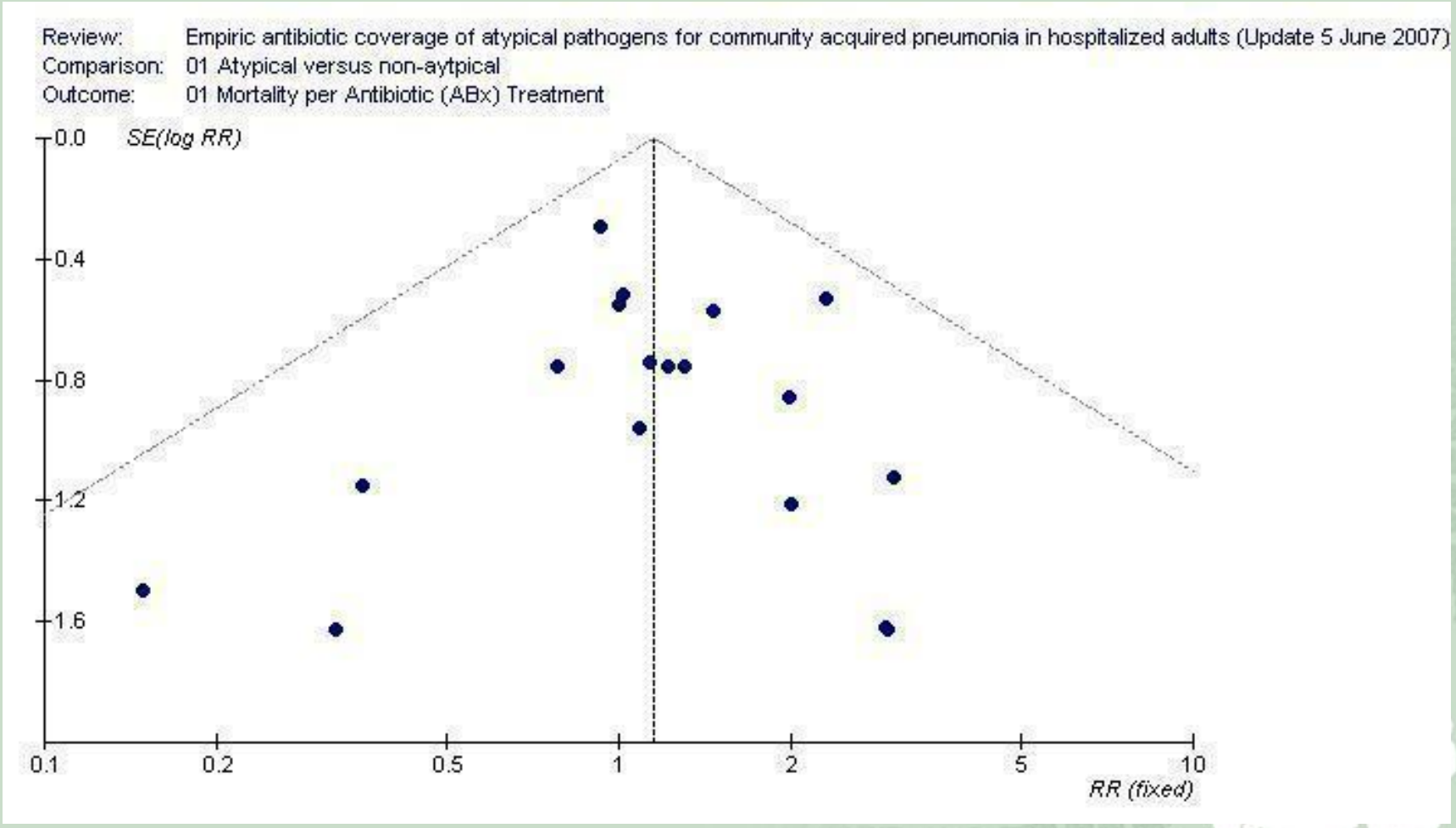
  No information was available : 16 studies. All studies of adequate allocation concealment were also of adequate allocation generation.

Blinding

- **double blind:10, single blinded :1, remaining (14 out of 25): open label.**

來自此系統性回顧有效證據重要嗎?

- 這些研究結果是否一致?
  - **The main outcome measure in all studies was clinical failure.**
    6 studies mandated radiological resolution for success definition and one asked for bacteriological eradication. In 4 studies definition of success was unclear.
  - **None of the studies named mortality as a primary outcome.**
  - **19 trials assessed bacteriological failure, defined by eradication.**
  - **There was no significant difference between the atypical arm and the non-atypical arm in the overall mortality rate (RR 1.15, 95% CI 0.85 to 1.56, comparison 1).**
  - **Overall mortality in both arms was similar when analyzing studies by randomization generation, allocation concealment and blinding, as well as in the ITT analysis.**
  - **In the funnel plot for overall mortality, which included 18 trials in which mortality was more than zero, results are symmetrically centered around the combined RR showing a funnel distribution**


Review: Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults (Update 5 June 2007)
Comparison: 01 Atypical versus non-aytpical
Outcome: 01 Mortality per Antibiotic (ABx) Treatment
SE(log RR)
0.0
0.4
0.8
1.2
1.6
0.1
0.2
0.5
1
2
5
10
RR (fixed)

應用?

- 我們的病人是否與研究中的病人差異很大，以至於無法應用其結果?
  - Adult , community-acquired pneumonia, hospitalized
  - 病人的治療是以BL +macrolide 爲主

    實驗結果主要是respiratory quinolone 和BL的比較
- 該項治療在我們診療環境中是否可行?
  - 可
- 我們的病人可能從該項治療中獲益或受害?
  - 無

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
病人目前使用cefuroxime + macrolide類藥物，有出現拉肚子的副作用。	配合意願高
生活品質	**社會脈絡**
用了cefuroxime + macrolide類藥物有拉肚子的副作用。可以考慮用只使用cefuroxime即可。	無

Audit（自我評估）

- 在進行實證醫學過程中我遇到以下問題
  - 對於Foreground question，比較無法Specific 列出PICO
  - 爲了要找到真的specific 符合病人case 的資料，花很多時間，且常常找不到。