

# Evidence-Based Medicine Conference

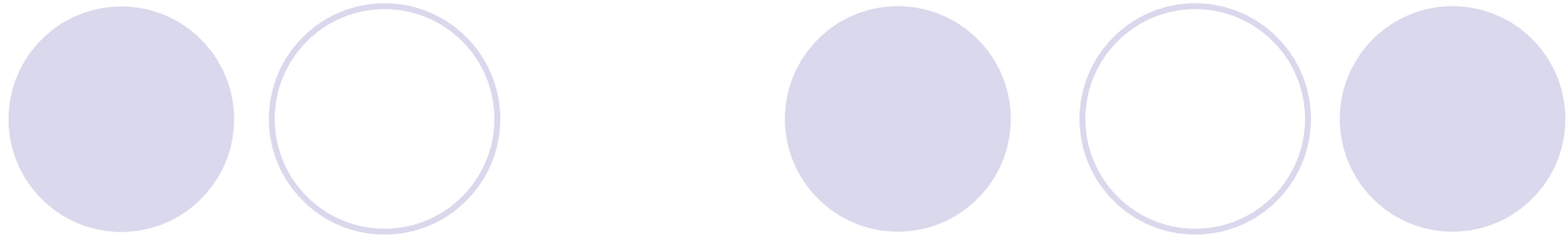
一般醫學內科PGY1 蔡松年  
指導老師：主治醫師 王程遠

Date:97/5/26

# 臨床情境



- This 76 years old male had underlying disease of **chronic obstructive pulmonary disease**, and hypertension.
- He suffered from acute onset of cough with sputum with progressive course for 3~4 days. Sore throat and rhinorhea was also complained, but denied fever. This morning, short of breath with chest discomfort was complained.
- Due to above, he went to our emergent room for help. At emergent room, chest x-ray revealed no obvious infiltration patch over bilateral lung. The lab data revealed, WBC:8800, Neut:74.4%, and, CRP:207.47, PH:7.33, PCO<sub>2</sub>:57. Under the impression of **chronic obstructive pulmonary disease with acute exacerbation**, he was admitted to our ward through emergent room.



- 這位病人住院時有cough with sputum, dyspnea，加上他有COPD和smoking的history。屬於COPD with acute exacerbation，需要住院治療。
- 治療上給予inhaled beta adrenergic agonists, anticholinergic bronchodilators, systemic corticosteroids, and antibiotics
- 除了CRP較高之外，並無明顯的toxic sign，因此，antibiotics是否需要使用呢？



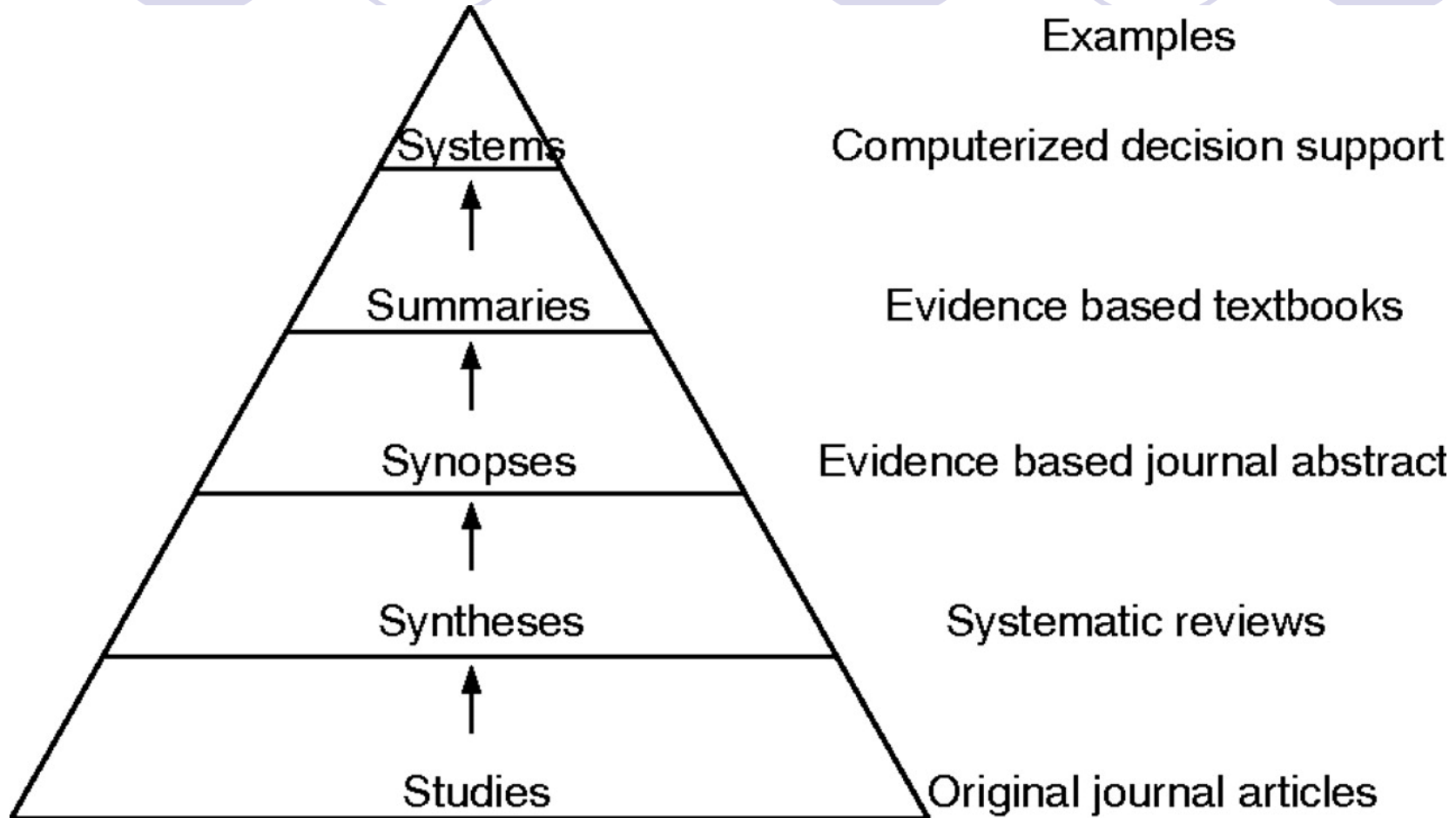
Asking

- 對於慢性阻塞性肺病急性惡化的病人  
(*COPD with acute exacerbation*)，使用  
抗生素治療與不使用抗生素治療於*mortality*  
*rate*上有無差別？

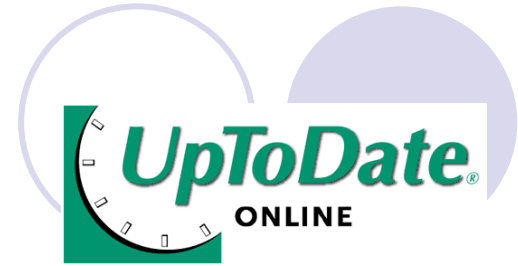
# 寫成PICOT

<b>P</b>	Chronic obstructive pulmonary disease (COPD) with acute exacerbation patient
<b>I</b>	Antibiotics
<b>C</b>	placebo
<b>O</b>	Mortality rate
<b>T</b>	Not defined

Acquired



# 搜尋summary



- Key word:

- acute exacerbation of chronic obstructive pulmonary disease
- Antibiotics

搜尋到的文章標題


- **Title:**

- **Management of acute exacerbations of chronic obstructive pulmonary disease**

- **Last literature review version 16.1: 一月 2008 | This topic last updated: 二月 12, 2008**

## 搜尋到的文章內容

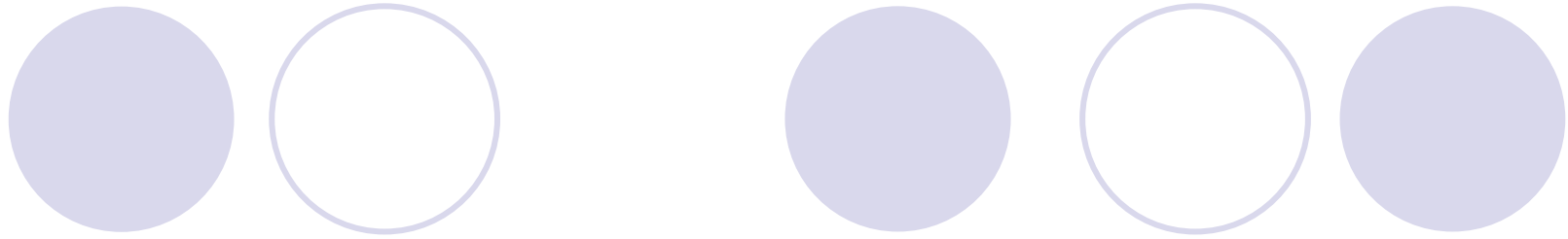
- **PRECIPITANTS** — Acute exacerbations of COPD are most commonly precipitated by **infection (bacterial or viral)** or **environmental factors such as air pollution or temperature**. It is estimated that **50 to 60 percent** of exacerbations are due to respiratory infections (including bacteria and viruses), **10 percent** are due to environmental pollution, and **30 percent** are of unknown etiology.
- **PHARMACOLOGIC TREATMENT** — The major components of managing an acute exacerbation of COPD include **inhaled beta adrenergic agonists, anticholinergic bronchodilators, corticosteroids, and antibiotics**.

- 
- **Antibiotics** — Antibiotics are frequently administered to patients having a COPD exacerbation. The importance, diagnosis, and treatment of infection in exacerbations of COPD is discussed separately. ([See "Role of infection in acute exacerbations of chronic obstructive pulmonary disease"](#)).

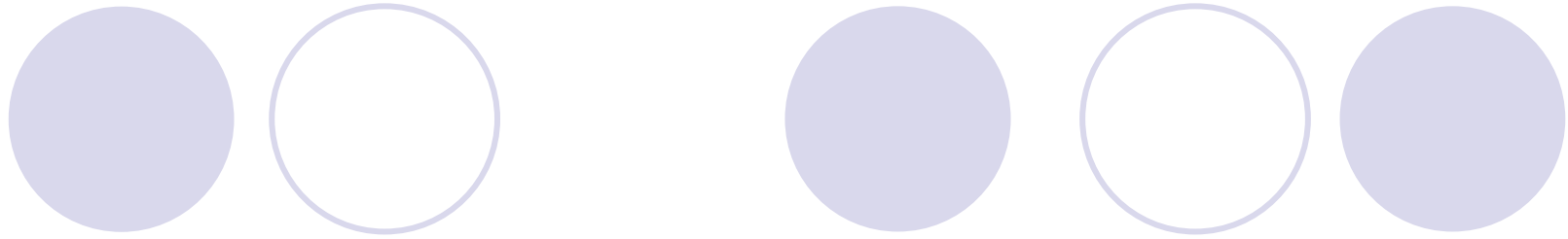
*From uptodate*

## Role of infection in acute exacerbations of chronic obstructive pulmonary disease

- Antibiotic therapy increases the **likelihood of clinical improvement** in patients having an exacerbation of COPD,
- particularly in patients with a **severe exacerbation**.
- Among patients **requiring mechanical ventilation**, antibiotic therapy may provide a mortality benefit.



- Antibiotic therapy is indicated for many patients with an exacerbation of COPD:
  - For all patients having an exacerbation of COPD that is characterized by increased sputum purulence, plus either increased dyspnea or an increased volume of sputum, we recommend antibiotic therapy (Grade 1B).
  - Antibiotics not be prescribed in patients whose exacerbation of COPD is **mild**, who have no risk factors for a poor outcome, and who have **only one** of the cardinal symptoms of increased dyspnea, sputum purulence, and sputum production (Grade 2B).



- The **optimal antibiotic regimen** for the treatment of exacerbations of COPD has **not been determined**.
- The choice of antibiotic should target **S. pneumoniae, H. influenzae, and M. catarrhalis**, while taking into account local patterns antibiotic resistance.
- For most patients with COPD, we suggest that antibiotics **not** be administered **for the purpose of preventing exacerbations** (**Grade 2C**).



*From uptodate*

# 將system搜尋的結果應用到臨床

- Our patient: sputum purulence(+/-), dyspnea(+), increase sputum(+)
- 因病人症狀屬於中度到重度 **AE of COPD**，因此，抗生素是否有必要使用.
- 我們一開始除了施予病人**inhaled beta adrenergic agonists, anticholinergic bronchodilators, systemic corticosteroids**治療外，也給病人**抗生素 (Moxifloxacin 400mg, QD, IVD)**的治療.



# 搜尋 Synopses: ACP Journal Club

- Key word:

- Chronic obstructive lung disease

- treatment

## 搜尋到的文章標題

- **Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)**
- ***This article meets all the criteria for ACP Journal Club but has not been abstracted because, in the judgment of the editors, its findings were less widely applicable to clinical practice in internal medicine***

搜尋Syntheses:

*Cochrane Database of Systematic Reviews*

- Key word:

- acute exacerbations of chronic obstructive pulmonary disease
- antibiotics



搜尋到的文章標題

- **Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)**

- **This record should be cited as:**

- Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of
  - chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews 2006*, Issue 2. Art. No.: CD004403. DOI

# 搜尋到的文章內容

- **Background:**

- Most patients with an exacerbation of chronic obstructive pulmonary disease (COPD) are treated with antibiotics. However **the value of their use remains uncertain**. Some controlled trials of antibiotics have shown benefit while others have not.

- **Objectives:**

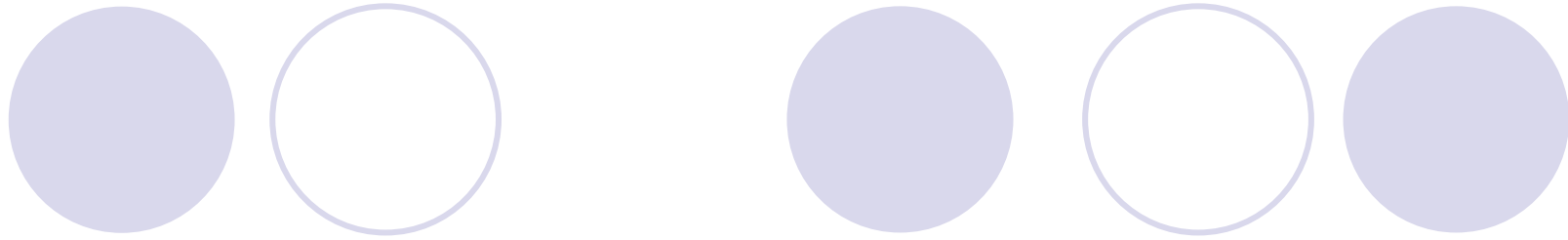
- To conduct a **systematic review** of the literature **estimating the value of antibiotics in the management of acute COPD exacerbations**.

- **Search strategy:**

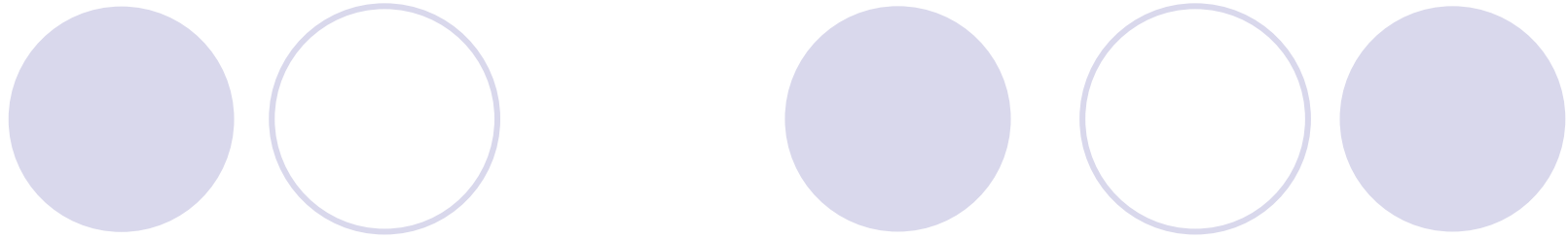
- We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2005); MEDLINE(1966 to December 2005); EMBASE (1974 to December 2005); Web of Science (December 2005), and other electronically available databases.

- **Selection criteria:**

- **Randomised controlled trials (RCTs)** in patients with **acute COPD exacerbations** comparing **antibiotic (for a minimum of five days) and placebo**.



- **Main results:**
- **Eleven trials** with 917 patients were included. **Ten trials** used increased cough, sputum volume and purulence diagnostic criteria for COPD exacerbation. 857 patients provided data for outcomes including **mortality**, treatment failure, increased sputum volume, sputum purulence, PaCO<sub>2</sub>, PaO<sub>2</sub>, peak flow and adverse events.
- Antibiotic therapy regardless of antibiotic choice **significantly reduced mortality** (RR 0.23; 95% CI 0.10 to 0.52 with NNT of 8; 95% CI 6 to 17),
- **reduced treatment failure** (RR 0.47; 95% CI 0.36 to 0.62 with NNT of 3; 95% CI 3 to 5) and
- **reduced sputum purulence** (RR 0.56; 95% CI 0.41 to 0.77 with NNT of 8; 95% CI 6 to 17).
- There was a **small increase in risk of diarrhoea** with antibiotics (RR 2.86; 95% CI 1.06 to 7.76).
- Antibiotics did not improve arterial blood gases and peak flow.



- **Conclusions:**
- This review shows that in COPD exacerbations with **increased cough and sputum purulence** antibiotics reduce the risk of: short-term mortality by 77%, decrease the risk of treatment failure by 53% and the risk of sputum purulence by 44%; with a small increase in the risk of diarrhoea.
- These results should be interpreted with caution due to the **differences in patient selection, antibiotic choice, small number of included trials and lack of control for interventions that influence outcome, such as use of systemic corticosteroids and ventilatory support.**
- Nevertheless, this review **supports antibiotics** for patients with COPD exacerbations with increased cough and sputum purulence **who are moderately or severely ill.**

## 將Synopsis and Synthesis的搜尋結果應用到病人身上

- 抗生素治療，就如同前面uptodate提過的，此篇paper的針對中度到重度的COPD with AE 的病人是建議使用的。
- 我們的case屬於中度，因此建議使用抗生素治療。
- 效果：
  - reduced mortality NNT=8
  - reduced treatment failure NNT=3
  - reduced sputum purulence NNT=8



# 搜尋Studies, Pubmed

- Key word:

- acute exacerbations of chronic obstructive lung disease
- antibiotics

# 搜尋到的文章標題

- *Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis*

○ Quon BS, Gan WQ, Sin DD.

- Department of Medicine, Respiratory Division, University of British Columbia, Vancouver, BC, Canada. (*Chest*. 2008; 133:756-766)

# 搜尋到的文章內容

- **Background:**

- Systemic corticosteroids, antibiotics, and noninvasive positive pressure ventilation (NPPV) are recommended for patients with acute exacerbation of COPD.
- However, their clinical benefits in various settings are uncertain.
- We undertook a systematic review and metaanalysis to systematically evaluate the effectiveness of these therapies.

- **Methods:**

- MEDLINE and EMBASE were searched to identify relevant randomized controlled clinical trials published from January 1968 to November 2006. We identified additional studies by searching bibliographies of retrieved articles.

- **Results:**

- **Systemic corticosteroids** reduced treatment failure by 46% (95% confidence interval [CI], 0.41 to 0.71), length of hospital stay by 1.4 days (95% CI, 0.7 to 2.2), and improved FEV1 by 0.13 L after 3 days of therapy (95% CI, 0.04 to 0.21). Meanwhile, the risk of hyperglycemia significantly increased (relative risk, 5.88; 95% CI, 2.40 to 14.41).
- **Antibiotics reduced treatment failure by 46% (95% CI, 0.32 to 0.92, p=0.002) and in-hospital mortality by 78% (95% CI, 0.08 to 0.62).**
- **NPPV** reduced the risk of intubation by 65% (95% CI, 0.26 to 0.47), in-hospital mortality by 55% (95% CI, 0.30 to 0.66), and the length of hospitalization by 1.9 days (95% CI, 0.0 to 3.9).

- **Conclusions:**

- For acute COPD exacerbations,
- **systemic corticosteroids** are effective in reducing treatment failures,
- **while antibiotics reduce mortality and treatment failures in those requiring hospitalization and**
- **NPPV** reduces the risk of intubation and in-hospital mortality, especially in those who demonstrate respiratory acidosis.



對找到的文章  
進行**appraisal**

# 證據等級

Level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT[註1]所做成的綜合性分析(SR[註2] 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

<b>A</b>	consistent level 1 studies
<b>B</b>	consistent level 2 or 3 studies <i>or</i> extrapolations from level 1 studies
<b>C</b>	level 4 studies <i>or</i> extrapolations from level 2 or 3 studies
<b>D</b>	level 5 evidence <i>or</i> troublingly inconsistent or inconclusive studies of any level

# 10 questions to help you make sense of reviews-2

## Detailed Questions

- **Did the reviewers try to identify all** *Consider:*
  - – *which bibliographic databases were used*
  - – *if there was follow-up from reference lists*
  - – *if there was **personal contact with experts***
  - – *if the reviewers **searched for unpublished** studies*
  - – *if the reviewers searched for **non-English-language** studies*
- **Did the reviewers assess the quality of the included studies?**
  - *Consider:*
    - – *if a clear, pre-determined strategy was used to*
  - *determine which studies were included. Look for:*
    - – *a **scoring system***
    - – ***more than one assessor***

# 10 questions to help you make sense of reviews-3

## Detailed Questions

- **If the results of the studies have been combined, was it reasonable to do so?**
  - *Consider whether:*
    - – *the results of each study are clearly displayed*
    - – *the results were similar from study to study*  
*(look for tests of heterogeneity)*
    - – *the reasons for any variations in results are discussed*
- **How are the results presented and what is the main result?**
  - *Consider:*
    - – *how the results are expressed (e.g. odds ratio, relative risk, etc.)*
    - – *how large this size of result is and how meaningful it is*
    - – *how you would sum up the bottom-line result of the review in one sentence*

# 10 questions to help you make sense of reviews-4

## Detailed Questions

- **How precise are these results?**

- *Consider:*

- – if a *confidence interval* were reported.
- *Would your decision about whether or not to use this intervention be the same at the upper confidence limit as at the lower confidence limit?*
- – if a *p-value* is reported where confidence intervals are unavailable

- **Can the results be applied to the local population?**

- *Consider whether:*

- – the *population sample* covered by the review
- *could be different from your population in ways that would produce different results*
- – *your local setting differs much from that of the review*
- – *you can provide the same intervention in your setting*

# 10 questions to help you make sense of reviews-5

## Detailed Questions



- **Were all important outcomes considered?**
  - *Consider outcomes from the point of view of the:*
    - – *individual*
    - – *policy makers and professionals*
    - – *family/carers*
    - – *wider community*
- **Should policy or practice change as a result of the evidence contained in this review?**
  - *Consider:*
    - – *whether any benefit reported outweighs any harm and/or cost.*
    - – *If this information is not reported can it be filled in from elsewhere?*

# 總結

<b>Reduced mortality rate</b>	Cochrane	RR 0.23; 95% CI 0.10 to 0.52 with <b>NNT of 8 (total mortality rate)</b> ; 95% CI 6 to 17
	2008 Chest	95% CI, 0.08 to 0.62, <b>RRR=78% (inhospital mortality rate), p=0.002</b>
<b>Reduced treatment failure</b>	Cochrane	RR 0.47; 95% CI 0.36 to 0.62 with <b>NNT of 3</b> ; 95% CI 3 to 5
	2008 Chest	95% CI, 0.32 to 0.92 <b>RRR=46%, p=0.002</b>
<b>Reduced sputum purulence</b>	Cochrane	RR 0.56; 95% CI 0.41 to 0.77 with <b>NNT of 8</b> ; 95% CI 6 to 17
<b>Increase in risk of diarrhoea</b>	Cochrane	RR 2.86; 95% CI 1.06 to 7.76

# 總結與應用在病人身上

<b>P</b>	Chronic obstructive pulmonary disease (COPD) with acute exacerbation patient
<b>I</b>	Antibiotics 需選擇能cover S. pneumoniae, H. influenzae, and M. catarrhalis的種類
<b>C</b>	placebo
<b>O</b>	<u>outcomes</u>
<b>T</b>	Antibiotics 需使用幾天，尚無明確定論，在Cochrane study中，所選的trial皆使用至少五天。

# Audit



- 在進行實證醫學過程中我遇到以下問題
  - 爲了要找到合用且有附全文的資料，花很多時間。質疑**EBM**的效率。(未來遇到更多的臨床問題，會有時間對每個問題花上**5**小時以上按金字塔找下來嗎?)

經過實證醫學的驗證，我對於病人病情的想法或治療策略有了以下改變

- 對於中至重度COPD with AE的病人，除了inhaled beta adrenergic agonists, anticholinergic bronchodilators, systemic corticosteroids, 甚至ventilator治療之外，接會加上antibiotics 治療。
- 至於輕度COPD with AE且沒有toxic sign的病人，可能暫時不考慮用antibiotics（但能需再尋找更多證據佐證）。