

# Evidence Based Medicine

Presented by R3王貞婷



# Clinical case

- A 67y/o female is a case of bacterial meningitis. Empiric antibiotics including Meropenem and Vancomycin was prescribed. But the consciousness still had no obvious improvement (coma).
- Acute bacterial meningitis remains a disease with a high mortality rate. Despite empiric antibiotics, do we have choice of adjuvant therapy?



# Clinical problem

- As for TB meningitis, could we use corticosteroids as adjunctive therapy for bacterial meningitis?



# Formulate A PICO Question

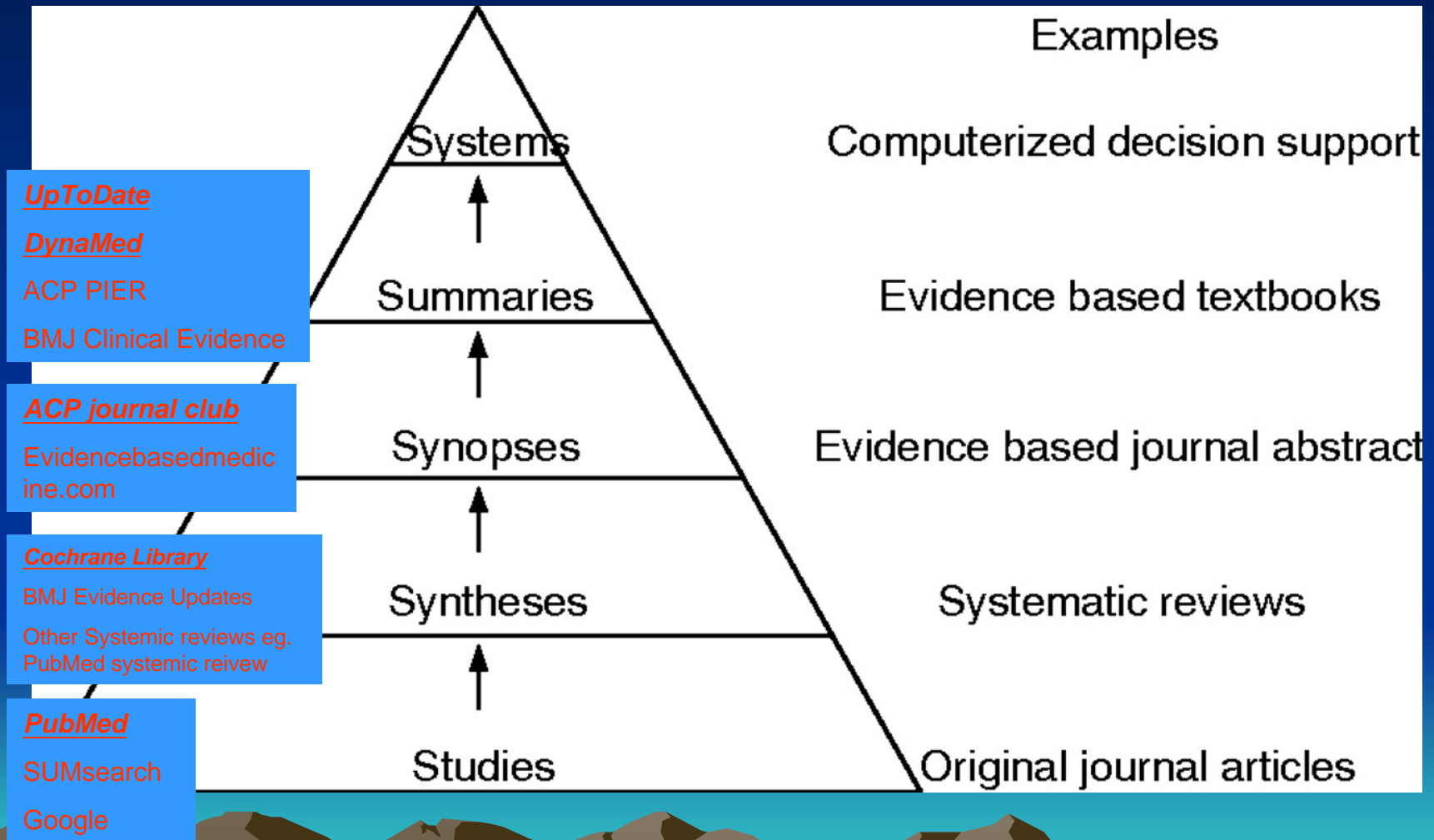
|          |                              |  |
|----------|------------------------------|--|
| <b>P</b> | <b>Patient or population</b> | Patients with acute bacterial meningitis         |
| <b>I</b> | <b>Intervention</b>          | Corticosteroids as adjuvant therapy              |
| <b>C</b> | <b>Comparison</b>            | Placebo group                                    |
| <b>O</b> | <b>Outcomes</b>              | Rate of mortality, rate of neurological sequelae |

# Key words for PICO item

- Bacterial meningitis
- Steroids
- Corticosteroids
- Dexamethasone



# Acquire



# Results of search

- The Cochrane Library

Combine bacterial meningitis, steroids → 1/5



# Results of search

- Pubmed (Medline)  
Combine bacterial meningitis,  
steroids → 2/966



# Results of search

- ACP journal club

Combine bacterial meningitis, steroids → 0/2



# Results of search

- UpToDate

Combine bacterial meningitis, steroids → 1/15



# Level of Evidence

**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

# Corticosteroids for acute bacterial meningitis (Review)

van de Beek D, de Gans J, McIntyre P, Prasad K

*The Cochrane Library*

2008

Level of evidence: 1a



# Background

- Acute bacterial meningitis remains a disease with a high mortality rate (10-30%).
- Late sequelae such as cranial nerve impairment, especially **hearing loss**, occur in 5 to 40% of patients.
- The clinical outcome of acute bacterial meningitis has been related to the severity of the inflammatory process in the subarachnoidal space.



# Background

- Treatment with **corticosteroids** results in a reduction of the inflammatory response in the cerebrospinal fluid (CSF).
- We conducted a meta-analysis of randomised controlled trials (RCTs) of adjuvant corticosteroids in the treatment of acute bacterial meningitis.



# Search strategy

- In this updated review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006); MEDLINE (1966 to July 2006); EMBASE (1974 to June 2006); Current Contents (2001 to June 2006); and reference lists of all articles.



# Search strategy

- Patients of any age and in any clinical condition, treated with antibacterial agents and randomized to **corticosteroid therapy** (or placebo) of any type, could be included.
- At least case **fatality rate** or **hearing loss** had to be recorded for inclusion.



# Characteristics of studies

- The study intervention consisted of **dexamethasone** in 17 of 20 studies; dosages ranged from 0.4 to 0.9 mg/kg and the duration ranged from two to four days.
- Study medication was administered with or before the first dose of antibiotic in nine studies, and in seven studies after the first doses.



# Results

- Eighteen studies involving 2750 people were included.
- Overall, adjuvant corticosteroids were associated with lower case fatality (relative risk (RR) 0.83, 95% CI 0.71 to 0.99), lower rates of severe hearing loss (RR 0.65, 95% CI 0.47 to 0.91) and long-term neurological sequelae (RR 0.67, 95% CI 0.45 to 1.00).
- In children, corticosteroids reduced severe hearing loss (RR 0.61, 95% CI 0.44 to 0.86).

# Results

- Corticosteroids reduced mortality in patients with meningitis due to *Streptococcus pneumoniae* (RR 0.59, 95% CI 0.45 to 0.77) and reduced severe hearing loss in children with meningitis due to *Haemophilus influenzae* (RR 0.37, 95% CI 0.20 to 0.68).
- Corticosteroids were protective against short-term neurological sequelae in patients with bacterial meningitis in high-income countries (RR 0.56, 95%CI 0.3 to 0.84); in low-income countries this RR was 1.09 (95%CI 0.83 to 1.45) (not significantly).

# Results

- For children with bacterial meningitis admitted in **high-income countries**, corticosteroids showed a protective effect against severe hearing loss (RR 0.61, 95% CI 0.41 to 0.90).
- Overall, adverse events were not increased significantly with the use of corticosteroids.

# Discussion

- The first confounding factor is **selection bias**. Several included studies on childhood bacterial meningitis had exceptional low mortality rates; nine studies had mortality rates of 3% or less.
- For patients admitted in a late stage of disease, adjuvant corticosteroids are less protective and might even be harmful. This will lead to an underestimate of the treatment effect.



# Discussion

- This meta-analysis showed a beneficial effect of adjunctive corticosteroids in acute bacterial meningitis.
- In summary, it recommend the use of corticosteroids in adults with acute bacterial meningitis and in children with acute bacterial meningitis in high-income countries.
- A four-day regimen of dexamethasone (0.6 mg/kg daily) given before or with the first dose of antibiotics.



# Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data

*Diederik van de Beek, Jeremy J Farrar, Jan de Gans, Nguyen Thi Hoang Mai, Elizabeth M Molyneux, Heikki Peltola, Tim E Peto, Irmeli R, Mathew Scarborough, Constance Schultz, Guy E Thwaites, Phung Quoc Tuan, A H Zwind*

Lancet Neurology, 2010

Level of evidence: 1b



# Background

- In past studies, it suggested that the main beneficial effect of the corticosteroid dexamethasone was to reduce the risk of hearing loss in children with *Haemophilus influenzae* type *b* meningitis.
- *Additional* data extended the likely benefit to those with *Streptococcus pneumoniae* meningitis.



# Background

- A Cochrane meta-analysis of data from 20 randomised controlled trials and involving 2750 people showed an overall mortality benefit and a reduction in neurological sequelae in patients treated with adjuvant corticosteroids.
- Adjunctive corticosteroids seem to benefit some patients with bacterial meningitis but not others, and how to select patients who are likely to benefit is unclear.

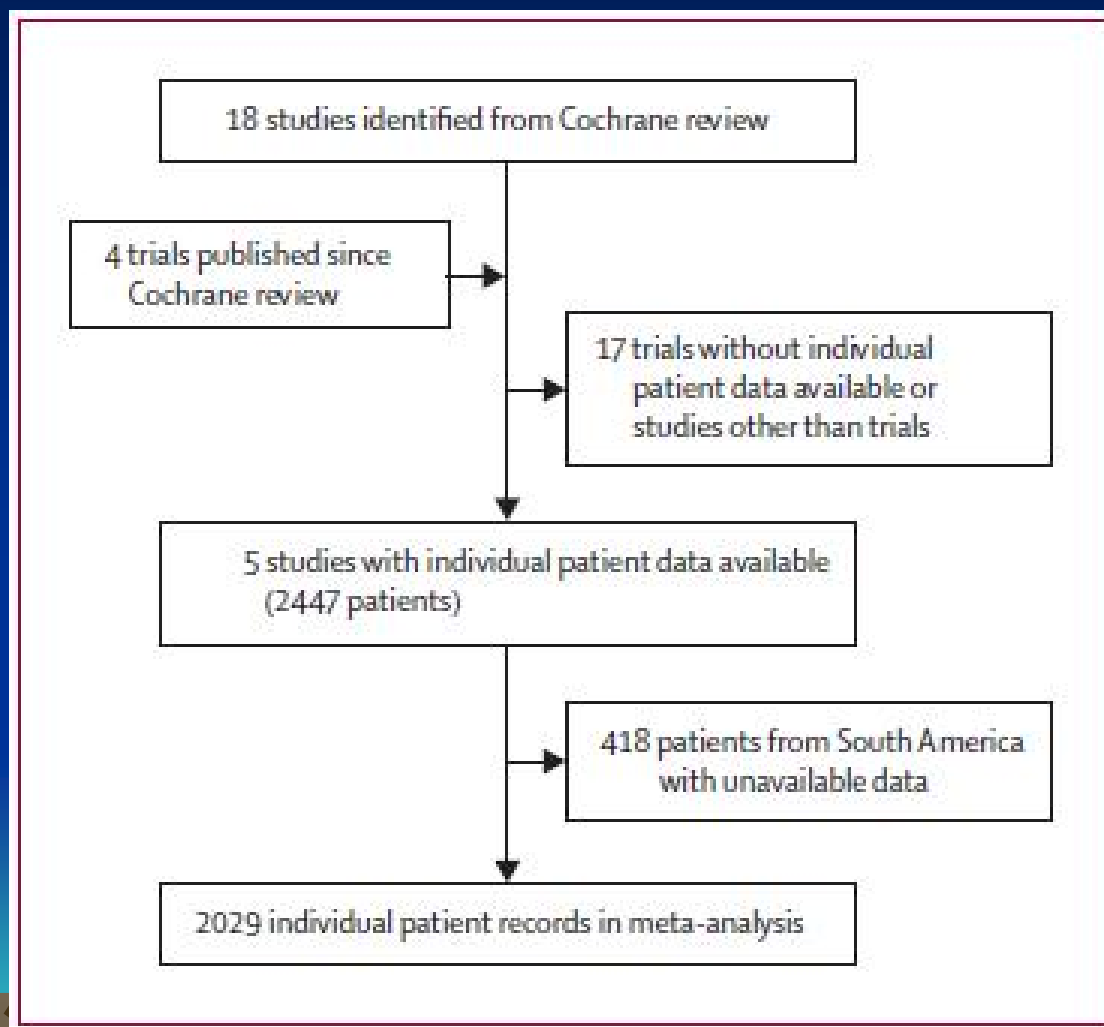


# Methods

- Relevant trials were identified previously as part of a Cochrane review (20 randomised controlled trials involving 2750 people ).
- Individual patient data from five randomised, double-blind, placebo-controlled trials of dexamethasone for bacterial meningitis published since 2001 were included in the analysis.



# Methods



# Results

- Data from 2029 patients from five trials were included in the analysis (833 [41.0%] aged <15 years).
- Dexamethasone was not associated with a significant reduction in death (*OR 0.97, 95% CI 0.79–1.19*), *severe neurological sequelae or bilateral severe deafness (OR 0.92, 0.76–1.11)*.
- Dexamethasone seemed to reduce hearing loss among survivors (*OR 0.77, 0.60–0.99,  $p=0.04$* ).

# Discussion

- The aim of this analysis was to establish whether any subgroups of patients with acute bacterial meningitis might benefit from adjunctive dexamethasone.
- This analysis of 2029 patients from five trials showed that treatment with adjunctive dexamethasone did not significantly reduce mortality, neurological disability, or severe hearing loss in bacterial meningitis.



# Discussion

- In summary, these data indicate that patients with bacterial meningitis neither benefit from nor are harmed by treatment with adjunctive dexamethasone.



# **Dexamethasone to prevent neurologic complications of bacterial meningitis in adults**

*UpToDate, 2009*



# Background

- Early intravenous administration of glucocorticoids (usually dexamethasone) has been evaluated as adjuvant therapy to diminish the rate of hearing loss and other neurologic complications, and mortality in selected patients with bacterial meningitis.



# In Developed Regions

- A prospective, randomized, double-blind trial in 301 patients from Europe with bacterial meningitis.
- The patients were randomly assigned to intravenous dexamethasone (10 mg every six hours for four days) or placebo with the first dose administered 15 to 20 minutes before or at the time of antibiotic administration.



# In Developed Regions

- Significant reductions in mortality and all unfavorable outcomes were only seen with dexamethasone therapy in patients with **S. pneumoniae** meningitis (**Grade 1B**).
- Among the patients with pneumococcal meningitis, significant benefit was seen only in those with an intermediate neurologic deficit on admission, defined as a Glasgow coma scale of 8 to 11.



# In Developing Regions

- A study from sub-Saharan Africa found no benefit from treatment with dexamethasone. In this randomized trial of adults in Malawi, 465 patients (95 percent of whom were HIV-positive) received dexamethasone or placebo for four days.
- There was also no difference in mortality when the analysis was restricted to patients with pneumococcal meningitis (odds ratio 1.10; 95% CI 0.68 to 1.77).



# In Developing Regions

- The benefit of dexamethasone in developing regions is less clear than for developed countries.
- In regions with high HIV prevalence such as Africa, there does not appear to be any clinical benefit to the administration of dexamethasone (**Grade 1B**).
- In regions with lower HIV prevalence, we suggest administering dexamethasone in patients who have bacterial meningitis confirmed by Gram stain or a rapid diagnostic test (**Grade 2B**).



# Recommendations

- When indicated, dexamethasone is given 15 to 20 minutes before or at the time of antibiotic administration.
- Two dose regimens have shown efficacy:
  - **0.15 mg/kg every six hours** for four days in the European trial (developed regions)
  - **0.4 mg/kg every 12 hours** for four days in the Vietnamese trial (developing regions)



# Conclusions

- The systemic review study recommend the use of corticosteroids (a four-day regimen of dexamethasone given before or with the first dose of antibiotics) in adults with acute bacterial meningitis and in children with acute bacterial meningitis in high-income countries. (Cochrane Library, 2008)
- Another meta-analysis of individual data indicate that patients with bacterial meningitis neither benefit from nor are harmed by treatment with adjunctive dexamethasone. (Lancet Neurology, 2010)



# Conclusions

- In developing regions with lower HIV prevalence, we suggest administering dexamethasone in patients who have bacterial meningitis confirmed by Gram stain or a rapid diagnostic test. (UpToDate, 2009)
- When indicated, dexamethasone is given 15 to 20 minutes before or at the time of antibiotic administration. The dose of 0.4 mg/kg every 12 hours for four days was suggested in developing regions. (UpToDate, 2009)



Thanks for your attention!

