EBM

Instructor: Dr. 吳大緯
Presenter: PGY 程朝暐

Clinical Scenario

- 對於nosocomial pneumonia associated with multidrug-resistant Pseudomonas aeruginosa 使用 colistin ，使用inhalation VS parenteral administration 何種效果較好？

Asking-提出臨床問題

- Background questions
  - (1) question
  - (2) answer
  - (3) apply

- Foreground questions
  - (1) PICOT
  - (2) search data
    - a. Summary
    - b. Synopses
    - c. Synthesis
    - d. Study

Background Question

What is **Colistin** ?

Colistin

- a group of basic polypeptide antibiotics that inhibit only aerobic gram-negative bacteria.
- binding to phospholipids in the cytoplasmic membrane, with disruption of membrane permeability, macromolecular and ion disequilibria, and cell lysis.
- Intrinsic resistance is caused in part by inability of the drug to gain access to the cytoplasmic membrane; acquired resistance is rarely observed.

Colistin

- The potency and spectrum of activity of polymyxin are similar to those of the aminoglycosides.
- because of more marked nephrotoxicity, only polymyxins B and E (**colistin**) are used clinically.
- Polymyxin E (**colistin**)
  - a parenteral agent for the treatment of infection caused by multiply resistant, nosocomial pathogens

Adverse Drug Reactions

- after topical or oral administration, Adverse reactions are uncommon, although nausea, vomiting, and diarrhea are caused by administration of large doses (600 mg) by mouth.
- parenteral administration, side effects are similar to those caused by aminoglycosides.
  - Reversible dizziness
  - paresthesias especially affecting the face
  - incoordination caused by vestibulotoxicity and proteinuria
  - microscopic hematuria
  - progressive azotemia
  - acute tubular necrosis
  - Respiratory paralysis owing to neuromuscular blockade occurs rarely;

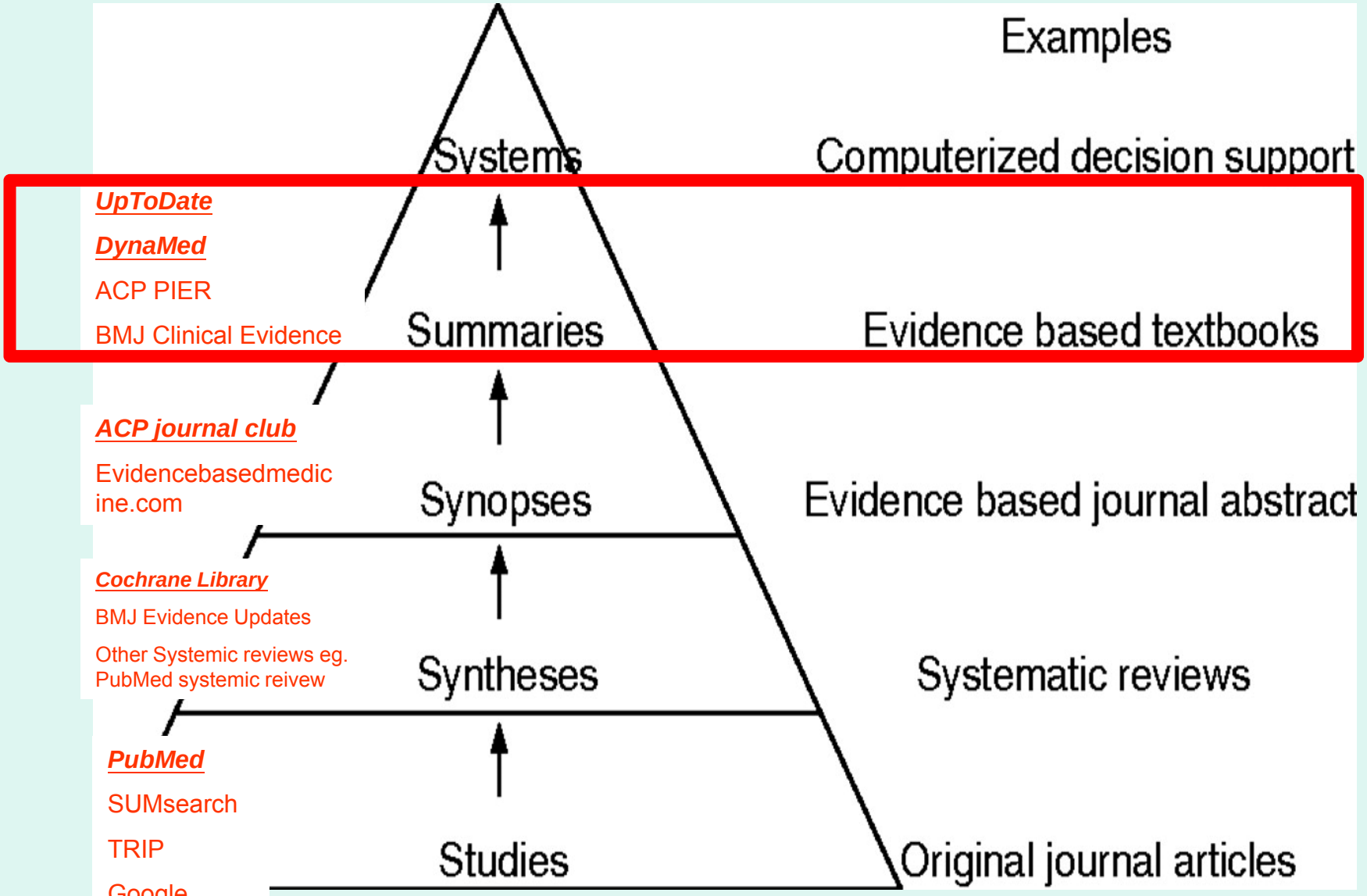
Foreground Question

Patient / Problem	Patient with nosocomial pneumonia associated with multidrug-resistant Pseudomonas aeruginosa use colistin
Intervention	inhalation
Comparison	parenteral administration
Outcome	Effectiveness
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 (system, synopses, synthesis)
- 最後再找尚未經過嚴格評讀的study

Search strategy: 5S model

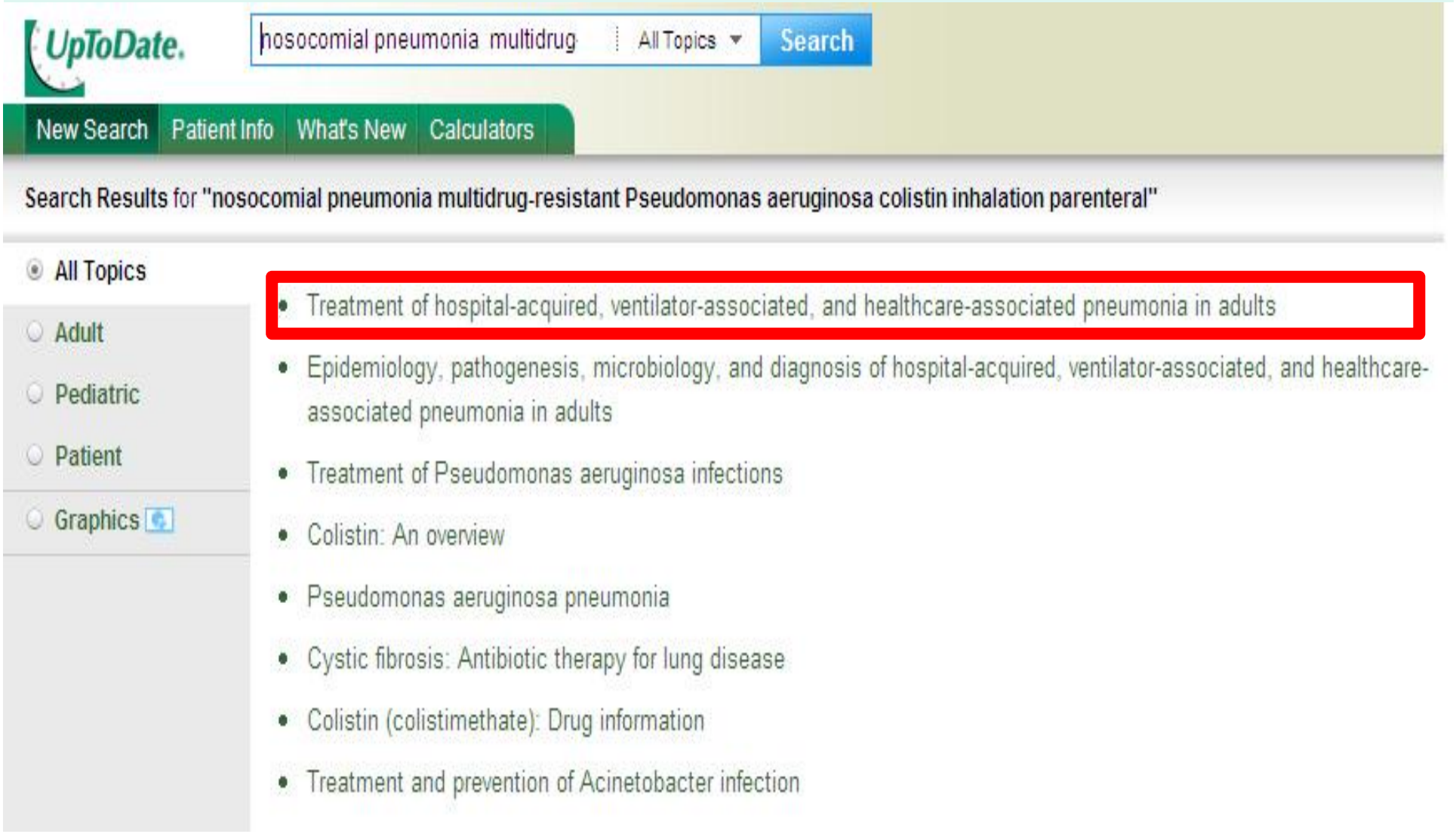


Brian Haynes, R Evid Based Med 2006;11:162-164

EBM ONLINE

Summaries

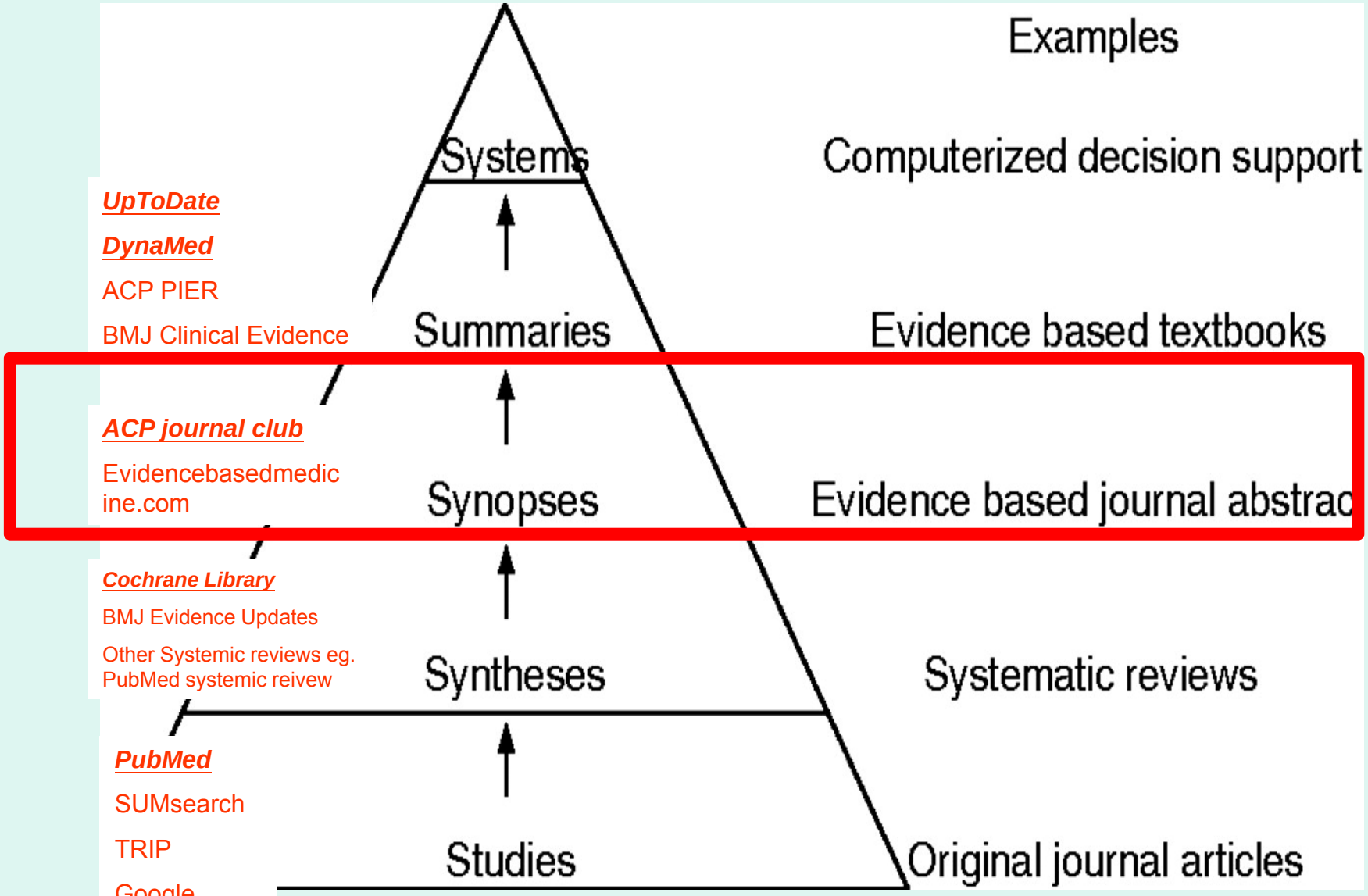
Key words: nosocomial pneumonia, multidrug-resistant Pseudomonas aeruginosa, colistin, inhalation, parenteral



Summaries

- Empiric coverage for patients WITH risk factors for MDR pathogens —
  - Addition of an alternative agent, such as intravenous **colistin**, may be appropriate if highly resistant Pseudomonas spp or Acinetobacter spp is suspected.
  - In some cases, inhaled colistin may be appropriate as adjunctive therapy in combination with systemic antimicrobials

Search strategy: 5S model



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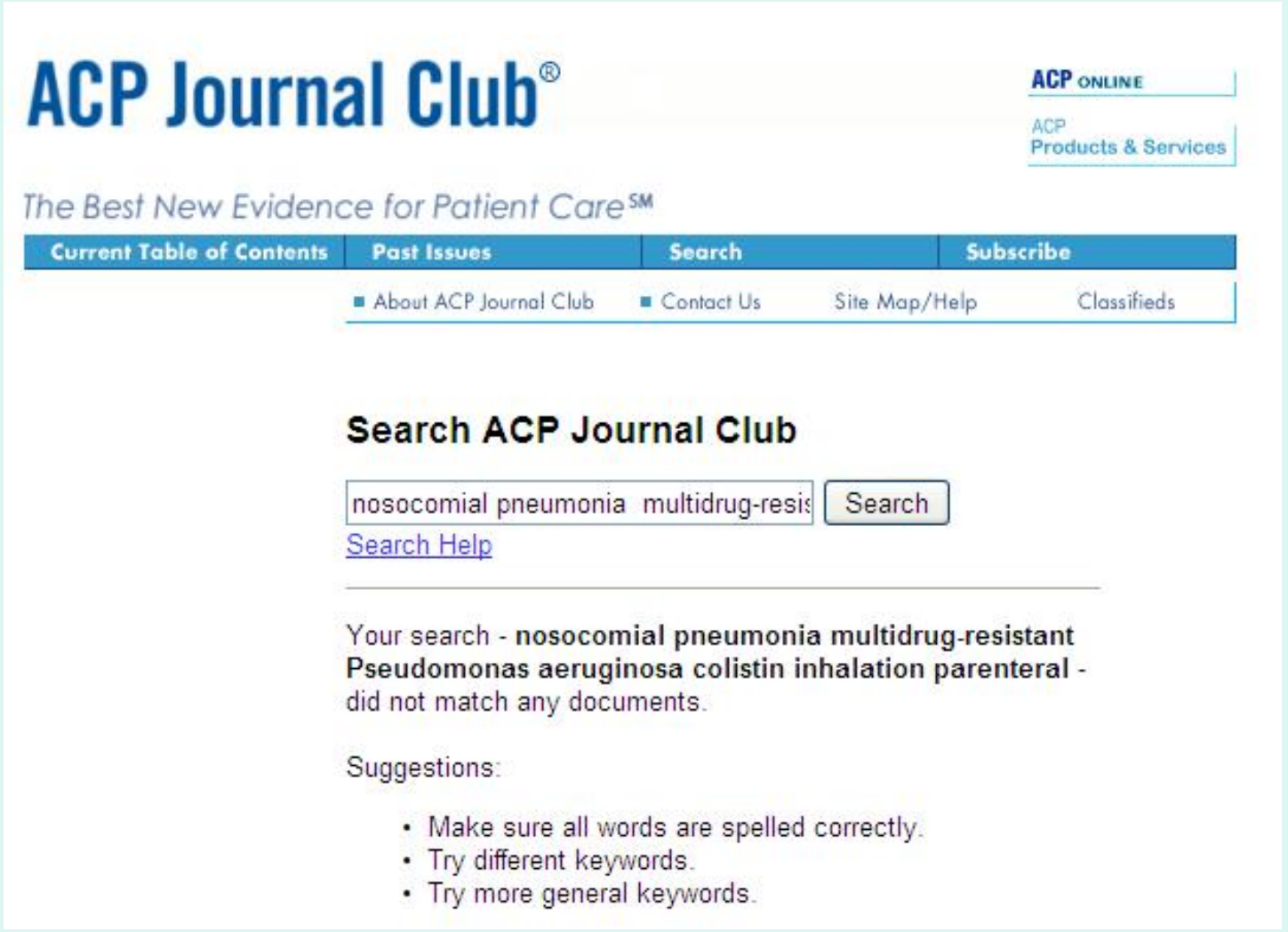
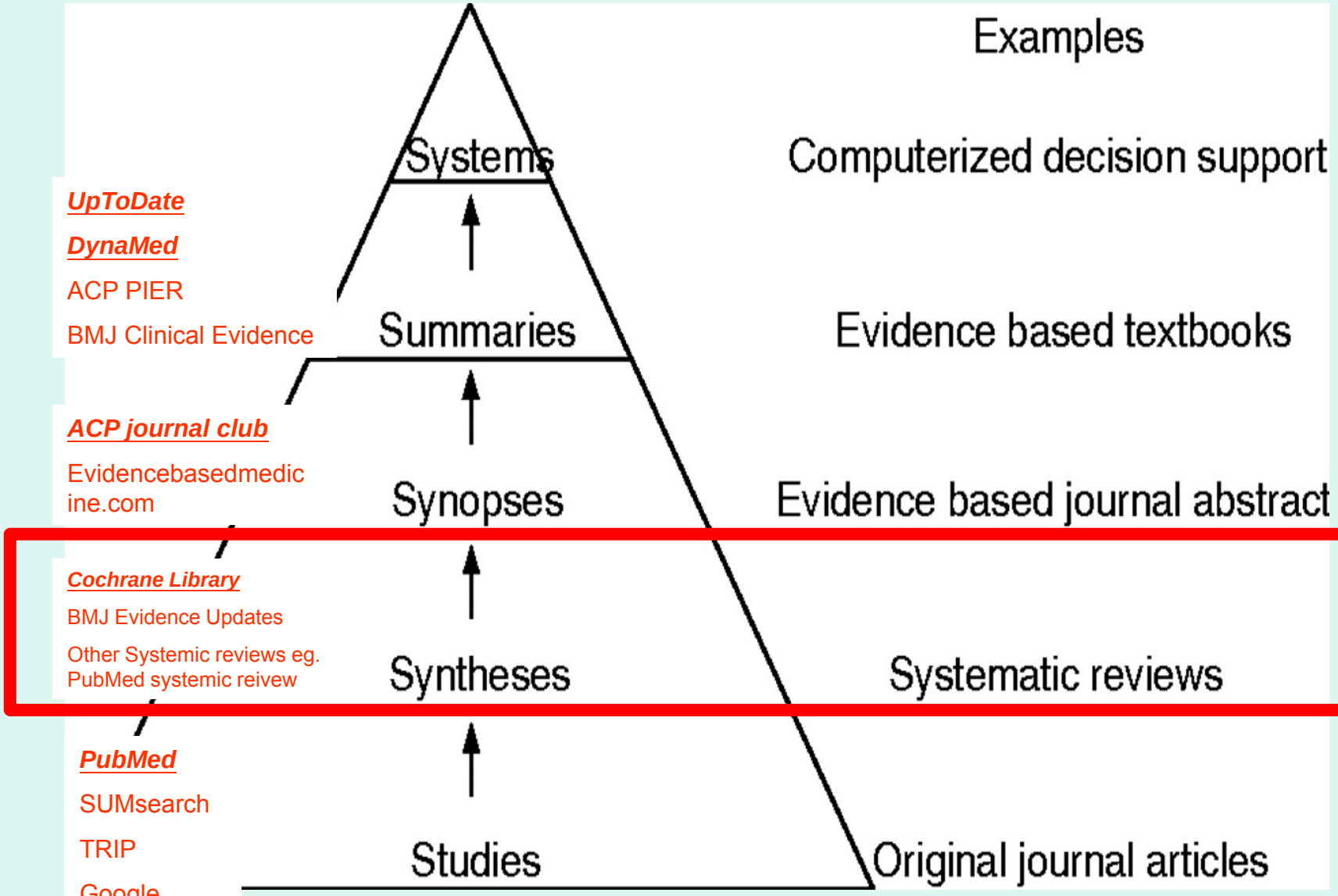
Synopses:

ACP Journal Club®

Key words: nosocomial pneumonia, multidrug-resistant Pseudomonas aeruginosa, colistin, inhalation, parenteral



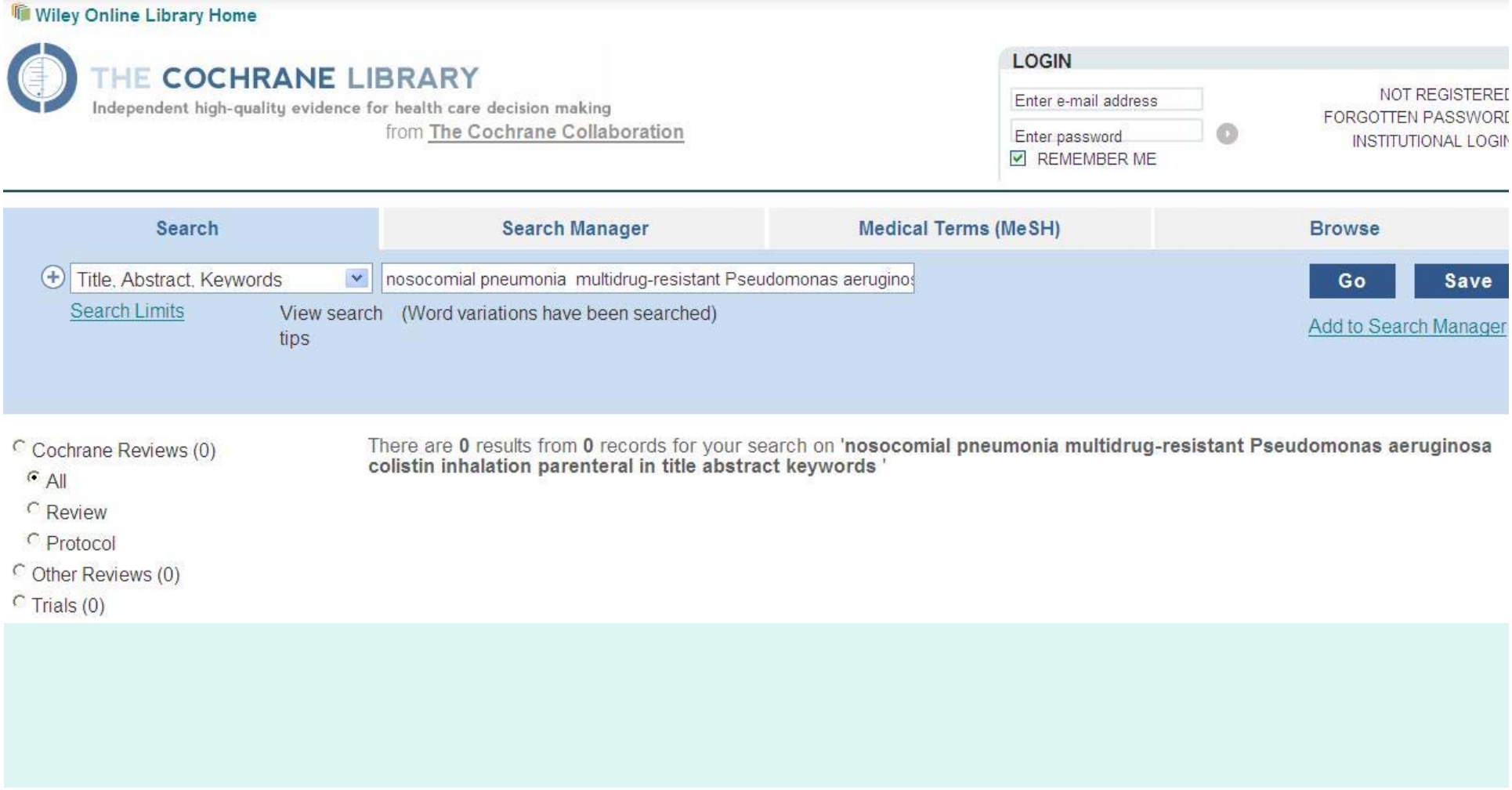
Search strategy: 5S model



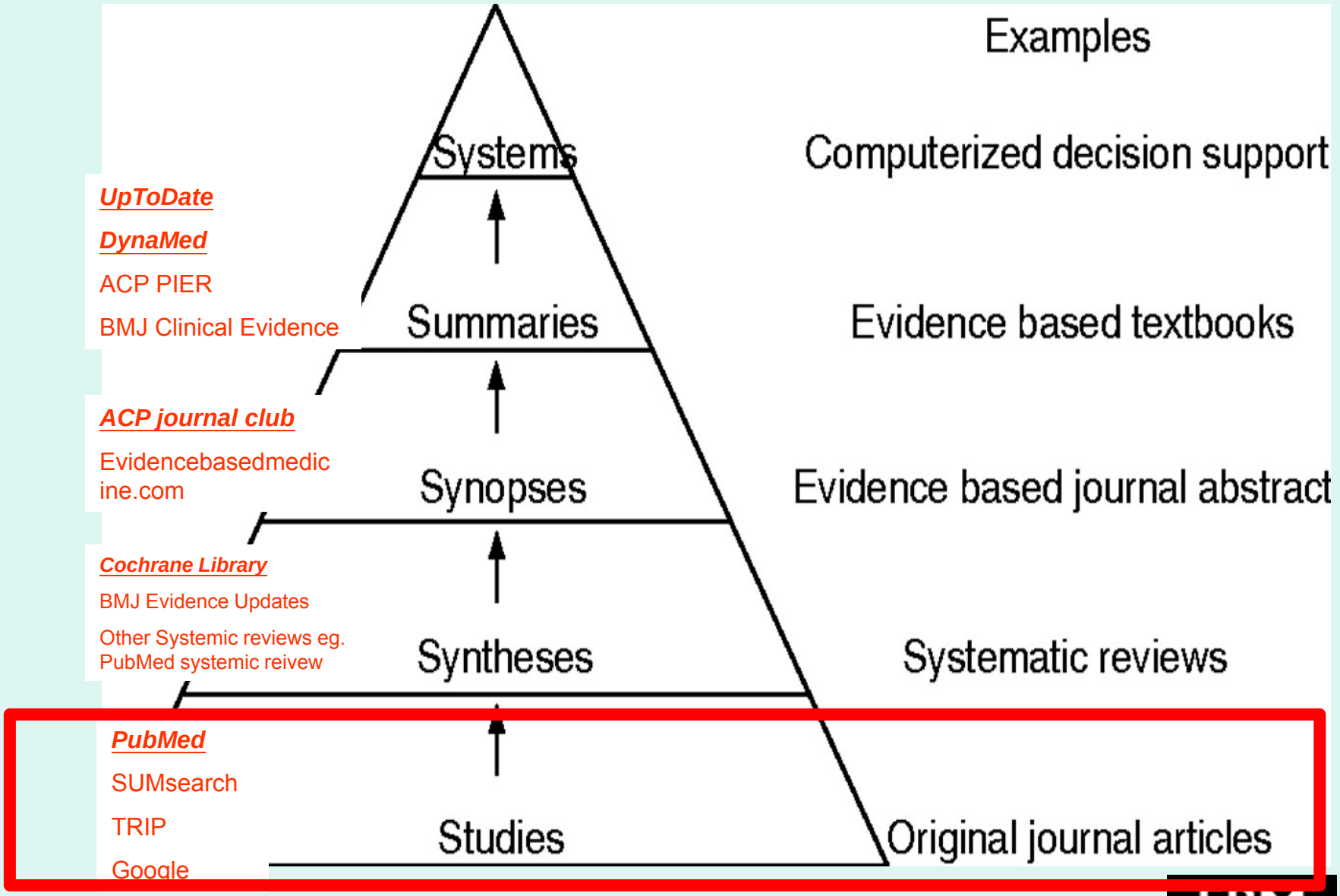
Brian Haynes, R Evid Based Med 2006;11:162-164

Syntheses:

Key words: nosocomial pneumonia, multidrug-resistant Pseudomonas aeruginosa, colistin, inhalation, parenteral



Search strategy: 5S model



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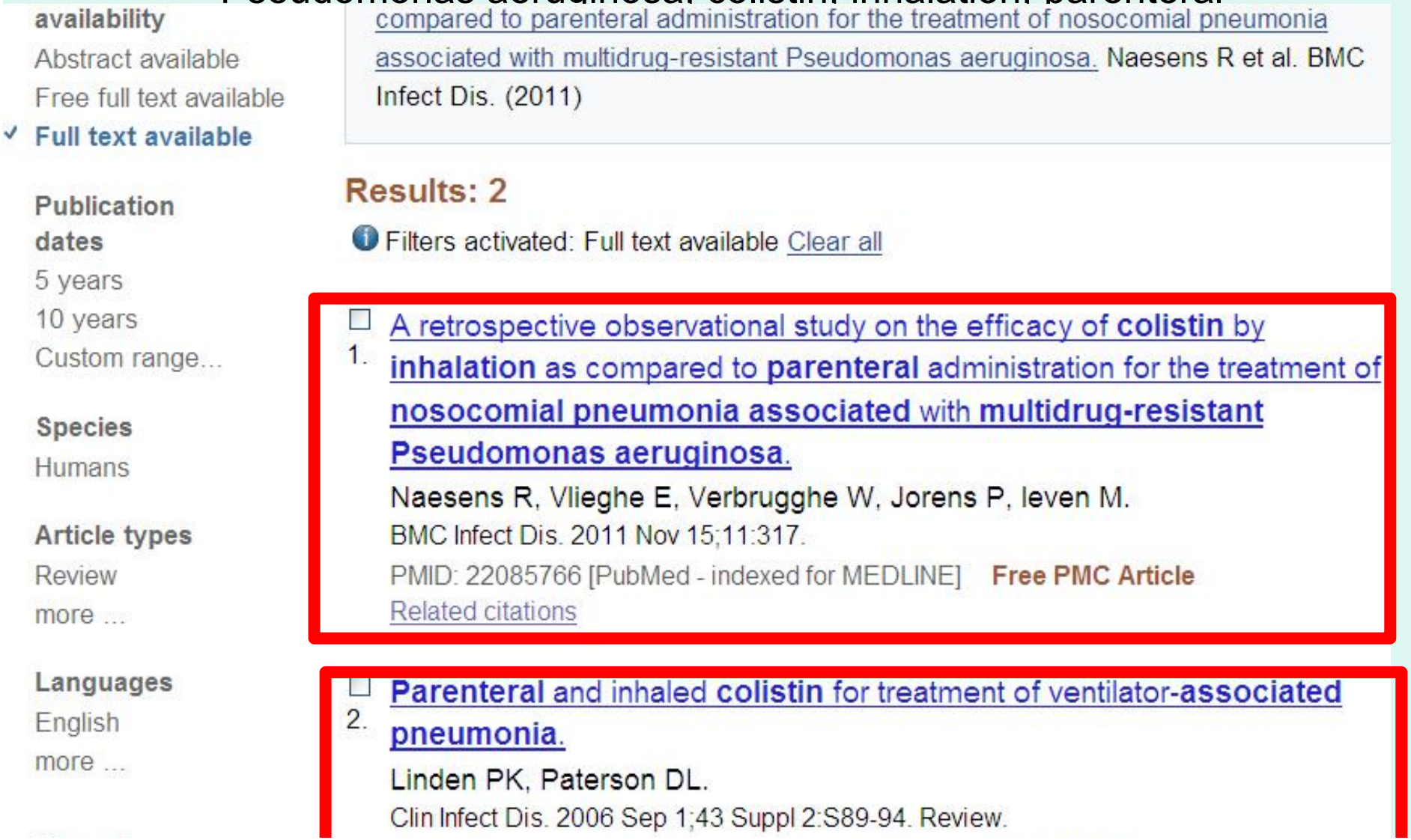
Studies:

Key words: nosocomial pneumonia, multidrug-resistant Pseudomonas aeruginosa, colistin, inhalation, parenteral



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compared to parenteral administration for the treatment of nosocomial pneumonia associated with multidrug-resistant Pseudomonas aeruginosa. Naesens R et al. BMC Infect Dis. (2011)

Results: 2

Filters activated: Full text available Clear all

1. A retrospective observational study on the efficacy of **colistin** by **inhalation** as compared to **parenteral** administration for the treatment of **nosocomial pneumonia associated** with **multidrug-resistant Pseudomonas aeruginosa**.
Naesens R, Vlieghe E, Verbrugghe W, Jorens P, Ieven M.
BMC Infect Dis. 2011 Nov 15;11:317.
PMID: 22085766 [PubMed - indexed for MEDLINE] **Free PMC Article**
Related citations

2. **Parenteral** and inhaled **colistin** for treatment of ventilator-**associated pneumonia**.
Linden PK, Paterson DL.
Clin Infect Dis. 2006 Sep 1;43 Suppl 2:S89-94. Review.

Parenteral and Inhaled Colistin for Treatment of Ventilator-Associated Pneumonia

Peter K. Linden[1] and David L. Paterson[2]

[1]Abdominal Organ Transplant Intensive Care Unit, Department of Critical Care Medicine, and [2]Division of Infectious Diseases, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Table 1. Clinical and microbiological response rates from recent clinical studies of colistin for the treatment of pneumonia due to *Pseudomonas aeruginosa* or *Acinetobacter baumannii*.

First author [reference], year	Infecting organism (no. of patients)	Comparator	Clinical response, no./total (%)	Microbiological response, no./total (%)	Superinfections, no.
Levin [9], 1999	*P. aeruginosa* (6); *A. baumannii* (14)	None	5/20 (25)	NA for pneumonia	0
Garnacho-Montero [10], 2003	*A. baumannii* (14)	Imipenem	12/21 (57)	6/9 (67)	0
Linden [12], 2003	*P. aeruginosa* (18)	None	11/18 (61)	6/18 (33)	3
Markou [11], 2003	*P. aeruginosa* (11); *A. baumannii* (4)	None	9/15 (60)	8/15 (53)	0
Kasiakou [13], 2005	*P. aeruginosa* (8); *A. baumannii* (10)	None	10/18 (56)	NA	0

NOTE. NA, not available.

Table 2. Incidence of nephrotoxicity and neurotoxicity in recent clinical trials of colistin for treatment of pneumonia and other infections.

First author [reference], year	Incidence of nephrotoxicity, no./total (%)	Incidence of neurotoxicity, no./total	Treatment discontinuation
Levin [9], 1999	4/21 (19)[a]	None	None
Garnacho-Montero [10], 2003	5/14 (36)[b]	None	None
Linden [12], 2003	NA[c]	1/23	In 1 patient, because of neurotoxicity
Markou [11], 2003	3/21(14)[d]	None	None
Kasiakou [13], 2005	4/50 (8)[e]	None	None

NOTE. NA, not applicable.

[a] Defined as an increase in creatinine level during treatment in patients with a normal creatinine level at baseline.

[b] Defined as a serum creatinine level >2.0 mg/dL, a decline in calculated creatinine clearance of >50% from baseline, or the need for renal replacement therapy.

[c] Defined as a requirement for renal replacement therapy (21/23 undergoing renal replacement therapy at baseline).

[d] Defined as an increase in serum creatinine level of >1.0 mg/dL or renal replacement therapy.

[e] Defined as an increase in creatinine level of >50% from baseline to >1.3 mg/dL or renal replacement therapy.

Efficacy of aerosolized colistin in pneumonia

- Colistin delivery to the lungs via aerosolization (or nebulization)
  - often in combination with oral quinolone
  - chemoprophylaxis in patients with cystic fibrosis who are colonized with multidrug-resistant *P. aeruginosa*
  - adjunct to parenteral antipseudomonal antibiotics for pneumonia

Efficacy of aerosolized colistin in pneumonia

- In a small retrospective study of 8 patients with
  - pneumonia due to *A. baumannii* (*n* = 7)
  - *P. aeruginosa* (*n* = 1)
- aerosolized colistin (1.5 million-6 million U/day in 3 or 4 divided doses)
  - administered for a mean of 10.5 days (range, 3–32 days)
  - in conjunction with systemic colistin or other effective antibiotics
- The cure rate was 7 (88%) of 8
- higher than the 30 (67%) of 45 cure rate for parenteral colistin alone
- *Michalapoulos A, Kasiakou SK, Mastora Z, et al. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant gram-negative bacteria in patients without cystic fibrosis.* ***Crit Care*** *2005;9:53-9.*

Efficacy of aerosolized colistin in pneumonia

- Hamer reported improvement in 3 patients with VAP, which was temporally related to the addition of aerosolized colistin to antipseudomonal systemic therapy

- *Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant Pseudomonas aeruginosa with aerosolized colistin.* ***Am J Respir Crit Care Med*** *2000;162:328-30.*

對找到的文章
進行CRITICAL APPRAISAL

Naesens *et al. BMC Infectious Diseases* 2011, **11**:317
http://www.biomedcentral.com/1471-2334/11/317

BMC
Infectious Diseases

RESEARCH ARTICLE Open Access

A retrospective observational study on the efficacy of colistin by inhalation as compared to parenteral administration for the treatment of nosocomial pneumonia associated with multidrug-resistant *Pseudomonas aeruginosa*

Reinout Naesens[1*], Erika Vlieghe[2], Walter Verbrugghe[3], Philippe Jorens[3] and Margareta Ieven[1]

Background

- *Pseudomonas aeruginosa*
  - second most common cause (17%) of nosocomial pneumonia
  - the most common multidrug-resistant (MDR) gram-negative pathogen causing pneumonia in hospitalized patients
- Until recently, the polymyxin class was mainly used via inhalation
  - to treat high-density respiratory tract colonization due to MDR *P. aeruginosa* in patients with cystic fibrosis
  - since this class was thought to be unacceptably toxic when administered parenterally
- in recent years, colistin was observed to be probably less toxic than previously proposed
  - an acceptable efficacy to MDR gram-negative bacteria

Background

- Colistin is used as last treatment option for pneumonia associated with multidrug-resistant (MDR) *Pseudomonas* spp..
- Literature about the best administration mode (inhalation versus parenteral treatment) is lacking

Methods

- A retrospective study of
  - 20 intensive care patients with a pneumonia associated with MDR *P. aeruginosa*
  - receiving colistin sulphomethate sodium (Colistineb®)
  - between 2007 and 2009 was performed.
  - performed at the Antwerp University Hospital
- A strain was considered multidrug-resistant
  - if it was resistant to at least 6 of the following antibiotics: piperacillin-tazobactam, ceftazidime, cefepime, meropenem, aztreonam, ciprofloxacin, and amikacin.

Methods

- The administration mode, predicted mortality based on the SAPS3 score, SOFA score at onset of the colistin treatment, clinical and microbiological response, and mortality during the episode of the infection were analysed.
- statistical analysis of respectively the predicted mortality/SOFA score and mortality rate
  - non parametric Kruskal-Wallis and Fisher's Exact test

Methods

- nosocomial pneumonia was defined
  - pneumonia that occured ≥ 48 hours after hospital admission
- Pneumonia was diagnosed by
  - a new pulmonary infiltrate
  - at least 2 of the following criteria:
    - fever > 38°C, leukocytosis > 11,000 cells/mm3, or purulent respiratory secretions

Methods

- The etiology of the pneumonia was established by
  - isolation of the organism from
    - blood cultures
    - from endotracheal aspirates
    - mini-BALs irrespective of the bacterial count.

Methods

- ICU physicians decided to treat patients with parenterally administered colistin, together or without inhalation,
  - when they estimated that the infection was "more severe" or if another infection focus with *P. aeruginosa* was present.
- Patients were excluded for analysis
  - if they received ≤ 2 days of colistin therapy.

Methods

- favorable clinical response was defined
  - a resolution of presenting symptoms and signs at the end of the treatment
- unfavorable clinical response was defined
  - persistence or worsening of presenting symptoms and signs

Methods

- Renal function was monitored by serial measurement of the serum creatinine level. Creatinine at the onset of the colistin therapy, maximal creatinine during the colistin therapy, and prior renal replacement therapy (RRT) were recorded
- Renal failure was defined following the RIFLE criteria as described by Hartzell et al
- Neurotoxicity rates were not determined because of the lack of objective criteria in our patients.

Methods

- Colistin administration
- intravenously
  - 62500 IU/kg/day in 3 to 4 divided doses
  - adjusted for creatinine clearance if necessary
- inhalation
  - 2 mIU/aerosol t.i.d
  - In mechanically ventilated patients
    - standard nebulizers for the ventilators used:
      - Servo Ultra Nebulizer 145/345 for the Servo-I (Maquet, Solna, Sweden)
      - the 84 12 935 nebulizer for the Dräger Evita 4 Ventilator (Dräger, Lennik, Belgium)
  - spontaneous breathing
    - optimal aerosol particle deposition was executed by standard delivery system (Cirrus drug nebulizer, Intersurgical, Berkshire, UK).

Result

Table 1 Patient characteristics of the different treatment groups

	Inhalation	Parenteral + Inhalation	Parenteral	All patients treated by Inhalation	p-value (difference between groups?)
Number of patients (medical-surgical)	6 (1-5)	9 (5-4)	5 (3-2)	15	/
Age (years)	62.5 (15-84)	67.9 (59-76)	64.8 (46-77)	65.7 (15-84)	0.91
Gender (Male %)	66.7%	77.8%	60.0%	58%	0.83
SOFA-score at admission	5.2 (2-9)	6.4 (0-15)	10.0 (3-13)	5.9 (2-15)	0.18
SOFA-score start colistin	6.3 (1-15)	6.7 (2-11)	6.0 (3-9)	6.5 (1-15)	0.87
SAPS3-score	80.7 (70-88)	80.8 (70-95)	79.0 (73-85)	80.7 (70-95)	0.92
Length of stay (days)	55.0 (19-103)	73.0 (16-141)	40.0 (29-64)	65.8 (16-141)	0.16
Time between admission and development of the pneumonia (days)	28.0 (7-75)	25.1 (8-68)	19.6 (13-29)	16.7 (7-75)	0.99
Treatment duration (days)	27.2 (6-96)	19.3 (3-46)	21.0 (9-28)	22.5 (3-96)	0.87
Creatinine at onset colistin; RRT patients excluded (mg/dL)	0.8 (0.7-1.2)	2.3 (0.9-4.7)	0.9 (0.8-1.0)	1.6 (0.7-4.7)	0.39
Creatinine during colistin therapy; RRT patients exluded (mg/dL)	1.0(0.6-1.3)	2.6 (1.1-5.8)	1.9 (1.9-2.0)	1.9 (0.6-5.8)	0.36
Number of RRT patients	2/6	4/9	2/5	6/15	/

Data are presented as mean values with the range between brackets. RRT: renal replacement therapy.

Result

Table 2 Outcome of the different treatment groups

Treatment groups	Number of patients with *P. aeruginosa* susceptible to colistin AND one beta-lactam	Clinical failure when only susceptible to colistin	Clinical failure when susceptible to colistin and at least one other antibiotic agent	Microbiological failure	Favorable clinical response	Mortality
Inhalation	4/6	0/2	0/4	5/5 1 no control data	6/6	0/6
Inhalation + Parenteral	3/9; 1/9 was susceptible to aminoglycosides	1/5	1/4	9/9	7/9	3/9
Inhalation and inhalation + parenteral	8/15	1/7	1/8	14/14	13/15	3/15
Parenteral	2/5	2/3	1/2	5/5	2/5 p = 0.06 as compared to the inhalation group p = 0.27 as compared to the parenteral + inhalation group p = 0.07 as compared to both the inhalation and inhalation + parenteral group	5/5 p = 0.002 as compared to the inhalation group; p = 0.03 as compared to the parenteral + inhalation group; p = 0.003 as compared to both the inhalation and inhalation + parenteral group

Discussion

- The higher response rate of 100% (6/6) (p = 0.06) in colistin inhalation group 的可能原因
  - easily treat parenterally when they estimated that the infection was "more severe" or if another infection focus with *P. aeruginosa* was present
    - even though the clinical conditions (according to the SOFA and SAPS3 score) of all patient groups were comparable,
  - 4 out of 6 strains were susceptible to a beta-lactam
    - which was also part of the patients' antibiotic regimen.
  - the efficacy of aerosolized colistin in pneumonia might have contributed to the result.

Conclusion

- aerosolized colistin
  - promising adjunct when used in combination with parenteral therapy (colistin or beta-lactams) over parenteral therapy alone.
- Since colistin is a last-line drug for infections with highly resistant *Pseudomonas* spp., there is an urgent need for randomized, controlled trials to further delineate its role in the ICU setting.

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

AAMPICOT for Therapy Paper

Item	Criteria	Comments (評論並說明你的根據)
Answer	此文獻有沒有回答我的問題	Yes
Authors	作者群是這領域的專家嗎？	Yes
	有沒有利益衝突？	Unknown
Method	本文獻研究設計是屬於以下那一類 SR,RCT,Cohort,Case-contro, Case series or report,Expert opinion	Case control
Population	取樣是否為隨機取樣？	No
	取的樣本是否具代表性？其特性是否接近我的病人？	Yes
	分組是否是隨機分組？	No
	分組是否採用盲法？	No

Intervention	給予實驗組的處置是否描述清楚，並且是臨床可行的？	Yes
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？	Yes
Outcome	測量了那些結果？是否用客觀的方式測量？請問NNT,NNH各是多少？	Mortality, favorable clinical response, creatinine
	這些結果是否有統計學上的重要性？	Yes
	這些結果是否有臨床上的重要性？	Yes
	是否呈現結果的「數值」，「p值」，「信賴區間」，「檢力」？	Yes
Time	測量結果的時間點是否合宜？	Yes
	追蹤時間是否夠長？	Yes
	文獻發表時間？	2011

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
多重抗藥性Pseudomonas aeruginosa 感染	加上吸入性藥物，非侵入性治療，病人意願高
生活品質	社會脈絡
對在ICU病人的生活品質並無太大差異	健保是否給付

Thank You for Your Attention!