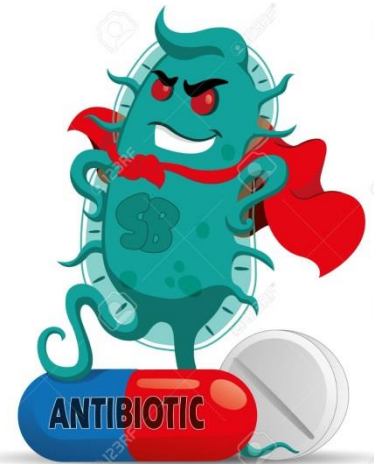# 延長β-lactam類抗生素輸注時間能提升敗血症病人的治癒率嗎？

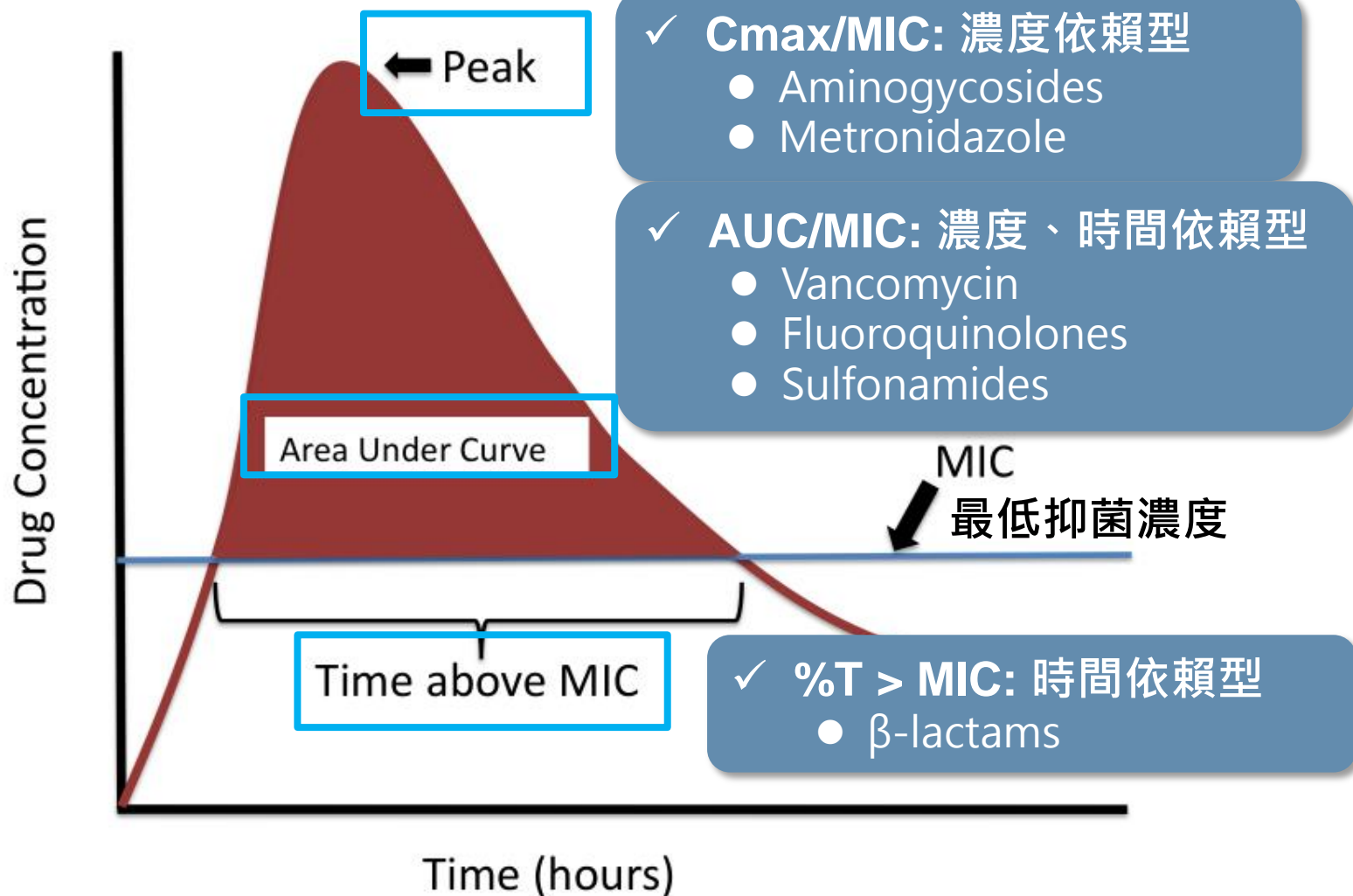主報者：簡佳穎 藥師

引言人：郭莉娜 主任

萬芳醫院藥劑部

Background

▸ Despite the availability of multiple antibiotic options, bacterial infections continue to cause substantial morbidity and mortality.

▸ Changes in both bacterial and host factors created the need for new antibiotics, revival of neglected old antibiotics, and optimized use of the currently available ones.

抗生素的藥效動力學特性

Cmax/MIC: 濃度依賴型
- Aminogycosides
- Metronidazole

AUC/MIC: 濃度、時間依賴型
- Vancomycin
- Fluoroquinolones
- Sulfonamides

MIC
最低抑菌濃度

%T > MIC: 時間依賴型
- β-lactams

- MIC: Minimum Inhibitory Concentration
- AUC: Area Under Curve

抗生素的藥效動力學特性

‣ Potential optimization of β-lactams plasma concentrations could improve their clinical effectiveness

   ‣ the percentage of time their free plasma concentration is higher than the pathogen's minimum inhibitory concentration (%fT>MIC)

Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis:
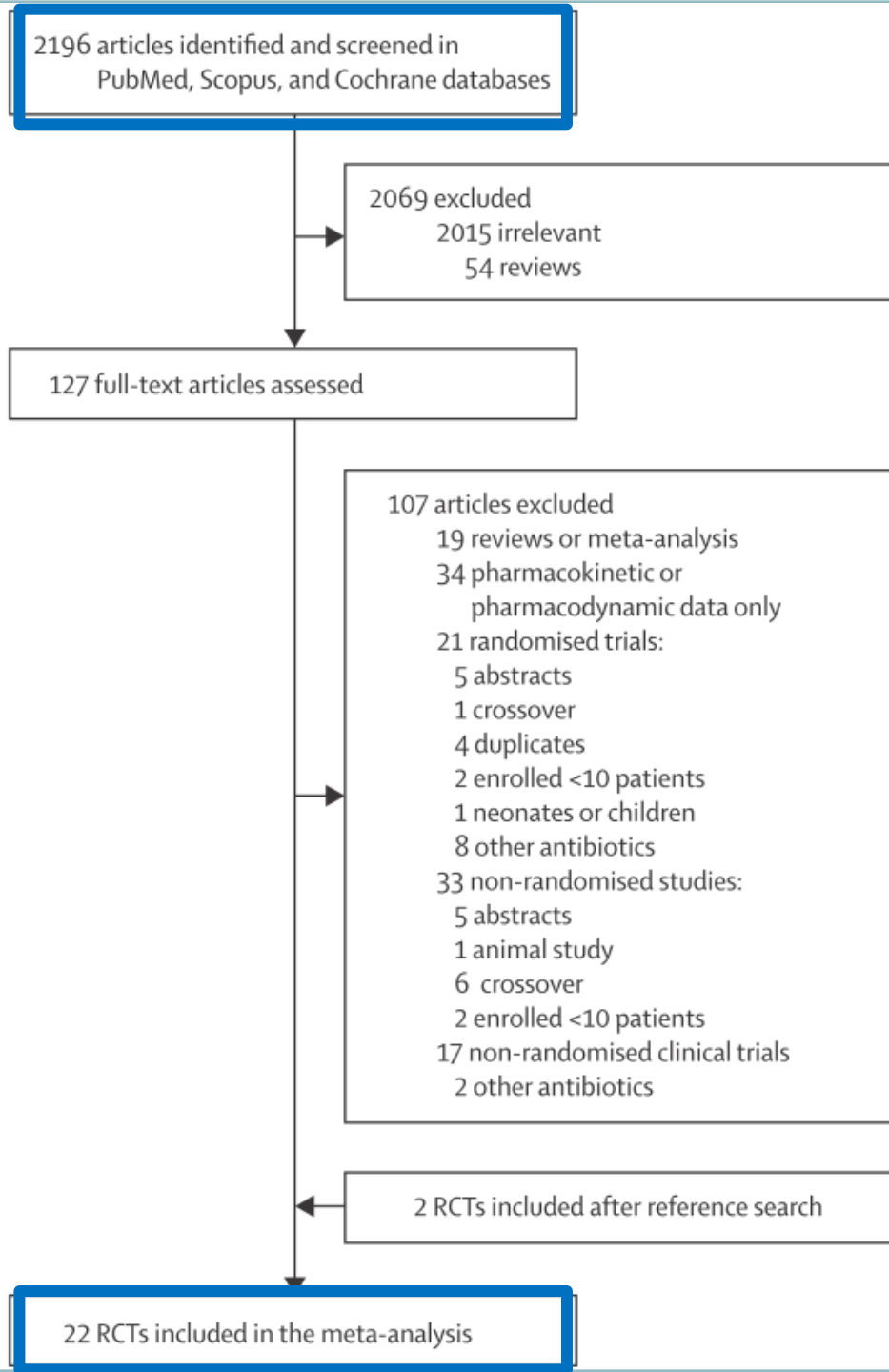a systematic review and meta-analysis of randomized trials.

Abstract

Aim:
- To identify [...] sus short-term infus[...] in patients with seps[...]

Method:
- Study sel[...]
- The quali[...]
- Methodol[...] sk of bias
- Meta-ana[...]

2196 articles identified and screened in PubMed, Scopus, and Cochrane databases

2069 excluded
  2015 irrelevant
  54 reviews

127 full-text articles assessed

107 articles excluded
  19 reviews or meta-analysis
  34 pharmacokinetic or pharmacodynamic data only
  21 randomised trials:
    5 abstracts
    1 crossover
    4 duplicates
    2 enrolled <10 patients
    1 neonates or children
    8 other antibiotics
  33 non-randomised studies:
    5 abstracts
    1 animal study
    6 crossover
    2 enrolled <10 patients
  17 non-randomised clinical trials
    2 other antibiotics

2 RCTs included after reference search

22 RCTs included in the meta-analysis

Abstract

▸ **Findings:**

- ▸ **The GRADE tool-** the quality of evidence for mortality was high.

- ▸ Prolonged infusion was associated with lower all-cause mortality than short-term infusion (risk ratio [RR] 0·70, 95% CI 0·56–0·87).

- ▸ Heterogeneity was not observed (p=0·93, I²=0%).

- ▸ The funnel plot and the Egger's test (p=0·44) showed no evidence of publication bias.

▸ **Interpretation:**

- ▸ Prolonged infusion of β-lactams might benefit all hospitalized patients with sepsis.

- ▸ Further studies in specific subgroups of patients according to age, sepsis severity, degree of renal dysfunction, and immunocompetence are warranted.

▸

Added value of this study

▸ Not limited by
  ▸ inclusion of non-randomized studies
  ▸ inclusion of RCTs on concentration-dependent antibiotics or on antibiotics with narrower or different antibacterial spectrum
  ▸ the presence of inconsistency
▸ Largest number of included patients from diverse regions.

院內品項- Antipseudomonal carbapenems

商品名	Mepem 美平 250 mg/vial	Finibax 伏霸 250 mg/vial	Tienam 泰寧 500 mg/vial
成分	Meropenem	Doripenem	Imipenem / Cilastatin
外觀			

院內品項-
Antipseudomonal penicillins and cephalosporins

商品名	Pipe & Tazo 帝斯坦 2250 mg/vial	Tatumcef 祐坦賜福 2000 mg/vial	Cebid 速妥 1000 mg/vial	Supecef 斯沛服 500 mg/vial
成分	Piperacillin / Tazobatam	Ceftazidime (3rd generation)	Cefoperazone (3rd generation)	Cefepime (4th generation)
外觀				

CASP 系統性文獻回顧檢核表

(A)研究結果可信嗎?

(B) 研究結果為何?

(C)研究結果對於當地病人有幫助嗎?

1. 此篇系統性文獻回顧是否問了一個清楚、明確的問題?

問題/研究族群 **Problem/Patient**	Sepsis patients
給予的措施 **Intervention**	Prolonged (continuous or $\geqq$ 3 hours) infusion of antipseudomonal beta-lactams
對照 **Comparison**	Short-term ($\leqq$ 60 minutes) infusion of antipseudomonal beta-lactams
結果 **Outcome**	(1st outcome) All-cause mortality; (2nd outcome) Clinical efficacy, adverse events, and emergence of resistance

評讀結果 : ☑是　□ 否　□ 不明確

2. 作者是否尋找適當研究型態的文獻?

Hint:最好的研究類型
• 提及系統性文獻回顧的問題 • 有適當的研究設計(通常以**隨機對照**試驗的研究文獻評值介入措施的成效)

▸ **Any RCT** studying the comparative effectiveness and safety of prolonged (lasting ≥3 h or 24 h continuous infusion) versus short-term (bolus or up to 60 min intermittent infusion) administration of any antipseudomonal β-lactam for the treatment of adult patients with sepsis was considered eligible.

評讀結果 : ☑是 □ 否 □ 不明確

3. 你認為所有重要且相關的研究都被納入?

Hint: 尋找以下訊息

- 使用了那些資料庫
- 從參考資料清單中再進行搜尋
- 與專家進行個別聯繫
- 除了已發表的研究文獻,也搜尋**未發表**的研究文獻
- 搜尋非英文的研究文獻

▶ 2,196 articles identified and screened in **PubMed, Scopus, and Cochrane databases without date or language restrictions.**

▶ Reference list of selected articles were manually searched.

▶ Abstracts presented in international conferences were not searched.

評讀結果: □ 是 ☑ 否 □ 不明確

4. 系統性文獻回顧的作者是否評估所納入研究文獻的品質?

▶ Two authors (KZV and GLV) independently extracted data in pre-specified forms.

  ▶ Methodological assessment:

    ▶ **Cochrane risk of bias tool**

  ▶ Overall assessment of the evidence:

    ▶ **The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool**

評讀結果 : ☑是 □ 否 □ 不明確

5. 如果作者將研究結果進行合併，這樣的合併是否合理?

Hint: 考慮是否

- 文獻回顧的結果來自類似的研究
- 所有納入的研究的結果有清楚呈現
- 不同研究的結果相似
- 結果有差異的原因有被討論
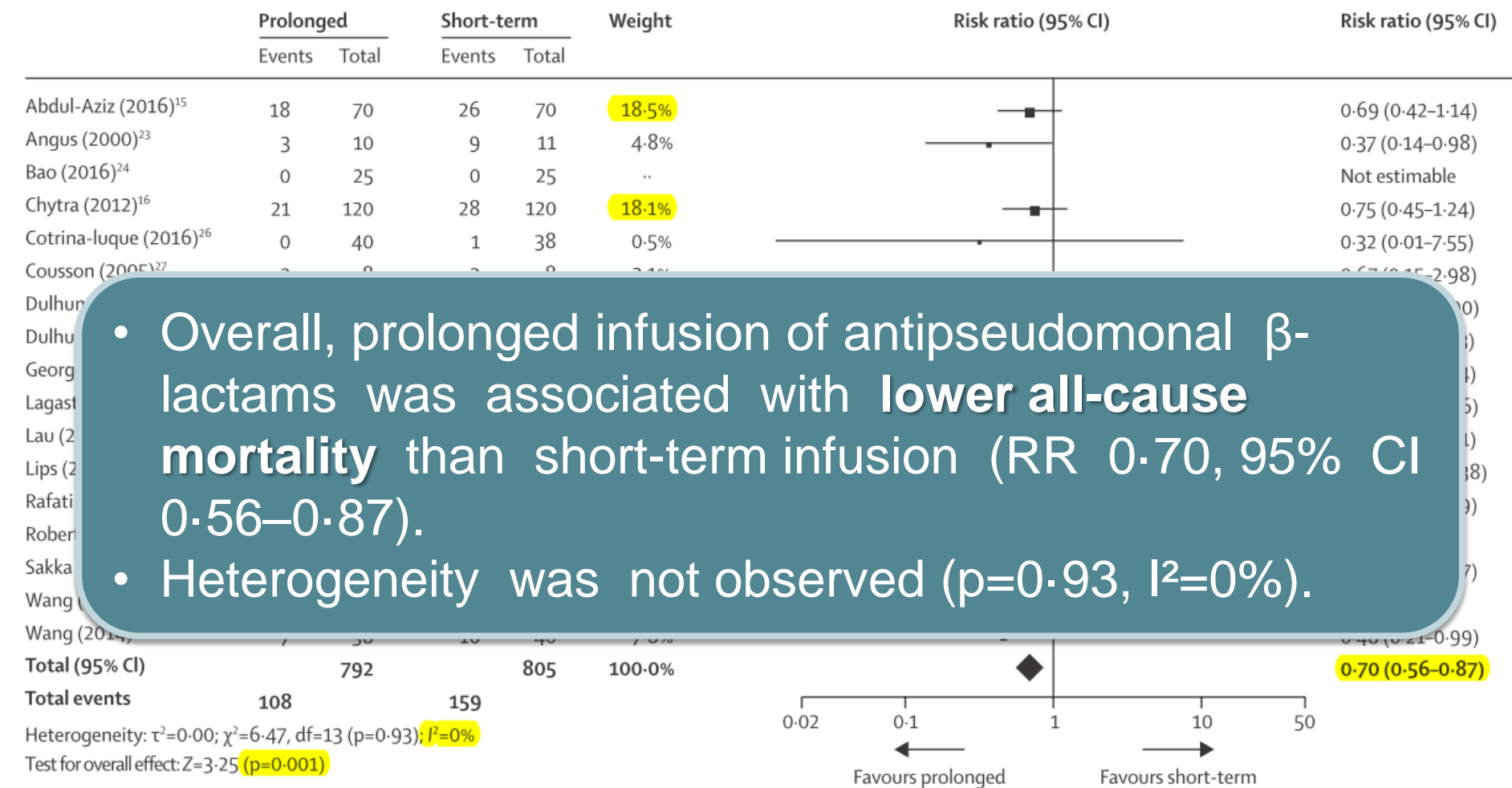
▸ Methods- Data analysis

  ▸ We calculated pooled risk ratios (RR) and 95% CI using the Mantel-Haenszel random-effects model.

  ▸ Statistical heterogeneity among studies was assessed by **χ² test** (p<0·10 indicated significant heterogeneity) and **I²** (degree of heterogeneity).

▸ **Heterogeneity was not observed (p=0·93, I²=0%).**

評讀結果 : ☑是　□ 否　□ 不明確

6. 這篇系統性文獻回顧的整體結果為何?
7. 結果精準嗎?

	Prolonged		Short-term		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Abdul-Aziz (2016)[15]	18	70	26	70	18·5%	0·69 (0·42–1·14)
Angus (2000)[23]	3	10	9	11	4·8%	0·37 (0·14–0·98)
Bao (2016)[24]	0	25	0	25	..	Not estimable
Chytra (2012)[16]	21	120	28	120	18·1%	0·75 (0·45–1·24)
Cotrina-luque (2016)[26]	0	40	1	38	0·5%	0·32 (0·01–7·55)

- Overall, prolonged infusion of antipseudomonal β-lactams was associated with **lower all-cause mortality** than short-term infusion (RR 0·70, 95% CI 0·56–0·87).
- Heterogeneity was not observed (p=0·93, I²=0%).

| Total (95% CI) | | 792 | | 805 | 100·0% | 0·70 (0·56–0·87) |
| Total events | 108 | | 159 | | | |

Heterogeneity: τ^2=0·00; χ^2=6·47, df=13 (p=0·93); I^2=0%
Test for overall effect: Z=3·25 (p=0·001)

0·02 0·1 1 10 50

← Favours prolonged   Favours short-term →

▸ **Figure 2**: Forest plot of mortality among patients treated with prolonged versus short-term infusion of antipseudomonal antibiotics

Although the prolonged infusion of both carbapenems and penicillins with β-lactamase inhibitors was associated with lower mortality than short-term infusion, **prolonged infusion of cephalosporins was not.**

	Prolonged Events	Total	Short-term Events	Total	Weight	Risk ratio (95% CI)	Risk ratio (95% CI)
Bao (2016)[24]	0	25	0	25	..		Not estimable
Cephalosporins							
Abdul-Aziz (2016)[15]	8	11	0	2	7·4%		4·25 (0·33–54·77)
Angus (2000)[23]	3	10	9	11	31·3%		0·37 (0·14–0·98)
Cousson (2005)[27]	2	8	3	8	18·0%		0·67 (0·15–2·98)
Georges (2005)[28]	3	26	3	24	18·0%		0·92 (0·21–4·14)
Lagast (1983)[30]	5	20	4	25	25·3%		1·56 (0·48–5·06)
Subtotal (95%CI)		75		70	100·0%		0·83 (0·40–1·74)
Total events	21		19				

Heterogeneity: τ²=0·20; χ²=5·57, df=4 (p=0·23); I²=28%
Test for overall effect: Z=0·48 (p=0·63)
Test for subgroup differences: χ²=0·30, df²=2 (p=0·86l; I²=0%)

0·02 0·1 1 10 50

← Favours prolonged   Favours short-term →

Heterogeneity: τ²=0·20; χ²=5·57, df=4 (p=0·23); I²=28%
Test for overall effect: Z=0·48 (p=0·63)
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0·02 0·1 1 10 50

← Favours prolonged   Favours short-term →
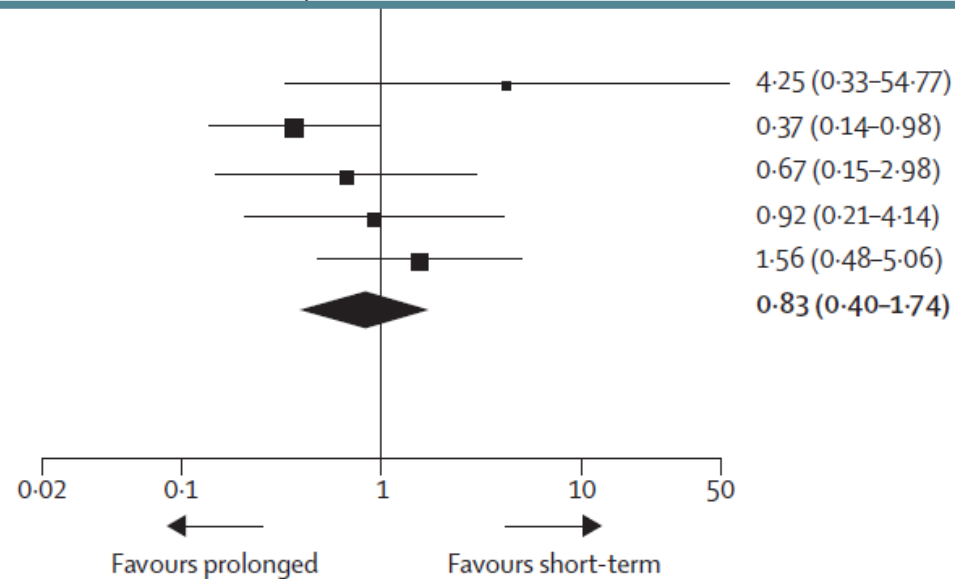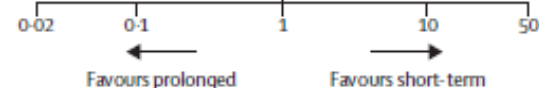
6. 這篇系統性文獻回顧的整體結果為何？
7. 結果精準嗎？

▸ **<u>Clinical cure or improvement</u>**

  ▸ Data reported in 18 RCTs.

  ▸ In both the ITT (11 RCTs, 1219 patients, RR 1·06, 95% CI 0·96–1·17, I²=39%) and per-protocol (ten RCTs, 1091 patients, 1·13, 1·00–1·28, p=0·06, 57%) analysis the difference between prolonged and short-term infusion was not significant.

6. 這篇系統性文獻回顧的整體結果為何？
7. 結果精準嗎？

Adverse events

- There was no difference in reported adverse events between the compared groups (seven RCTs, 980 patients, RR 0·88, 95% CI 0·71–1·09, I²=0%).

- Data regarding adverse events and resistant strains were not studied regularly in the included RCTs.

- Safety assessment was difficult because of under-reporting of adverse events.

6. 這篇系統性文獻回顧的整體結果為何？
7. 結果精準嗎？

▶ **<u>Development of resistance</u>**

- ▶ Data were provided by four RCTs.

- ▶ In two of them resistant strains were not isolated in either treatment group.

- ▶ No difference in development of resistance was observed in the other two RCTs (RR 0·60, 95% CI 0·15–2·38).

8. 此研究結果是否可應用到當地的族群？

▸ **Patients from diverse regions**:

  ▸ Asia-Pacific (10), followed by Europe (9), and America (3).

▸ **The mean or median age**:

  ▸ <45 y/o (5), 45-65 y/o (12), >65 (1), data not reported (4).

▸ **APACHE II**:

  ▸ (APACHE II ≧20, severely ill) in at least one group (11)

  ▸ (APACHE II <20, less severely ill) (5)

  ▸ Not reported (6)

▸ **Site or type of infection:**

  ▸ Nosocomial lung infections were the most common.

評讀結果：☑是　□否　□不明確

9. 是否所有重要的臨床結果都有被考量到？

▶ **Outcome of the study:**

  ▶ All-cause mortality

  ▶ Clinical cure or improvement

  ▶ Adverse event

  ▶ Development of resistance

▶ Other information I would like to know…

  ▶ Duration of hospital stay

  ▶ Cost-effectiveness analysis

評讀結果： □ 是　☑ 否　□ 不明確

10. 付出的傷害和花費換得介入措施所產生的益處是否值得？

▸ **Safety**

  ▸ No significant difference in reported adverse events between the compared groups.

▸ **Cost**

  ▸ Not discussed in the study.

▸ **Effectiveness**

  ▸ **Relative risk:** 30% lower with prolonged infusion compared with short-term infusion.

  ▸ **Number need to treat (NNT)= 16.4**

評讀結果： ☑ 是　□ 否　□ 不明確

▸

CASP Appraisal Tool [Systematic review]	Result
1. Did the review address a clearly focused question?	Yes
2. Did the authors look for the right type of papers?	Yes
3. Do you think all the important, relevant studies were included?	No
4. Did the review's authors do enough to assess quality of the included studies?	Yes
5. If the results of the review have been combined, was it reasonable to do so?	Yes
6. What are the overall results of the review?	-
7. How precise are the results?	-
8. Can the results be applied to the local population?	Yes
9. Were all important outcomes considered?	No
10. Are the benefits worth the harms and costs?	Yes

Limitations of the study

▸ The outcomes might not apply to older patients (>65 years).

▸ Some clinically meaningful heterogeneity between studies is highly likely (open-label antibiotic use at variable doses, infection severity and type, and patient comorbidity).

▸ Small study effects contributing to the favorable outcome for prolonged infusion should be considered.

▸ The definition and severity of sepsis are not in accordance to the current definitions.

▸

Conclusion

▶ Almost all subgroup and sensitivity analyses showed that prolonged infusion was associated with at least a trend towards lower all-cause mortality than short-term infusion.

▶ Prolonged infusion of β-lactams might benefit all hospitalized patients with sepsis; however, further studies in specific subgroups of patients are warranted.

Future work

▸ Further studies in specific subgroups of patients (such as age, sepsis severity, degree of renal dysfunction, susceptibility of bacteria, and immunocompetence) are warranted.

臨床應用- 本院【感染管制委員會通告】

▸ 經2015年11月23日抗微生物製劑小組會議決議，感染管制委員會共識，為提升時間依賴型抗生素治療效益，自2016年1月起，擬延長特定抗生素輸注時間至少達3~4小時，懇請相關單位開單醫師協助。

  ▸ 抗生素品項：Piperacillin/tazobactam、Tienam®(Imipenem/Cilastatin)、Mepem® (Meropenem)

  ▸ 藥品輸注時間：3 ~ 4 小時(extended infusion)

  ▸ 執行單位：成人加護病房(ICU-1及ICU-2)、亞急性呼吸照護病房(RCC)

  ▸ 施行時間：2016年1月起

  ▸ 納入條件：於ICU-1、ICU-2、RCC使用前述抗生素，含在外單位已開立相關藥品者均改成extended infusion。

延長β-lactam類抗生素輸注時間能降低敗血症病人的死亡率嗎？
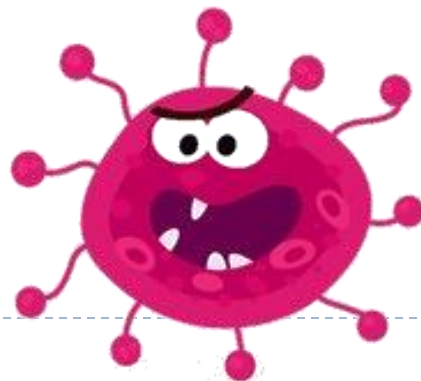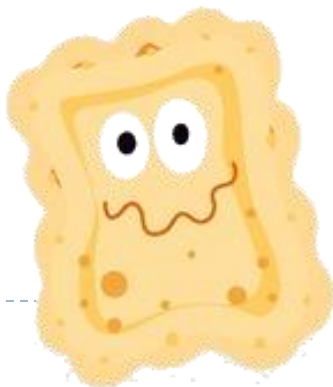
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對照 **Comparison**	Short-term (≦60 minutes) infusion of antipseudomonal beta-lactams
結果 **Outcome**	(1st outcome) All-cause mortality; (2nd outcome) Clinical efficacy, adverse events, and emergence of resistance

感謝聆聽
Have a nice day ☺

綠(同意)　：31人
黃(需討論)：20人
紅(不同意)：0人

Journal Club@WFH

4月10日,2018