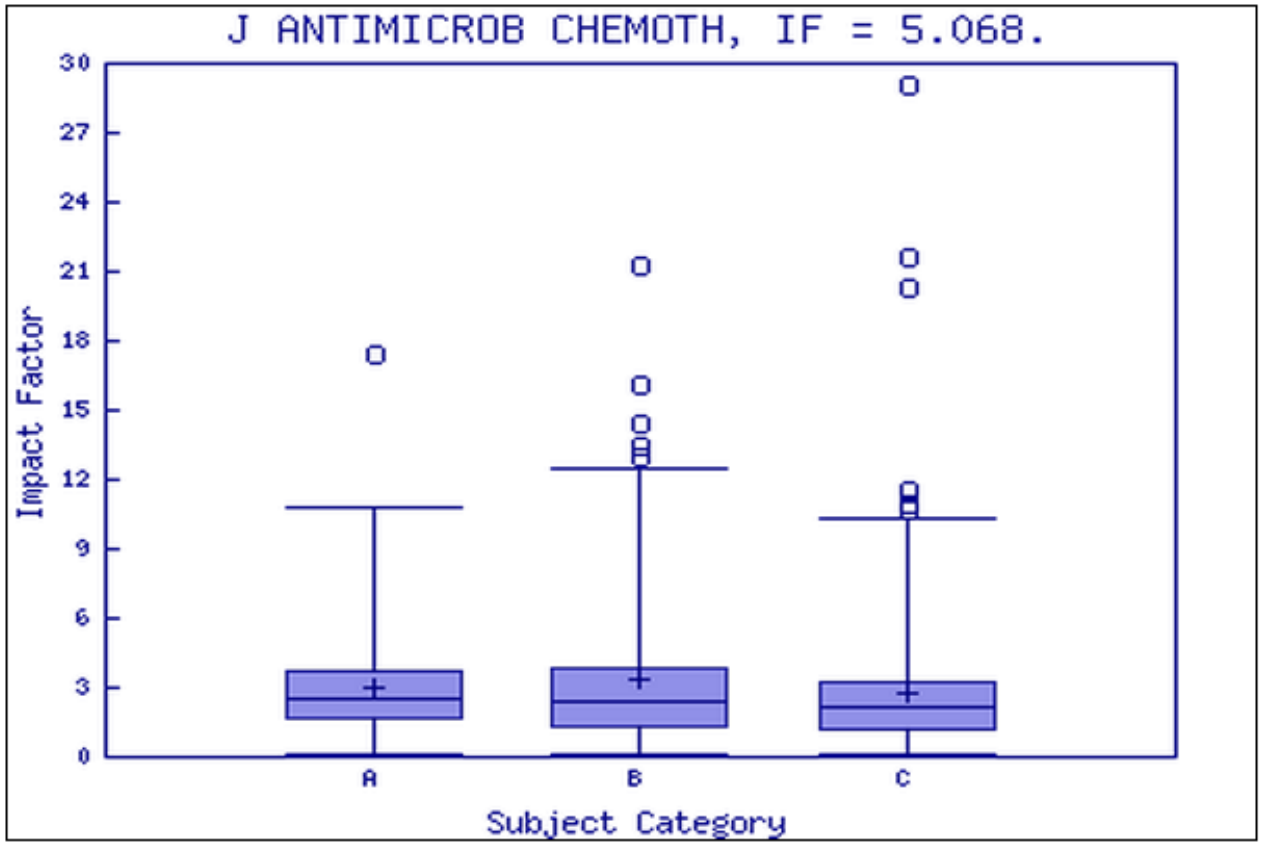
Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis

Cataldo MA, Tacconelli E, Grilli E, Pea F, Petrosillo N.et al.
J Antimicrob Chemother 2012; 67: 17–24.
PMID:22028203

Present by 陳齡芳

2013.05.14.

J Antimicrob Chemother



Key

A - INFECTIOUS DISEASES

B - MICROBIOLOGY

C - PHARMACOLOGY & PHARMACY

台北市立萬芳醫院病房細菌培養各檢體之菌種排名(2011年)

菌種排名	Blood 1320	n	%	Tip 311	n	%	Sputum 12725	n	%	Throat 137	n	%	Mid-Urine 1856	n	%	Stool 53	n	%	Wound/Pus 1449	n	%
1	*S.aureus* (MRSA : 51.8%)	112	8.5	*S.epidermidis* (MRSE : 100%)	36	11.6	Normal respiratory flora	4829	37.9	Usual throat flora	101	73.7	*Escherichia coli* (ESBL : 18.6%)	365	19.7	*Salmonella species*	18	34.0	*S.aureus* (MRSA : 51.1%)	182	12.6
2	*Escherichia coli* (ESBL : 15.7%)	102	7.7	*Acinet.baumannii* (CRAB : 76.7%)	30	9.6	*Ps.aeruginosa* (CRPA : 27.3%)	1723	13.5	Normal respiratory flora	10	7.3	*candida albicans*	313	16.9	*S.aureus* (MRSA : 33.3%)	9	17.	*Escherichia coli* (ESBL : 18.8%)	138	9.5
3	*S.capitis*	102	7.7	*candida albicans*	30	9.6	*Acinet.baumannii* (CRAB : 75.5%)	1268	10.0	*Haem.influenzae*	3	2.2	*Ps.aeruginosa* (CRPA : 5.9%)	169	9.1	*Ps.aeruginosa* (CRPA : 14.3%)	7	13.2	*Enteroco.faecalis* (VRE : 0.0%)	130	9.0
4	*S.epidermidis* (MRSE : 89.2%)	102	7.7	*C.parapsilosis*	25	8.0	*Kl.pneumoniae* (ESBL : 49.1%)(CRE : 4.0%)	1109	8.7	*Kl.pneumoniae* (ESBL : 0.0%)	3	2.2	*Torulopsis glabrata*	122	6.6	*candida albicans*	6	11.3	*Ps.aeruginosa* (CRPA : 7.0%)	115	7.9
5	*Kl.pneumoniae* (ESBL : 28.8%)(CRE : 5.0%)	80	6.1	*Ps.aeruginosa* (CRPA : 30.4%)	23	7.4	*candida albicans*	690	5.	*S.aureus* (MRSA : 33.3%)	3	2.2	*Kl.pneumoniae* ESBL : 40.7%)(CRE : 0.8%)	118	6.4	*Aeromonas caviae*	3	5.7	*Proteus mirabilis*	82	5.7
6	*Acinet.baumannii* (CRAB : 31.1%)	74	5.6	*S.aureus* (MRSA : 77.8%)	18	5.8	*S.aureus* (MRSA : 71.8%)	652	5.1	*Strep.pneumoniae*	3	2.2	*Enteroco.faecium* (VRE : 24.3%)	115	6.2	*Salmonella group B species*	3	5.7	*Acinet.baumannii* (CRAB : 76.4%)	72	5.0
7	*Enteroco.faecium* (VRE : 29.8%)	57	4.3	*Enteroco.faecium* (VRE : 21.4%)	14	4.5	*Stenotrophomonas maltophilia*	459	3.6	*Strep.pyogenes*	3	2.2	*Enteroco.faecalis* (VRE : 0.0%)	90	4.8	*Aeromonas hydrophilia*	1	1.9	*candida albicans*	60	4.1
8	*candida albicans*	56	4.2	*candida tropicalis*	11	3.5	*Escherichia coli* (ESBL : 41.1%)(CRE : 0.6%)	331	2.6	*Acinet.baumannii* (CRAB : 0.0%)	2	1.5	*candida tropicalis*	87	4.7	*Aeromonas veronii*	1	1.9	*Kl.pneumoniae* (ESBL : 35.6%)(CRE : 3.4%)	59	4.1
9	*C.parapsilosis*	53	4.0	*Enteroco.faecalis* (VRE : 0.0%)	11	3.5	*Proteus mirabilis*	205	1.6	*candida albicans*	2	1.5	*Acinet.baumannii* (CRAB : 79.3%)	58	3.1	*candida tropicalis*	1	1.9	*S.epidermidis* (MRSE : 79.6%)	54	3.7
10	other	582	44.1	other	113	36.3	other	1459	11.5	other	7	5.1	other	419	22.6	other	4	7.5	other	557	38.4

Introduction

- Vancomycin has for a long time been considered the gold standard for the therapy of methicillin-resistant Staphylococcus aureus (MRSA) infections.

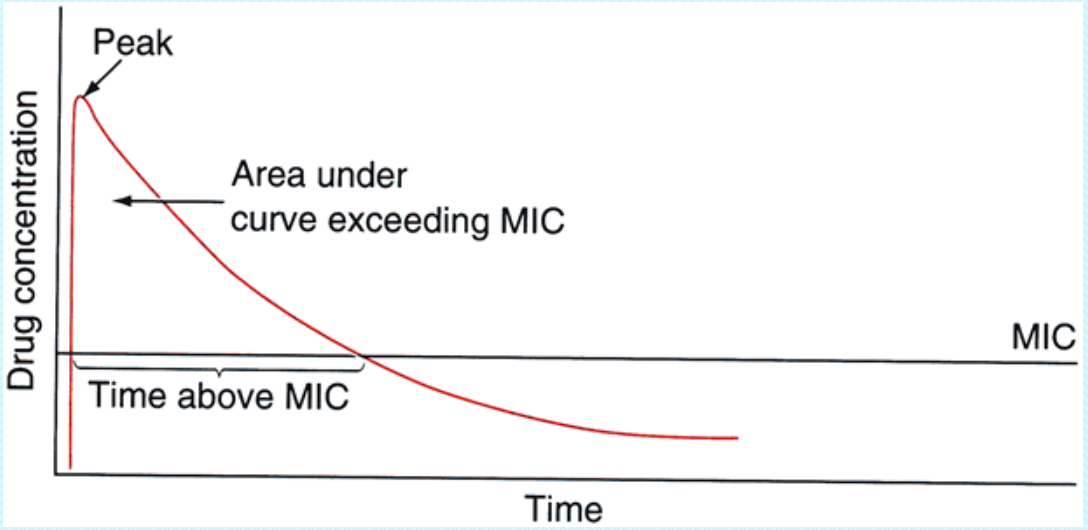
- The just recently released guidelines from the Infectious Diseases Society of America (IDSA) confirm the prominent role of the drug in the treatment of these infections.

- Notably, the most recently approved antibiotics—linezolid,daptomycin and tigecycline—did not show a significant superiority for clinical cure rate of MRSA infections.

Introduction

- Clinical failure in patients with severe MRSA infections has been increasingly reported in recent years.

- In vitro data indicate that the time above the MIC is the most important pharmacodynamic parameter for its efficacy.



Introduction

- Previous studies have shown that continuous infusion (CoI) of vancomycin may enable faster and more consistent attainment of therapeutic serum concentrations of antibiotic compared with intermittent infusion (InI) and that CoI was a protective factor for intensive care unit (ICU) mortality in patients with MRSA ventilator-associated pneumonia.

Curr Opin Crit Care 2008; 14: 390–6.
Clin Pharmacokinet 2008; 47: 147–52.
Crit Care Med 2005; 33: 1983–7.

Introduction

- The main aim of this systematic review was to summarize available evidence on the effect of CoI of vancomycin compared with InI in adult patients with infections due to Gram-positive bacteria.

[系統性文獻回顧 Systematic Review]

步驟 1：研究探討的問題為何？	
研究族群／問題 (Problems)	ICU, medical surgical ward, cardio-surgery patients Adult patients (>18 years old) with Gram-positive infection treated with vancomycin were included.
介入措施 (Intervention)	continuous vancomycin infusion (CoI)
比較 (Comparison)	intermittent vancomycin infusion(InI)
結果 (Outcomes)	nephrotoxicity rate and overall mortality

步驟 2：系統性文獻回顧的品質如何？
(FAITH)(**Find**/Appraisal/Include/ total up/ Hetrogeneity)

良好的文獻搜尋至少應包括二個主要的資料庫，並且加上文獻引用檢索(參考文獻中相關研究、Web of Science, Scopus 或 Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文，並且應同時使用 MeSH 字串及一般檢索詞彙(text words)。

Published articles (from January 1956 to May 2011) reporting the use of CoI of vancomycin in human patients were identified through computerized literature searches using **MEDLINE, EMBASE and Cochrane** databases and by reviewing the references of retrieved articles.

Index search terms included the medical subjects heading 'vancomycin' and 'continuous' or 'dosing' or 'intermittent' or 'infusion' or 'discontinuous' or 'administration'. **No restriction of languages was applied**. No attempt was made to obtain information about unpublished studies. Reviewed articles were maintained in a master log and any reason for exclusion from analysis was documented in the rejected log.

評讀結果：　■ 是　否　不清楚

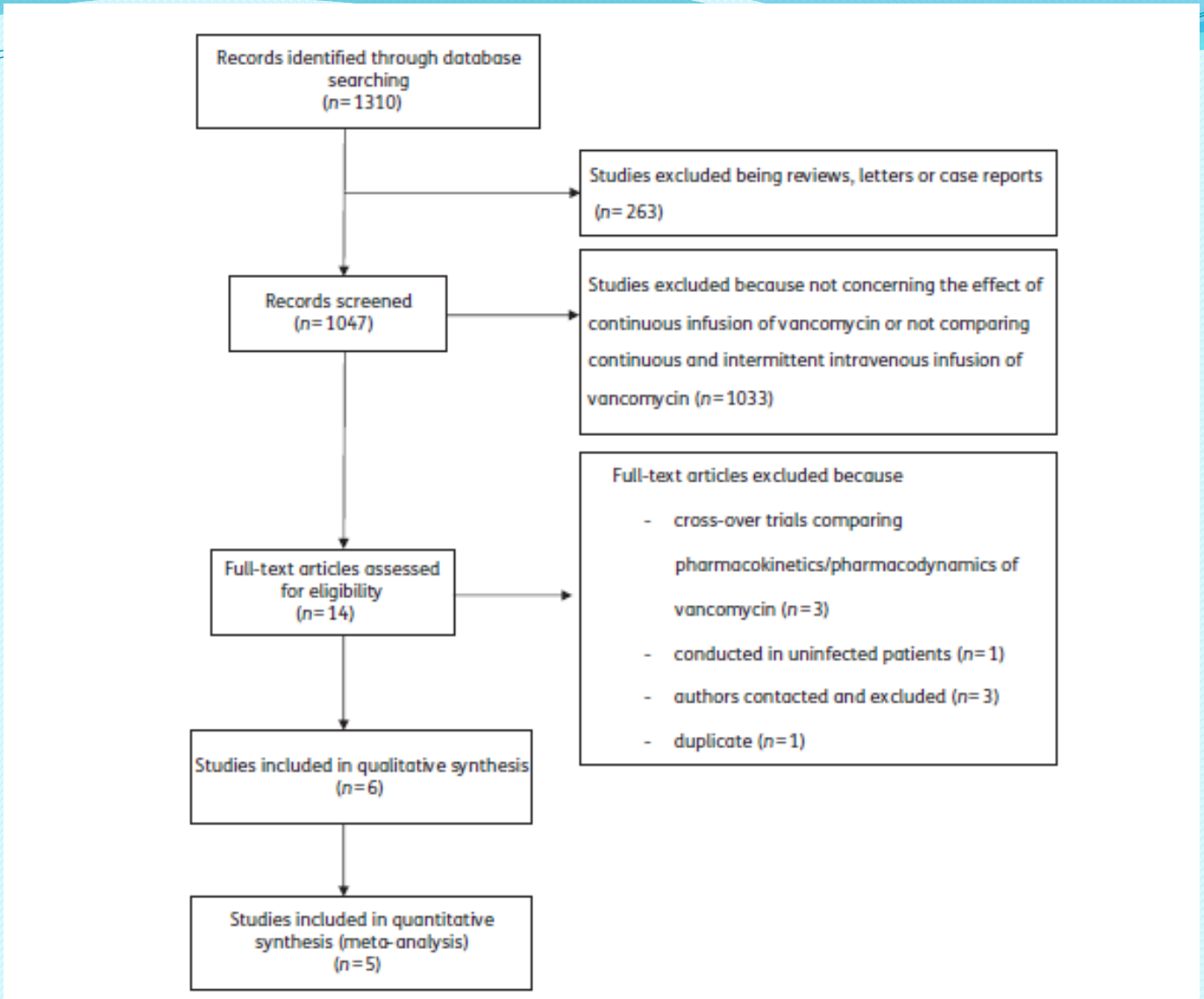


Figure 1. selection process of studies included in the meta-analysis.
Six studies were included, 20–25 comprising 443 patients treated with vancomycin:
(267 by CoI and 176 by InI)

A - 文獻是否經過嚴格評讀 (Appraisal)？

應根據不同臨床問題的文章類型，選擇適合的評讀工具，並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)

Quality appraisal:
Included studies were appraised for methodological quality independently by two authors (M. A. C. and E. G.) without blinding to journal or study authorship. Discrepancies were resolved by discussion or involvement of a third review author if required.

The quality of **observational studies** was assessed using the Newcastle-Ottawa scales.(assessing the quality of nonrandomised studies in meta-analyses

A - 文獻是否經過嚴格評讀 (Appraisal)？

Table 3. Quality appraisal of observational studies (indicators from Newcastle-Ottawa scale[31])

	Quality indicators								
References	1[a]	2[b]	3[c]	4[d]	5A[e]	5B[f]	6[g]	7[h]	8[i]
Wysocki *et al.*[20]	yes	partial[j]	yes	no	yes	yes	yes	yes	NR
Di Filippo *et al.*[21,k]	yes	yes	yes	no	no	no	yes	yes	NR
Vuagnat *et al.*[23]	selected group	yes	yes	yes	no	no	yes	yes	no (61%)
Hutschala *et al.*[24]	selected group	yes	yes	no	no	no	yes	yes	NR
Ingram *et al.*[25]	selected group	yes	yes	no	yes	yes	yes	yes	NR

NR, not reported.
[a]Indicates exposed cohort truly representative.
[b]Non-exposed cohort drawn from the same community.
[c]Ascertainment of exposure from a secure record.
[d]Outcome of interest not present at start of study.
[e]Cohorts comparable on basis of site and aetiology of infection.
[f]Cohorts comparable on other factors.
[g]Assessment of outcome from record linkage or independent blind assessment.
[h]Follow-up long enough for outcomes to occur.
[i]Complete accounting for cohorts.
[j]Same hospital, but not the same period of hospitalization.
[k]This study was not included in any pooled analysis.

A - 文獻是否經過嚴格評讀 (Appraisal)？

The following risks of bias in **randomized trials** were assessed, according to the criteria developed by the Cochrane Effective Practice and Organisation of Care **(EPOC)** group:

30 generation and concealment of allocation

Baseline measurement

Baseline characteristics

Incomplete outcome data

Blinded assessment of primary outcomes

Protection against contamination and selective outcome reporting.

評讀結果： ■ 是　否　不清楚

I - 是否只納入 (included) 具良好效度的文章？

僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有一項研究結果是極小偏誤的試驗。

- Study selection and data extraction
  - Eligibility assessment and extraction of data were performed independently by two investigators (M. A. C. and E. G.). Each investigator was blinded to the other investigator's data extraction. In case of disagreement between the two reviewers, a third reviewer was consulted (E. T.).
  - Data from each study were verified for consistency and accuracy, and were then entered into a standardized computerized database.

I - 是否只納入 (included) 具良好效度的文章？

Abstracted information included author, year of study and publication, country in which the study was conducted, study design, number of patients enrolled, population characteristics (ward of hospitalization and type and aetiology of infection), vancomycin MICs for the bacterial isolates responsible for the included infections, characteristics of vancomycin administration (type of infusion, dosage, administration of bolus, dose adjustment and length of therapy), determination of vancomycin serum concentration (Cmin for InI and Css for CoI), AUC24 values,adverse effects, clinical failure and overall mortality.

評讀結果： ■ 是　否　不清楚

Table 1. Characteristics of studies included in the systematic review

Year	Design	Setting	Type of infection	Pathogens	No. of patients		No. of patients concurrently treated with other antibiotics		Nephrotoxicity definition	Mean CREA at baseline (μM)	
					CoI	InI	CoI	InI		CoI	InI
1995[20]	PrC[a]	ICU	bacteraemia/ pneumonia	MRSA	13	13	NR	NR	rise[b] in CREA of 44.2 μM or more[c] or a rise of 88.4 μM or more[d]	113	143
1998[21]	ReC	ICU	bacteraemia/ pneumonia	MRSA/MRCNS	11	14	11 MON/AG	14 MON/AG	NA	NR	NR
2001[22]	RCT	ICU	severe hospital acquired	MRSA/MRCNS	61	58	13 FA; 6 AG	13 FA; 16 AG	50% increase in CREA[e]	98	88
2004[23]	PrC	medical/surgical ward	osteomyelitis	MRSA/MRCNS	23	21	5 RIF; 4 CIP	9 RIF; 2 CIP	50% increase in CREA[e]	84.6	84.7
2009[24]	ReC	cardio-surgical ICU	post-cardiac surgery	Gram-positive	119	30	31 CAR/CEPH; 14 AG	8 CAR/CEPH; 3 AG	increase in CREA[f] of at least 0.3 mg/dL, a percentage increase in CREA of at least 50% or a reduction in urine output	79	79
2009[25]	ReC[g]	OPAT unit	all	Gram-positive	40	40	NR	NR	50% increase in CREA[e]	74.8	75.1

AG; aminoglycosides; C, cohort; CAR; carbapenems; CEPH, cephalosporins; CIP, ciprofloxacin; CREA, serum creatinine; FA, fusidic acid; MON, monobactams; MRCNS; methicillin-resistant coagulase-negative staphylococci; NA, not applicable; NR, not reported; OPAT, outpatient parenteral antimicrobial therapy; Pr, prospective; Re, retrospective; RIF, rifampicin.

[a]Patients receiving CoI were matched with historical patients who received InI; matching criteria were site of infection, sex, body weight, severity of illness, duration of therapy, value of serum creatinine concentration before vancomycin therapy and age.

[b]The rise was determined by subtracting the initial creatinine concentration from the highest creatinine concentration measured during therapy or within 48 h after therapy.

[c]If the initial creatinine was less than 3 mg/100 mL (265.2 μM).

[d]If the initial creatinine was 3 mg/100 mL or above.

[e]From the day treatment was started to the end of treatment.

[f]An abrupt (within 48 h) reduction in kidney function.

[g]Patients from a cohort study were matched based on the propensity score estimating the probability of being given CoI of vancomycin. Factors used in the propensity score matching process were diabetes mellitus, baseline serum creatinine and MRSA aetiology.

T - 作者是否以表格和圖表「總結」(total up) 試驗結果？

應該用至少 1 個摘要表格呈現所納入的試驗結果。若結果相近，可針對結果進行統合分析(meta-analysis)，並以「森林圖」(forest plot)呈現研究結果，最好再加上異質性分析

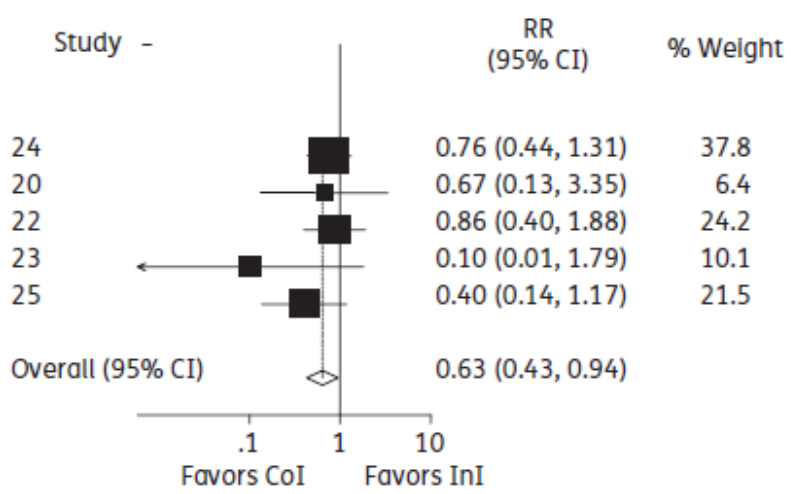


Figure 2. Forest plot summary (fixed effect) of the unadjusted RR of the studies included in the meta-analysis comparing nephrotoxicity rates in patients treated with CoI versus InI of vancomycin.

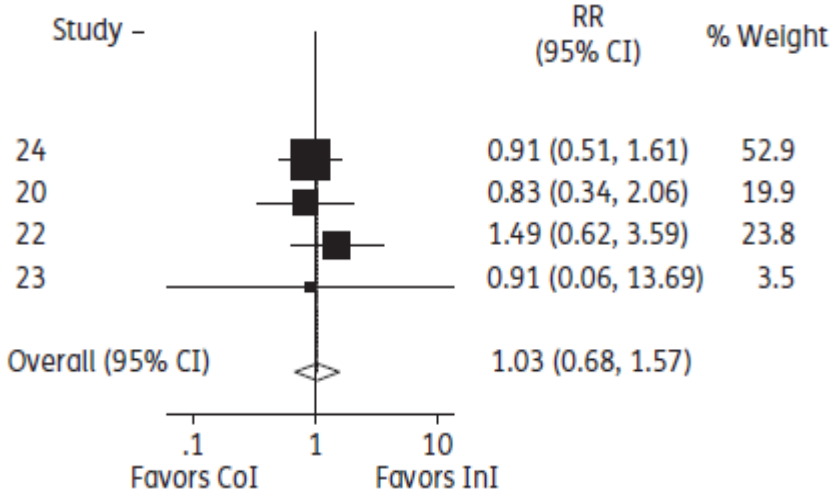


Figure 3. Forest plot summary (fixed effect) of the unadjusted RR of the studies included in the meta-analysis comparing overall mortality rates in patients treated with CoI versus InI of vancomycin.

T - 作者是否以表格和圖表「總結」(total up) 試驗結果？

Table 2. Characteristics of vancomycin administration in the included studies

Reference	Loading dose	Vancomycin dosage		Target vancomycin serum concentration		Mean length (days) of vancomycin treatment	
		CoI	InI	CoI	InI	CoI	InI
Wysocki *et al.*[20]	15 mg/kg	30 mg/kg/day	15 mg/kg bid	C_{ss} 20–30 mg/L	C_{max} 20–40 mg/L and C_{min} 5–10 mg/L	16	16
Di Filippo *et al.*[21]	500 mg	83 mg/h	500 mg qid	NA	NA	6	6
Wysocki *et al.*[22]	15 mg/kg	30 mg/kg/day	15 mg/kg bid	C_{ss} 20–25 mg/L	C_{min} 10–15 mg/L	13	14
Vuagnat *et al.*[23]	20 mg/kg	40 mg/kg/day	20 mg/kg bid	C_{ss} 20–25 mg/L	C_{max} < 50 mg/L and C_{min} 20–25 mg/L	101	66
Hutschala *et al.*[24]	20 mg/kg	15 mg/kg/h	according to target C_{min}[a]	C_{ss} 20–25 mg/L	C_{min} 15 mg/L	9	9
Ingram *et al.*[25]	NR	at discretion of the attending physician	at discretion of the attending physician	NA	NA	22	20

bid, twice a day; C_{max}, vancomycin peak concentration; C_{min}, vancomycin trough concentration; C_{ss}, vancomycin steady-state concentration; NA, not applicable; qid, four times a day.
[a]Authors did not report a standard dose for InI but stated that dosage was adjusted according to serum creatinine concentration and vancomycin concentration. The daily doses of infused vancomycin were comparable between treatment groups. Eighty-three percent of patients in the InI group received a single daily dose to reach the target vancomycin concentration.

T - 作者是否以表格和圖表「總結」(total up) 試驗結果？

Table 4. Vancomycin serum drug exposure values in the included studies

	Vancomycin serum concentration (mg/L), ±SD		AUC_{24} (mg/L/h), ±SD	
Reference	CoI (C_{ss})	InI (C_{min})	CoI	InI
Wysocki *et al.*[20]	24±6	6±8	—	—
Di Filippo *et al.*[21]	24±4	30±6	—	—
Wysocki *et al.*[22]	24±8	15±9	577±120	653±232
Vuagnat *et al.*[23]	26±6	22±9	—	—
Hutschala *et al.*[24]	25±4	17±5	529±98	612±213
Ingram *et al.*[25]	14±6	10±5	—	—

AUC_{24}, area under the serum concentration–time curve over 24 h; C_{min}, vancomycin trough concentration; C_{ss}, vancomycin steady-state concentration.

評讀結果：　是　否　■不清楚

H - 試驗的結果是否相近 - 異質性 (Heterogeneity)？

在理想情況下，各個試驗的結果應相近或具同質性，若具有異質性，作者應評估差異是否顯著(卡方檢定)。根據每篇個別研究中不同的PICO及研究方法，探討造成異質性的原因。

Nephrotoxicity

Five of six studies were assessable for the nephrotoxicity risk.[20,22–25] Compared with InI, administration by CoI significantly reduced the risk of nephrotoxicity of vancomycin (RR 0.6, 95% CI 0.4–0.9; $P=0.02$; Figure 2). No significant heterogeneity between the studies was documented ($I^2=0$).

Regarding the severity of nephrotoxicity, two studies reported data regarding patients who required dialysis. In the RCT, dialysis was required for 5% (3/58) of patients in the InI group and for 10% (6/61) in the CoI group.[22] Hutschala *et al.*[24] reported that dialysis was required for 30% (9/30) of patients in the InI group and for 24% (28/119) in the CoI group. The difference between groups was not statistically significant in both studies.

Mortality

Four of six studies were included in the evaluation of the overall mortality.[20,22–24] The combined RR for the overall mortality in patients treated with CoI versus InI was 1.03 (95% CI 0.7–1.6; $P=0.9$; Figure 3). There was no significant heterogeneity between studies ($I^2=0$). After excluding from the analysis one study that did not differentiate patients who died from those lost to follow-up,[23] the combined RR did not differ. CoI of vancomycin did not seem to be effective in significantly reducing the mortality rate, neither among patients with MRSA infections[20,22,23] (total number of included patients, 189; RR 1.2, 95% CI 0.6–2.2; $P=0.6$), nor among ICU patients[20,22,24] (total number of included patients, 193; RR 1.03, 95% CI 0.7–1.6; $P=0.9$).

Notably, heterogeneity of definitions and lack of data in studies did not allow us to carry out a meta-analysis on the impact of the method of vancomycin administration on the serum vancomycin concentration, treatment failure and adverse effects rates.

評讀結果：　是　否　■不清楚

Clinical application ???

Favor continuous or intermittent ?

Does it worth in *PharmacoEconomics*

Which one was more convenient for nursing and drug administration.

Consideration drug drug interaction


本研究是否可用於臨床?
同意3人
懷疑 14人
不同意2人
P. 22
T - 作者是否以表格和圖表「總結」 (total up) 試驗結果？

Discussion Point [1]

- Vancomycin 在臨床上的運用最大副作用就是腎毒性，依據此篇文獻結果，相較於非持續性靜脈輸注，持續性靜脈輸注對於病人腎毒性的相對危險性較低。
  - 單純以藥物動力學而言，持續性靜脈輸液顯然可以成功地克服腎毒性的缺點。
  - 然而，內科病人多為年長、多共病及靜脈狀態不良(找不到多條靜脈輸注途徑)，藥物投與上恐有執行困難。
  - 目前治療Gram positive infection disease 之用藥有許多其他選擇(如Linzolind, Daptomycin, Tygacil)，並且腎毒性副作用較少，可依病人狀況選用。

Discussion Point 2

- 若持續性靜脈輸注Vancomycin對於病人腎毒性較低，且死亡率也較低時，才會有更大的動機使用此治療方式，但本篇文章在死亡率方面並無差異。
- 如有年輕病人、血管功能無慮，或疾病比較單純等，可考慮在給予Vancomcyin時，使用持續性靜脈輸注方式。
- 針對試驗的結果是否相近，異質性可藉由森林圖(forest plot)呈現，無庸置疑是偏向一致性高的結果，研究結果尚稱可以相信。
- 臨床使用Vancomcyin時，副作用發生率無直接數字呈現。


thank
you
very much!