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

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Objectives: To summarize available evidence on the effect of continuous infusion (CoI) of vancomycin compared with intermittent infusion (InI) in adult patients with Gram-positive infections.

Methods: MEDLINE, EMBASE and Cochrane databases were searched. Randomized clinical trials (RCTs) and observational studies that comparatively assessed CoI and InI of vancomycin in terms of mortality, clinical cure, toxicity rates and serum drug exposure [trough concentration (C_{min}) for InI and steady-state concentration (C_{ss}) for CoI; area under the curve at 24 h (AUC_{24}) for both] were included. Meta-analysis was conducted combining and analysing the relative risk (RR) and computing a summary RR of the effects with 95% confidence interval (CI). The standardized mean difference was calculated for continuous outcomes. The I^2 test was calculated to assess heterogeneity across studies.

Results: One RCT and five observational studies were included in the analysis. Compared with InI, CoI of vancomycin was associated with a significantly lower risk of nephrotoxicity (RR 0.6, 95% CI 0.4–0.9, $P=0.02$; $I^2=0$). Overall mortality was not different between the two groups (RR 1.03, 95% CI 0.7–1.6, $P=0.9$; $I^2=0$).

Conclusions: Our meta-analysis suggests that administration of vancomycin for the treatment of Gram-positive infections by CoI is associated with a significantly lower risk of nephrotoxicity when compared with InI of the drug. RCTs are needed to define the impact on mortality rate and on the pharmacodynamic activity in terms of AUC/MIC ratio.

Keywords: MRSA, antimicrobial treatment, continuous infusion, intermittent infusion, vancomycin, Gram-positive infections

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.[1] Notably, the most recently approved antibiotics—linezolid, daptomycin and tigecycline—did not show a significant superiority for clinical cure rate of MRSA infections.[2–8]

However, several issues affect vancomycin use in daily clinical practice. First, clinical failure in patients with severe MRSA infections has been increasingly reported in recent years.[9–11] There is still not definitive evidence on the optimal dosage of vancomycin and the impact of pharmacokinetic and pharmacodynamic parameters on patient outcome. *In vitro* data indicate that the time above the MIC is the most important pharmacodynamic parameter for its efficacy.[12,13] Experimental animal models[14] and human data from patients with MRSA infections showed some concentration-dependent activity as well.[15] The most efficacious method of administration of vancomycin has been debated for a long time. 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.[16–18] The consensus review from the American Society of Health-System Pharmacists (ASHP), the IDSA and the Society of Infectious Diseases Pharmacists (SIDP) for therapeutic monitoring of

vancomycin and the IDSA guidelines for the treatment of MRSA infections do not recommend the use of a CoI regimen, since an improvement in patient outcome versus intermittent dosing is considered unlikely.[1,19] Nevertheless, many clinicians prefer to administer vancomycin by CoI. Published studies comparing the effectiveness and the tolerability of CoI versus InI of vancomycin showed inconclusive results.[20–29]

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.

Methods

Methods of the analysis and inclusion criteria were specified in advance and documented in a protocol.

Article identification

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 (National Library of Medicine, Bethesda, MD, USA), 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.

Eligibility criteria

Types of studies

Hypothesizing that data from randomized clinical trials (RCTs) were limited, observational studies were considered eligible where RCTs were found not to be available. Reviews, letters, editorials, case reports and studies focusing only on pharmacokinetic/pharmacodynamic parameters were excluded. Studies comparing the effects of CoI and InI of vancomycin on the following outcomes were included: mortality, clinical cure, toxicity rates and vancomycin serum drug exposure.

Types of participants

Adult patients (>18 years old) with Gram-positive infection treated with vancomycin were included.

Outcomes

Primary outcomes of the meta-analysis included nephrotoxicity rate and overall mortality. The clinically assessable population comprised patients who satisfied the criteria for eligibility set in each of the included studies. Secondary outcomes of the meta-analysis included clinical failure, adverse effect rates and vancomycin serum drug exposure [trough concentration (C_{min}) for InI and steady-state concentration (C_{ss}) for CoI; area under the curve at 24 h (AUC_{24}) for both]. We used data conforming to any outcome definitions reported in each study.

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. 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 (C_{min} for InI and C_{ss} for CoI), AUC_{24} values, adverse effects, clinical failure and overall mortality.

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 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.

The quality of observational studies was assessed using the Newcastle-Ottawa scales.[31] In addition, the presence of performance bias (concerning the quality of the information regarding who received what intervention) and of detection bias (concerning correct assessment of outcomes) was assessed in the observational studies.

Statistical analysis

Systematic review was conducted combining and analysing the relative risk (RR) and computing a summary RR of the effects with 95% confidence interval (CI). The standardized mean difference (SDM) was calculated for continuous outcomes. The analysis was performed using the inverse variance fixed effects method, since fixed and random models computed the same overall estimate and 95% CI, showing the absence of 'extra' variability across combined studies. Sensitivity analysis was performed stratifying for type of Gram-positive infection, clinical setting, administration of bolus of vancomycin and dosage adjustment according to vancomycin serum concentration. Meta-analysis was done if more than two studies reporting data on the same outcomes were available. The I^2 test was calculated to assess whether results varied no more than might have been expected by the play of chance (random sampling); significant heterogeneity was considered for I^2 >50%. The publication bias was measured by the Begg funnel plot[32] and the Egger test.[33]

Analysis was performed using the software program Intercooled Stata (release 9.0; Stata Statistical Software, College Station, TX, USA).

Results

Figure 1 shows the 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.

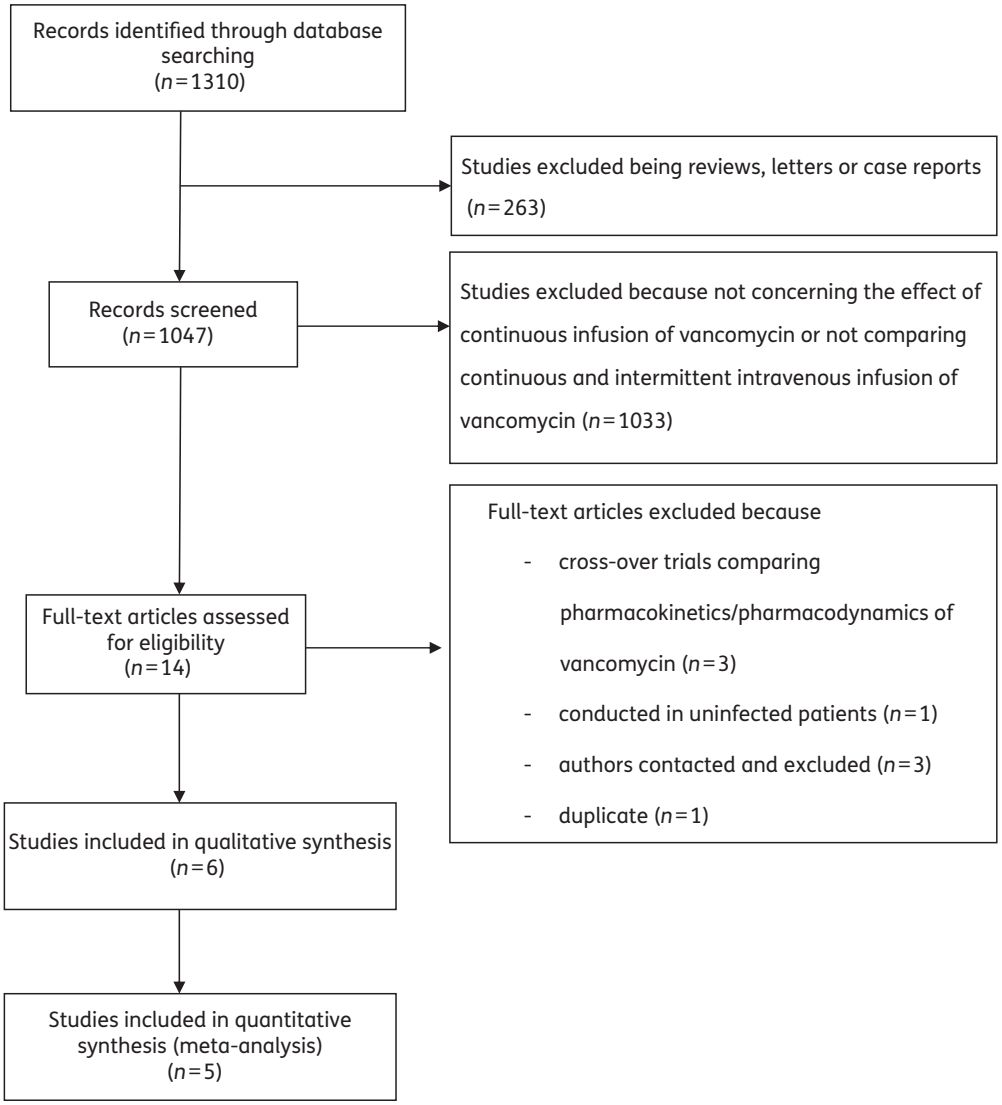

Figure 1. Flow chart depicting the selection process of studies included in the meta-analysis.

Study description

A summary description of the included studies is reported in Table 1. All studies included patients treated between 1983 and 2008. Five studies were performed in Europe[20–24] and one in Asia.[25] Table 2 details vancomycin administration in the included studies. The vancomycin MIC values were reported in two studies[22,23] that used the agar dilution method and the Etest, respectively. Vuagnat *et al.*[23] reported that MICs of bacterial isolates from patients treated with InI were 1.8±0.6 mg/L (range 1–3 mg/L) and from those treated with CoI were 1.9±0.8 mg/L (range 1–4 mg/L). In the RCT, vancomycin MICs were measured in 40 randomly selected strains and were 1 mg/L in 28% and 36% of strains in the InI and CoI group, respectively, and 2 mg/L in 72% and 50% of strains in the InI and CoI group, respectively.[22]

Quality of included studies

Regarding the risk of bias in the RCT, the method used to generate the allocation sequence was adequate, whereas the allocation concealment was not described. Baseline measurement and characteristics were provided and were similar between groups. Missing outcomes were not reported. Primary outcome was blinded assessed. Protection against contamination was not described. The trial was free from selective outcome reporting.

Table 3 shows the quality appraisal of the included studies. Regarding other risks of bias in the observational studies, detection bias could have occurred, considering that no blinded assessment of outcome was done in all studies; however, there was no difference among the two groups of treatment.

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 ($I^2=0$).

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.

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.

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; $P=0.9$).

Vancomycin exposure

All studies[20–25] analysed the C_{min} and the C_{ss} (Table 4). Due to the high statistical heterogeneity between studies ($I^2=90\%$), the meta-analysis was not carried out. The causes of heterogeneity were not explored due to the low number of included studies.

The AUC_{24} values were reported in two of six studies.[22,24] Mean values were comparable in the two treatment groups (Table 4).

Treatment failure

Only two studies provided treatment failure rates in the two groups of infusion.[22,23] Both reported no significant difference between the two groups.

Adverse effects

Pooled analysis was not performed, given the lack of complete data on adverse effects and the heterogeneity of definitions. In the Vuagnat *et al.*[23] study, adverse drug reactions leading to withdrawal of vancomycin therapy were significantly more frequent in the InI group. Reported adverse effects were acute renal injury, allergic reaction, severe neutropenia, catheter phlebitis and severe depression in the group receiving InI of vancomycin, whereas only catheter phlebitis was reported in the group receiving CoI.[23] In two studies it was reported that red man syndrome occurred only in few patients under InI, even if the difference was not statistically significant.[22,24]

Analysis of publication bias

The Begg's funnel plot and the Egger test indicated that there was no evidence of publication bias.

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

References	Quality indicators								
	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.

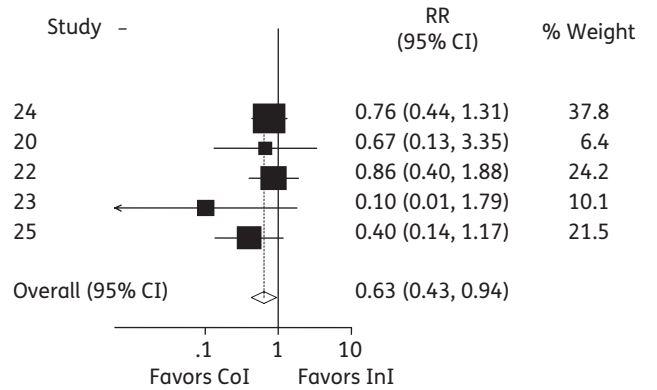

Figure 2. Forest plot summary (fixed effect) of the unadjusted RR of the studies included in the meta-analysis comparing nephrotoxicity rates in patients treated with CoI versus InI of vancomycin.

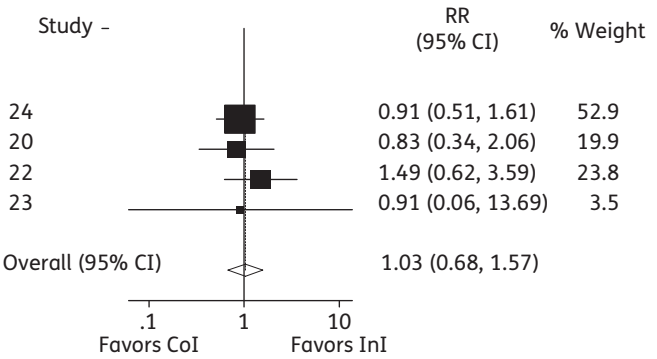

Figure 3. Forest plot summary (fixed effect) of the unadjusted RR of the studies included in the meta-analysis comparing overall mortality rates in patients treated with CoI versus InI of vancomycin.

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

Reference	Vancomycin serum concentration (mg/L), ±SD		AUC_{24} (mg/L/h), ±SD	
	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.

Discussion

Our meta-analysis shows that CoI of vancomycin, when compared with InI under the same daily dosage, was associated with a significantly lower risk of drug-related nephrotoxicity in patients treated for Gram-positive infections.

Renal toxicity, although relatively rare, is one of most dreaded adverse effects of vancomycin and has been associated with an increased risk of bad outcomes.[34] The lower risk of nephrotoxicity with CoI is probably due to the fact that the desired steady-state concentrations may be attained with lower daily doses than those needed to achieve a similar trough with InI,[17,22] thus avoiding the potential risk deriving from excessive drug exposure in terms of AUC.[35] Indeed, lower variability in plasma

concentrations when vancomycin is administered continuously has been described.[23,28]

Our meta-analysis was unable to demonstrate a significant difference in mortality rates in patients with Gram-positive infections treated with CoI versus InI of vancomycin. Major pitfalls for the analysis of mortality were the assessment of overall mortality instead of infection-related mortality (not analysed in all studies) and the heterogeneity of aetiology, site and severity of infections.

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.

The consensus review from ASHP, IDSA and SIDP underlines that vancomycin plasma concentration must be in excess of the bacterial MIC and recommends a plasma vancomycin C_{min} of 15–20 mg/L in *S. aureus*–complicated infections.[19] Some authors argue that the standard dosing regimen of 15 mg/kg every 12 h does not assure attainment of this goal.[26] In a study in which vancomycin plasma concentration was assessed after 36–48 h of InI and CoI, adequate vancomycin plasma concentrations for the treatment of MRSA infections were observed more frequently in patients treated by CoI.[26] However, as far as the time above the MIC is concerned, a cross-over trial comparing the two ways of infusion in patients with Gram-positive infections found that both regimens resulted in the MIC being exceeded 100% of the time.[28]

Analysis of costs was not included in the outcomes of our study, although a difference in hospital costs between the two ways of infusion does exist. Wysocki *et al.*[22] reported that the 10-day treatment cost per patient, including the cost of serum vancomycin determination, was significantly lower in the CoI group.

Our meta-analysis has several limitations. First, it was possible to include a low number of studies and only one RCT. However, meta-analyses were done including only studies reporting the same outcome, and the quality of observational studies included was fairly good. No significant difference was detected between the two groups of treatment for epidemiological and clinical factors. Moreover, the 'hierarchy' of study design has been debated. A study comparing the findings of separate meta-analyses of RCTs and observational studies assessing the same intervention found that the average results were similar.[36] Second, studies did not differentiate between the minor and major kidney injuries that occurred during vancomycin treatment, and many patients received other antibiotics that could have influenced both clinical outcomes and nephrotoxicity. Further sensitivity analysis could not be performed due to the heterogeneity of treatments.

In conclusion, our meta-analysis showed that administration of vancomycin for the treatment of Gram-positive infections by CoI was associated with a significantly lower risk of nephrotoxicity when compared with the InI of the drug. However, since this evidence is supported by four observational studies and one RCT, it cannot be considered conclusive. The research agenda needs to move to multicentre studies applying randomized allocation of the method of infusion, adequate sample size and standardized methods of vancomycin concentration measures and assessing the impact of the method of vancomycin administration on the mortality rate and on pharmacodynamic activity in terms of the AUC/MIC ratio. Cost-effectiveness analysis is also urgently needed.

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Transparency declarations

E. T. has served on the advisory board to Sanofi-Aventis and Astellas, and has been on the speakers' bureau for Pfizer and Novartis. F. P. has been a consultant for Astellas, has been a consultant for and on the speakers' bureau for Pfizer and has also been on the speakers' bureau for Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Novartis and Sanofi-Aventis. N. P. has served on the advisory board of Care Fusion and Janssen-Cilag, and has been on the speakers' bureau for MSD, Pfizer, Wyeth, Janssen-Cilag, Johnson & Johnson, Gilead, Novartis, Astellas, Sanofi Aventis and GSK. M. A. C. and E. G. have no conflicts of interest to declare.

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