

Review

Linezolid versus vancomycin for the treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials

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ABSTRACT

This review aimed to compare data regarding the effectiveness and safety of linezolid and vancomycin in the treatment of Gram-positive bacterial infections. PubMed and other databases were searched to identify relevant randomised controlled trials (RCTs). Nine RCTs studying 2489 clinically assessed patients were included in the meta-analysis. Overall, there was no difference between linezolid and vancomycin regarding treatment success in clinically assessed patients [odds ratio (OR) = 1.22, 95% confidence interval (CI) 0.99–1.50]. Linezolid was more effective than vancomycin in patients with skin and soft-tissue infections (OR = 1.40, 95% CI 1.01–1.95). However, there was no difference in treatment success for patients with bacteraemia (OR = 0.88, 95% CI 0.49–1.58) or pneumonia (OR = 1.16, 95% CI 0.85–1.57). Linezolid was associated with better eradication rates in all microbiologically assessed patients compared with vancomycin (OR = 1.33, 95% CI 1.03–1.71). There was no difference in total adverse effects possibly or probably related to the study drugs (OR = 1.14, 95% CI 0.82–1.59). However, nephrotoxicity was recorded more commonly in patients receiving vancomycin (OR = 0.31, 95% CI 0.13–0.74). In conclusion, linezolid is as effective as vancomycin in patients with Gram-positive infections. There is superior clinical and microbiological outcome with linezolid in complicated skin and soft-tissue infections caused by *Staphylococcus aureus*.

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1. Introduction

Gram-positive cocci are responsible for many severe infections in community and hospital settings, and the multidrug resistance of these organisms has increased markedly in the past decade [1,2]. This trend is particularly evident for meticillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA). More than 60% of nosocomial *S. aureus* isolates are MRSA in China [3]. By 2003, MRSA accounted for 59.5% of nosocomial *S. aureus* infections in Intensive Care Units in the USA [4]. In 2001–2006, the overall prevalence of MRSA was 42% for *S. aureus* from bacteraemia in the UK and Ireland [5].

MRSA infections are associated with considerable attributable mortality and morbidity as well as personal and public cost [6,7]. Vancomycin remains a standard treatment for MRSA infection [8], however vancomycin-resistant isolates of *S. aureus* have emerged in the USA and vancomycin-intermediate isolates are being increasingly reported worldwide [9,10]. Moreover, adverse effects (AEs), the need for intravenous (i.v.) access and growing resistance to vancomycin limit its use.

Linezolid is the first available oxazolidinone that inhibits bacterial protein synthesis by preventing formation of the 70S initiation complex [11,12]. Linezolid has in vitro and in vivo activity against a broad range of antibiotic-susceptible and -resistant Gram-positive bacteria [13], including activity against MRSA and *S. aureus* with intermediate resistance to glycopeptides [14,15]. Excellent tissue penetration and 100% oral bioavailability [16] are notable properties of linezolid. Linezolid is approved in Europe and the USA for the treatment of hospital-acquired and community-acquired pneumonia as well as complicated skin and skin-structure infections (SSSIs); additional approved indications in the USA include vancomycin-resistant *Enterococcus faecium* and MRSA infections and uncomplicated SSSIs.

Several randomised controlled trials (RCTs) have compared linezolid versus vancomycin for the treatment of Gram-positive cocci infections. There are two meta-analyses of linezolid [17,18], however both have some limitations. One meta-analysis compared linezolid with a glycopeptide or β -lactam for the treatment of Gram-positive bacterial infections and did not provide specific results for linezolid versus vancomycin; the other only compared linezolid versus vancomycin for *S. aureus* bacteraemia. More reported RCTs of linezolid versus vancomycin were not included in these two meta-analyses, especially those reported in the Asian population. Therefore, we performed a meta-analysis of RCTs to

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Table 1
Main characteristics of the randomised controlled trials included in the meta-analysis.

Study	Study design	Population	Drug regimen	Linezolid	Vancomycin	Enrolled patients	Intention to treat	Study quality score
Wilcox et al. (2009) [40]	MC	Patients (≥ 13 years) with suspected CRBSI and cSSSI	i.v. 600 mg q12h, followed or not by p.o. 600 mg q12h		i.v. 1 g q12h followed by oxacillin or dicloxacillin for confirmed MSSA infections ≤ 60 years, i.v. 1 g q12h; >60 years, i.v. 0.75 g q12h	739	363 vs. 363	2
Lin et al. (2008) [39]	MC, DB	Hospitalised patients (18–75 years) with pneumonia or cSSTI	i.v. 600 mg q12h		i.v. 1 g q12h	144	71 vs. 71	4
Wunderink et al. (2008) [42]	MC	Patients (≥ 18 years) with suspected MRSA VAP	i.v. 600 mg q12h, followed or not by p.o. 600 mg q12h		i.v. 1 g q12h	75 vs. 74	74 vs. 72	2
Kohno et al. (2007) [38]	MC	Patients (>20 years) with confirmed or suspected MRSA-related pneumonia, cSSTI or sepsis	i.v. or p.o. 600 mg q12h, followed by p.o.		i.v. 1 g q12h	154	100 vs. 51	2
Weigelt et al. (2005) [37]	MC	Hospital inpatients (≥ 18 years) with suspected or proven cSSSI	i.v. or p.o. 600 mg q12h, followed by p.o.		i.v. 1 g q12h, followed by p.o. semisynthetic penicillin for confirmed MSSA infections	1200	592 vs. 588	2
Kaplan et al. (2003) [36]	MC	Hospital inpatients (≤ 12 years) with known or suspected Gram-positive infections	i.v. 10 mg/kg q8h, followed by p.o. 10 mg/kg q8h		i.v. 10–15 mg/kg q6–24h, followed by p.o. appropriate antibiotics (mostly clindamycin)	219 vs. 102	215 vs. 101	2
Wunderink et al. (2003) [41]	MC, DB	Patients (≥ 18 years) with nosocomial pneumonia	i.v. 600 mg q12h		i.v. 1 g q12h	321 vs. 302	321 vs. 302	4
Stevens et al. (2002) [34]	MC, SB	Hospital inpatients (≥ 13 years) with suspected MRSA infections	i.v. 600 mg q12h, followed by p.o. 600 mg q12h		i.v. 1 g q12h	240 vs. 220	240 vs. 220	2
Rubinstein et al. (2001) [35]	MC, DB	Patients (≥ 18 years) with suspected nosocomial pneumonia	i.v. 600 mg q12h		i.v. 1 g q12h	402	203 vs. 193	3

MC, multicentre; DB, double-blind; SB, single-blind; CRBSI, catheter-related bloodstream infection; cSSSI, complicated skin and skin-structure infection; cSSSI, complicated skin and soft-tissue infection; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*; VAP, ventilator-associated pneumonia; i.v., intravenous; p.o., oral; q12h, every 12 h, q8h, every 8 h, q6–24h, every 6–24 h.

clarify whether the use of linezolid could be associated with improved outcomes in comparison with vancomycin for the treatment of infections caused by Gram-positive cocci, including SSSIs, pneumonia and bacteraemia.

2. Methods

2.1. Search strategy

A systematic literature search was conducted of PubMed (until June 2009), Current Contents and the Cochrane Central Register of Controlled Trials to identify relevant RCTs. The search strategy was as follows: 'linezolid', 'vancomycin', 'skin and soft tissue infection', 'pneumonia', 'bacteremia', 'Gram-positive cocci', '*S. aureus*', 'MRSA' and '*Enterococcus*'. Searches were limited to RCTs only. In addition, references of the initially identified articles were hand-searched and reviewed, including relevant review papers. Abstracts presented in scientific conferences were not searched for.

2.2. Study selection

Two reviewers (LB and CY) independently searched the literature and examined relevant RCTs for further assessment of data on effectiveness and toxicity. A study was considered eligible if it was a clinical RCT, if it studied the role of linezolid in comparison with vancomycin in the treatment of infections caused by Gram-positive cocci and if it assessed the effectiveness, toxicity or mortality of both therapeutic regimens. Only RCTs written in English were included in the analysis. Trials with blinded and unblinded design were included. RCTs done primarily in cancer or neutropenic patients were excluded. Experimental trials and trials focusing on pharmacokinetic or pharmacodynamic variables were also excluded. Additional antimicrobial agents (mainly those with effectiveness against Gram-negative rods that could be involved in polymicrobial infections of skin and lungs) could be used in the RCTs.

2.3. Data extraction

The following data were extracted from each study: (i) year of publication; (ii) patient population; (iii) number of patients [by intention to treat (ITT) and those assessed clinically and microbiologically]; (iv) antimicrobial agents and doses used; (v) clinical and microbiological outcomes, (vi) toxic effects; and (vii) mortality. The ITT population comprised patients who received at least one dose of the medications studied in the individual RCTs. The clinically assessed population comprised patients who fulfilled all inclusion and exclusion criteria in the individual RCTs, had complete follow-up and for whom data on treatment outcomes were available but not indeterminate. The microbiologically assessed population was a subset of the clinical population that had also microbiologically documented infections. The two reviewers independently extracted the relevant data. A quality review of each RCT was done to include details of randomisation, generation of random numbers, details of double-blinding procedure, information on withdrawals and allocation concealment. One point was awarded for the specification of each criterion, with a maximum score of 5. High-quality RCTs scored 3 or more points, whereas low-quality RCTs scored 2 or fewer points, according to a modified Jadad score [19].

2.4. Analysed outcomes

Treatment success, all-cause mortality and AEs probably or possibly related to study regimens were used as primary outcome measures for this meta-analysis. Treatment success was assessed

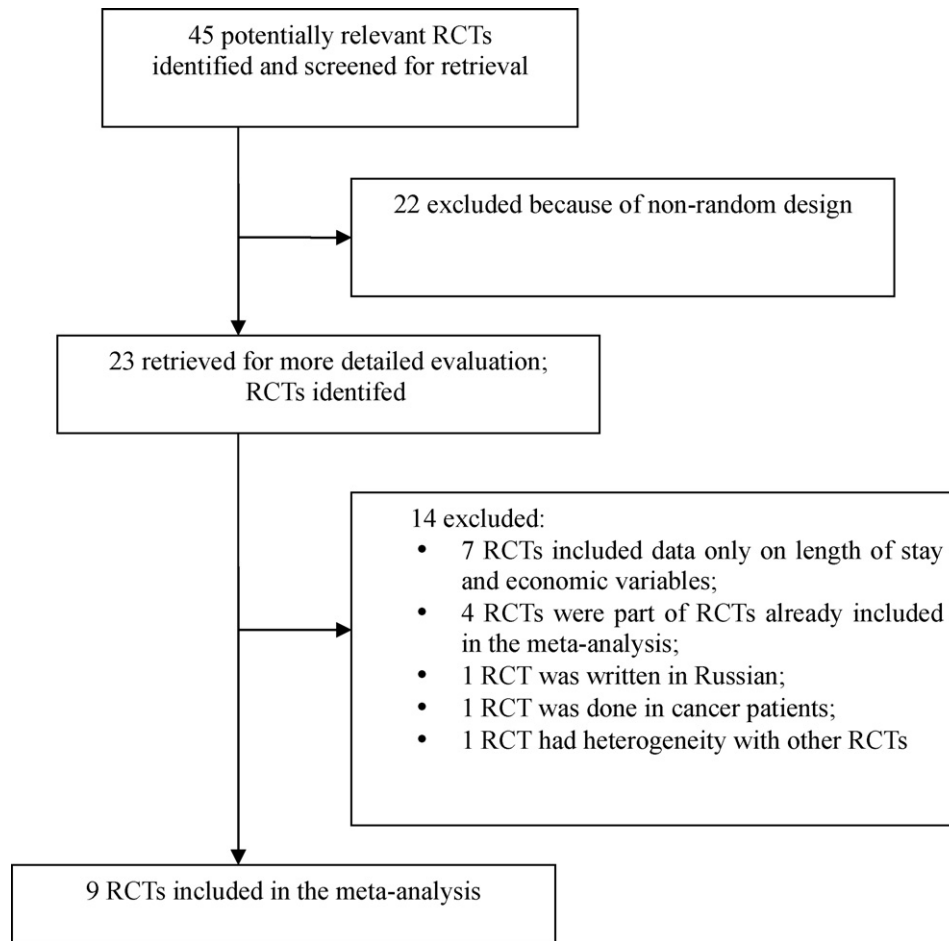


Fig. 1. Flow diagram of the randomised controlled trials (RCTs) reviewed.

in all patients and separately in patients with skin and soft-tissue infections (SSTIs), bacteraemia and pneumonia. All-cause mortality was analysed based on the reported data for mortality during the study period (e.g. during treatment and follow-up period). Outcomes on effectiveness were also analysed in the following groups: (i) patients with pneumonia, SSTIs and bacteraemia; and (ii) patients in the clinically assessed populations. Microbiological assessment and eradication (documented or presumed) of Gram-positive cocci (especially *S. aureus*, MRSA) were secondary outcomes.

2.5. Data analysis and statistical methods

Statistical analyses were done with Review Manager version 5.0 (Cochrane Collaboration) software. Heterogeneity between RCTs was assessed by χ^2 test ($P < 0.10$ was defined to indicate significant heterogeneity). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for all primary and secondary outcomes (including clinically assessed and microbiologically assessed populations) were calculated by the Mantel–Haenszel fixed-effects model (FEM) or the DerSimonian–Laird random-effects model (REM). For all

Table 2

Outcome data from the selected randomised controlled trials in the meta-analysis.

Study	Mean (S.D.) treatment duration (days)		Treatment success [n/N (%)]				Mortality	
	LZD	VAN	ITT at TOCV		CE at TOCV		LZD	VAN
			LZD	VAN	LZD	VAN		
Wilcox et al. (2009) [40]	9.2 (5.2)	8.7 (5.5)	–	–	193/251 (77)	172/218 (79)	–	–
Lin et al. (2008) [39]	12.2 (5.42)	10.7 (5.06)	–	–	49/59 (83)	37/57 (65)	5/71 (7.0)	2/71 (2.8)
Wunderink et al. (2008) [42]	10.8	11.5	–	–	20/30 (67)	10/20 (50)	4/74 (5.4)	6/72 (8.3)
Kohno et al. (2007) [38]	10.9 (5.0)	10.6 (5.1)	–	–	22/60 (37)	11/30 (37)	1/100 (1.0)	1/51 (2.0)
Weigelt et al. (2005) [37]	11.8 (4.9)	10.9 (5.3)	439/476 (92)	402/454 (89)	436/462 (94)	394/436 (90)	9/592 (1.5)	7/588 (1.2)
Kaplan et al. (2003) [36]	11.3 (5.0)	12.2 (6.4)	155/196 (79)	63/85 (74)	134/150 (89)	60/71 (85)	13/215 (6.0)	3/101 (3.0)
Wunderink et al. (2003) [41]	9.5 (4.5)	9.4 (4.5)	135/256 (53)	128/245 (52)	114/168 (68)	111/171 (65)	64/321 (20)	61/302 (20)
Stevens et al. (2002) [34]	12.6 (7.1)	11.3 (6.7)	109/192 (57)	93/169 (55)	41/56 (73)	38/52 (73)	44/240 (18)	33/220 (15)
Rubinstein et al. (2001) [35]	9.6 (4.4)	8.9 (4.4)	86/161 (53)	74/142 (52)	71/107 (66)	62/91 (68)	36/203 (18)	49/193 (25)
Total			924/1281 (72)	760/1095 (69)	1080/1343 (80)	895/1146 (78)	176/1816 (9.7)	162/1598 (10)

S.D., standard deviation; n , number of patients affected; N , total number of patients in the study; ITT, intention to treat; TOCV, test-of-cure visit; CE, clinically evaluable; LZD, linezolid; VAN, vancomycin.

Table 3
Effectiveness of linezolid for clinically assessed patients with pneumonia, bacteraemia and skin and soft-tissue infections (SSTIs).

Study	Pneumonia		Bacteraemia		SSTIs	
	LZD	VAN	LZD	VAN	LZD	VAN
Wilcox et al. (2009) [40]	–	–	70/93 (75)	59/73 (81)	123/158 (78)	113/145 (78)
Lin et al. (2008) [39]	19/26 (73)	18/33 (55)	–	–	30/33 (91)	19/24 (79)
Wunderink et al. (2008) [42]	20/30 (67)	10/20 (50)	–	–	–	–
Kohno et al. (2007) [38]	11/34 (32)	6/19 (32)	–	–	9/17 (53)	5/10 (50)
Weigelt et al. (2005) [37]	–	–	–	–	436/462 (94)	394/436 (90)
Kaplan et al. (2003) [36]	9/10 (90)	10/10 (100)	47/57 (82)	17/23 (74)	55/59 (93)	27/30 (90)
Wunderink et al. (2003) [41]	114/168 (68)	111/171 (65)	–	–	–	–
Stevens et al. (2002) [34]	9/12 (75)	12/16 (75)	9/15 (60)	7/10 (70)	27/34 (79)	22/30 (73)
Rubinstein et al. (2001) [35]	71/107 (66)	62/91 (68)	–	–	–	–
Total	253/387 (65)	229/360 (64)	126/165 (76)	83/106 (78)	680/763 (89)	580/675 (86)

LZD, linezolid; VAN, vancomycin.

Table 4
Microbiological outcomes from the randomised controlled trials in the meta-analysis.

Study	Treatment success (microbiological evaluation)		Pathogen eradication							
	LZD	VAN	<i>Staphylococcus aureus</i>		MRSA		<i>Enterococcus</i> spp.		Other streptococci	
			LZD	VAN	LZD	VAN	LZD	VAN	LZD	VAN
Wilcox et al. (2009) [40]	186/212 (88)	184/210 (88)	121/143 (85)	93/110 (85)	63/74 (85)	52/60 (87)	–	–	–	–
Lin et al. (2008) [39]	42/53 (79)	32/52 (62)	33/43 (77)	23/37 (62)	25/28 (89)	15/25 (60)	5/6 (83)	7/12 (58)	4/4 (100)	2/3 (67)
Wunderink et al. (2008) [42]	13/23 (57)	9/19 (47)	13/23 (57)	9/19 (47)	13/23 (57)	9/19 (47)	–	–	–	–
Kohno et al. (2007) [38]	29/62 (47)	11/30 (37)	29/62 (47)	11/30 (37)	29/62 (47)	11/30 (37)	–	–	–	–
Weigelt et al. (2005) [37]	312/330 (95)	278/310 (90)	214/246 (87)	167/238 (70)	124/140 (89)	97/145 (67)	–	–	13/15 (87)	17/18 (94)
Kaplan et al. (2003) [36]	82/93 (88)	40/46 (87)	36/39 (92)	24/26 (92)	15/17 (88)	9/10 (90)	12/15 (80)	3/4 (75)	5/5 (100)	2/3 (67)
Wunderink et al. (2003) [41]	47/76 (62)	42/79 (53)	28/52 (54)	27/62 (44)	12/19 (63)	10/23 (43)	–	–	14/18 (78)	12/13 (92)
Stevens et al. (2002) [34]	33/56 (59)	36/57 (63)	33/56 (59)	36/57 (63)	33/56 (59)	36/57 (63)	–	–	–	–
Rubinstein et al. (2001) [35]	36/53 (68)	28/39 (72)	25/41 (61)	15/23 (65)	15/23 (65)	7/9 (78)	–	–	9/9 (100)	9/9 (100)
Total	780/958 (81)	660/842 (78)	532/705 (75)	405/602 (67)	329/442 (74)	246/378 (65)	17/21 (81)	10/16 (63)	45/51 (88)	42/46 (91)

MRSA, methicillin-resistant *Staphylococcus aureus*; LZD, linezolid; VAN, vancomycin.

analyses, results from the FEM are presented only when there was no heterogeneity between RCTs; otherwise results from the REM are presented.

3. Results

3.1. Selected randomised controlled trials

From 45 papers screened, 23 published reports of RCTs with infections caused by Gram-positive cocci treated with a linezolid and vancomycin regimen were identified (Fig. 1). Of these studies, seven RCTs were excluded because they only studied the length of hospital stay and economic variables [20–26], four RCTs were excluded because they were part of RCTs already included in the meta-analysis and the data from these reports were used if additional useful information could be extracted [27–30], one RCT was excluded because it was written in Russian [31], one RCT was excluded because it was done in cancer patients [32] and

one RCT was excluded because it had heterogeneity with other RCTs [33]. Thus, nine RCTs were included in the meta-analysis [34–42].

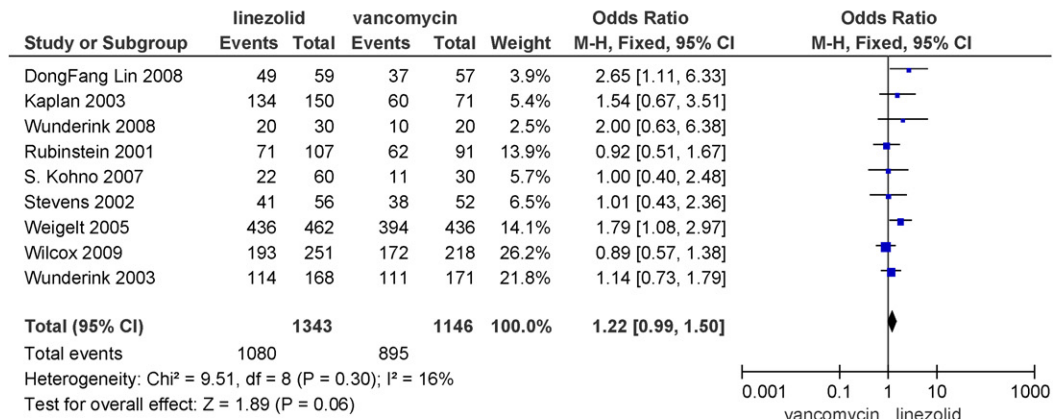
The main characteristics of the analysed RCTs are shown in Table 1. The mean quality score of the included RCTs was 2.6 (range 2–4). The quality of three RCTs (33.3%) was high (score ≥ 3). Among nine RCTs, four were a blinded design and five were non-blinded. Patients enrolled in eight RCTs [34,35,37–42] were ≥ 18 years old and patients in one RCT were ≤ 12 years old [36]. The dosages of the administered drugs are shown in Table 1. The route of linezolid administration was i.v. in three studies [35,39,41] and i.v. followed by oral in six studies [34,36–38,40,42]. Four RCTs [35,38,41,42] had routine measurement of vancomycin serum concentrations to ensure achievement and maintenance of a therapeutic concentration of the drug. Patients with concomitant presumed Gram-negative or mixed infections were treated with appropriate regimens, mainly aztreonam and aminoglycosides (data not shown).

Table 5
Reported adverse effects in the randomised controlled trials included in the meta-analysis.

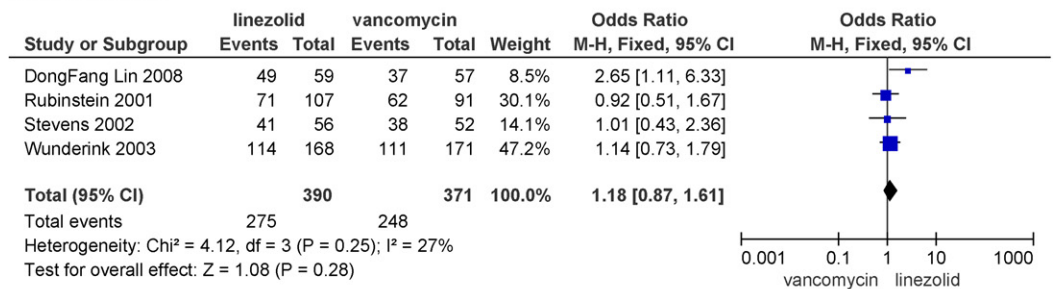
Study	Total adverse effects		Nephrotoxicity		Thrombocytopenia		Anaemia	
	LZD	VAN	LZD	VAN	LZD	VAN	LZD	VAN
Wilcox et al. (2009) [40]	42/363 (12)	33/363 (9.1)	3/363 (0.8)	9/363 (2.5)	7/363 (1.9)	7/363 (1.9)	20/363 (5.5)	25/363 (6.9)
Lin et al. (2008) [39]	18/71 (25.4)	12/71 (17)	1/71 (1.4)	0/71 (0)	2/71 (2.8)	0/71 (0)	1/71 (1.4)	1/71 (1.4)
Wunderink et al. (2008) [42]	19/74 (26)	23/72 (32)	–	–	2/74 (2.7)	6/72 (8.3)	9/74 (12)	7/72 (9.7)
Kohno et al. (2007) [38]	55/100 (55)	22/51 (43)	1/100 (1.0)	5/51 (9.8)	19/100 (19)	1/51 (2.0)	13/100 (13)	1/51 (2.0)
Weigelt et al. (2005) [37]	131/592 (22)	121/588 (21)	–	–	21/592 (3.5)	0/588 (0)	7/592 (1.2)	10/588 (1.7)
Kaplan et al. (2003) [36]	40/215 (19)	34/101 (34)	–	–	4/215 (1.9)	0/101 (0)	3/215 (1.4)	1/101 (1.0)
Wunderink et al. (2003) [41]	45/321 (14)	42/302 (14)	1/321 (0.3)	2/302 (0.7)	1/321 (0.3)	0/302 (0)	1/321 (0.3)	0/302 (0)
Stevens et al. (2002) [34]	44/240 (18)	18/220 (8)	0/240 (0)	2/220 (0.9)	4/240 (1.7)	0/220 (0)	–	–
Total	394/1976 (20)	305/1768 (17)	6/1095 (0.5)	18/1007 (1.8)	60/1976 (3.0)	14/1768 (0.8)	54/1736 (3.1)	45/1548 (2.9)

LZD, linezolid; VAN, vancomycin.

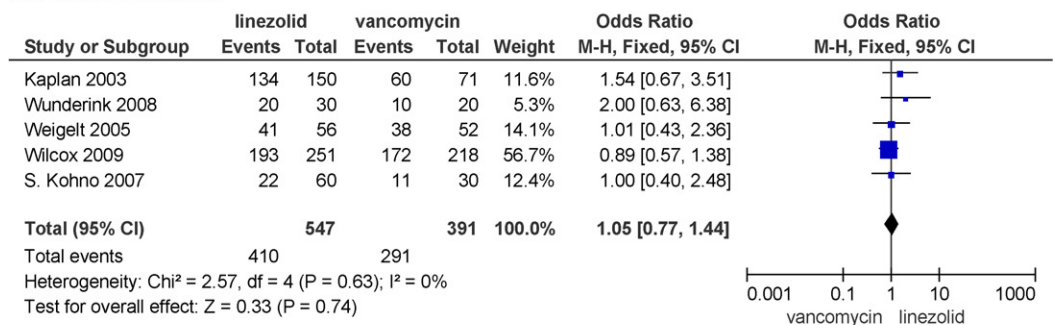
All studies



Blinded RCTs



Non-blinded RCTs



RCTs in adults

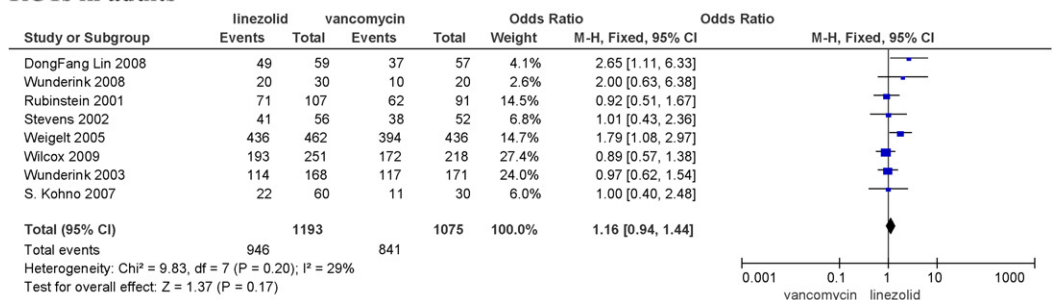


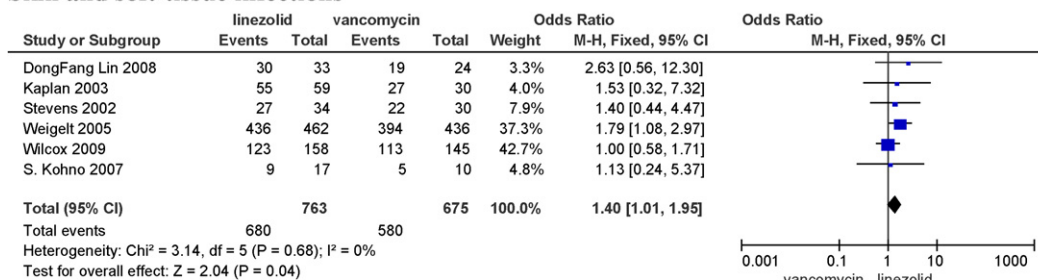
Fig. 2. Meta-analyses of treatment success for clinically assessed patients. RCT, randomised controlled trial.

3.2. Treatment success in clinically evaluable (CE) patients

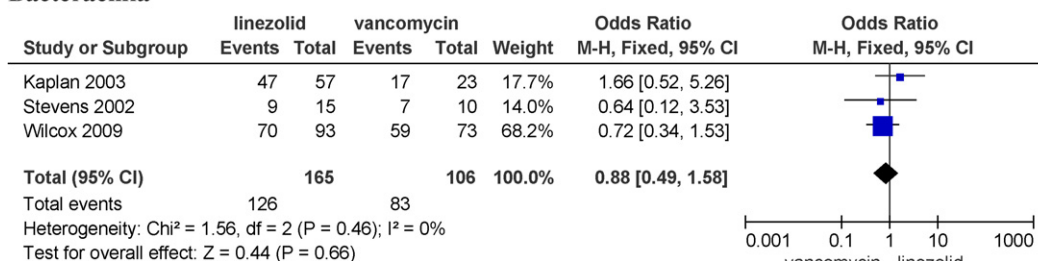
Table 2 presents the primary outcomes studied in the present meta-analysis. Data regarding treatment success of the administered antimicrobial regimens for CE patients were reported in all nine RCTs. Success of empirical treatment in clinically assessed patients was achieved in 80% of linezolid-treated patients and in

78% of vancomycin-treated patients (Table 2). There was no significant difference in treatment success between patients treated with linezolid and those treated with vancomycin (2489 patients, FEM, OR = 1.22, 95% CI 0.99–1.50) (Fig. 2). The same was true for clinically assessed patients from blinded RCTs (761 patients, FEM, OR = 1.18, 95% CI 0.87–1.61) (Fig. 2) and from non-blinded RCTs (938 patients, FEM, OR = 1.05, 95% CI 0.77–1.44) (Fig. 2). Eight RCTs reported

Skin and soft-tissue infections



Bacteraemia



Pneumonia

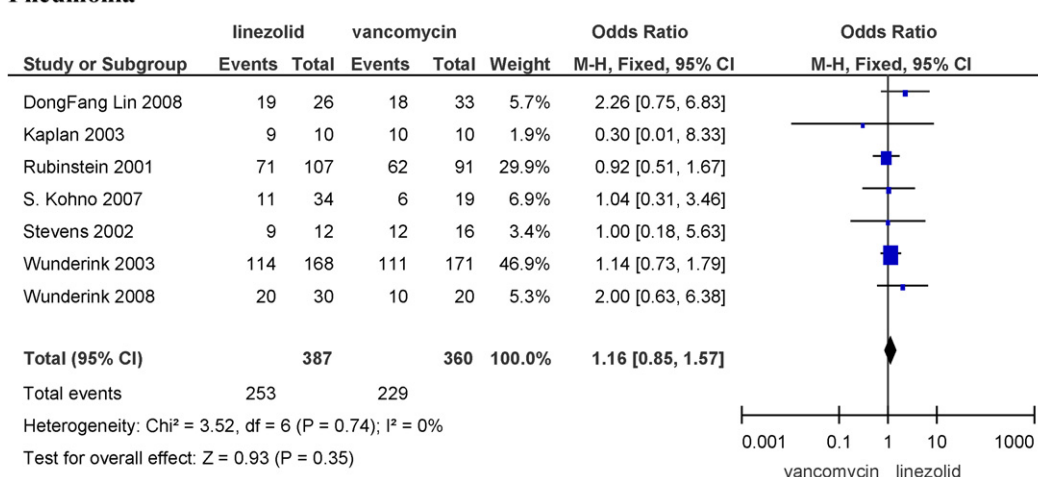


Fig. 3. Meta-analyses of treatment success for clinically assessed patients with skin and soft-tissue infections, bacteraemia and pneumonia.

outcomes in adult populations and one RCT reported outcomes in children. There was no significant difference between linezolid and vancomycin in treatment success in clinically assessed adult patients (2268 patients, FEM, OR = 1.16, 95% CI 0.94–1.44) (Fig. 2).

Table 3 summarises data for pneumonia, bacteraemia and SSTIs that were included in the meta-analysis. Six RCTs reported data on SSTIs [34,36–40]. Success of empirical treatment was achieved in 89% of linezolid-treated patients and in 86% of vancomycin-treated patients. Empirical treatment of patients with SSTIs with linezolid was associated with significantly better success than vancomycin (1438 clinically assessed patients, FEM, OR = 1.40, 95% CI 1.01–1.95) (Fig. 3).

Three RCTs reported outcomes for patients with bacteraemia [34,36,40]. Success of empirical treatment was achieved in 76% of linezolid-treated patients and in 78% of vancomycin-treated patients (Table 3). There was no significant difference in treatment success for bacteraemia between linezolid and vancomycin (271 clinically assessed patients, FEM, OR = 0.88, 95% CI 0.49–1.58) (Fig. 3).

Seven RCTs reported effectiveness outcomes for pneumonia [34–36,38,39,41,42]. Success of empirical treatment was achieved

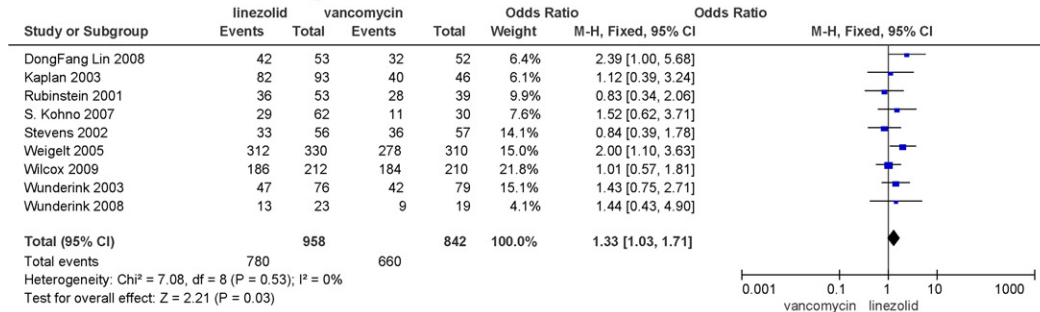
in 65% of linezolid-treated patients and in 64% of vancomycin-treated patients (Table 3). There was no difference in treatment success for pneumonia between linezolid and vancomycin (747 clinically assessed patients, FEM, OR = 1.16, 95% CI 0.85–1.57) (Fig. 3).

3.3. Treatment success in microbiologically evaluable (ME) patients

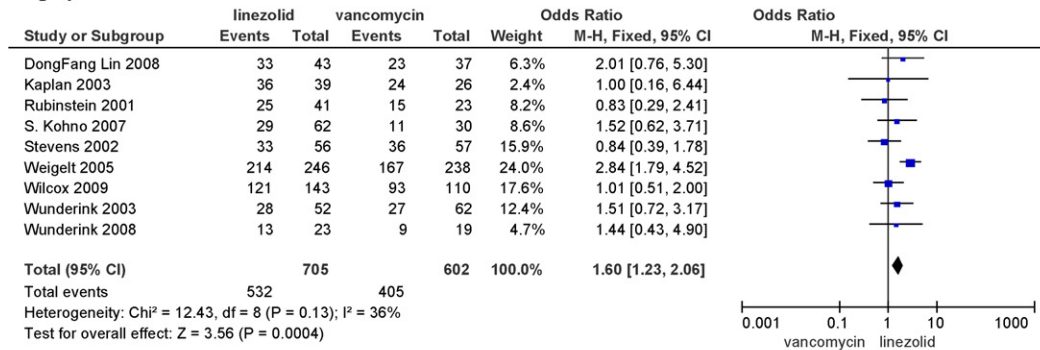
All nine RCTs included in the meta-analysis reported data on ME patients (Table 4). Empirical treatment of Gram-positive infections with linezolid was associated with better treatment success in ME patients than vancomycin treatment (1800 patients, FEM, OR = 1.33, 95% CI 1.03–1.71) (Fig. 4).

More specifically, empirical treatment with linezolid was associated with better eradication rates for *S. aureus* (1307 strains, FEM, OR = 1.60, 95% CI 1.23–2.06) (Fig. 4). However, empirical treatment with linezolid was not associated with increased eradication of MRSA strains (820 strains, REM, OR = 1.61, 95% CI 0.95–2.71) (Fig. 4) in comparison with vancomycin. Finally, there were no differences in eradication for enterococcal species (37 strains, FEM, OR = 2.34,

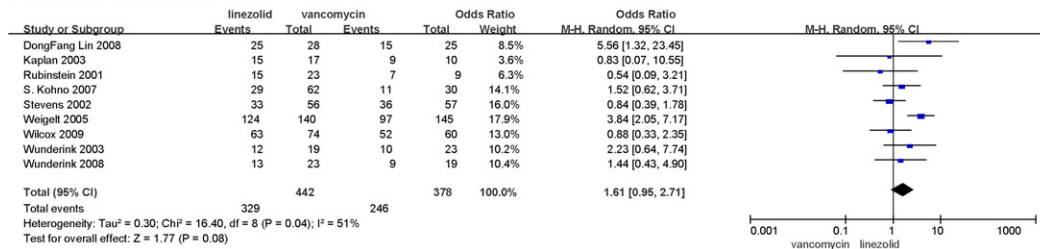
All studies with microbiological assessment



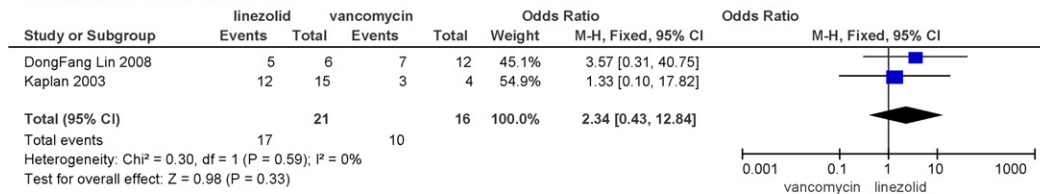
Staphylococcus aureus eradication



MRSA eradication



Enterococci eradication



Other streptococci eradication

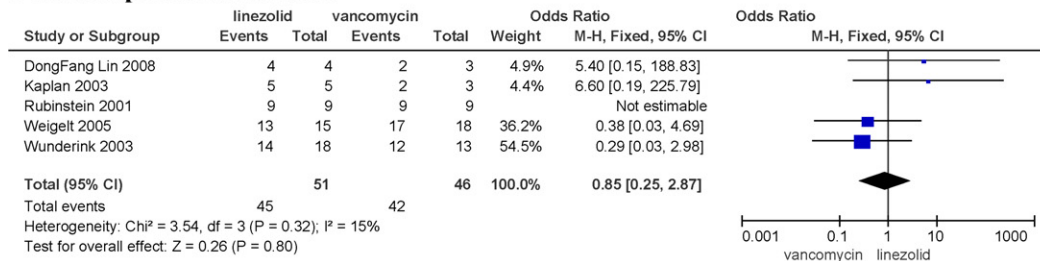


Fig. 4. Meta-analyses of treatment success for microbiologically assessed patients. MRSA, methicillin-resistant *Staphylococcus aureus*.

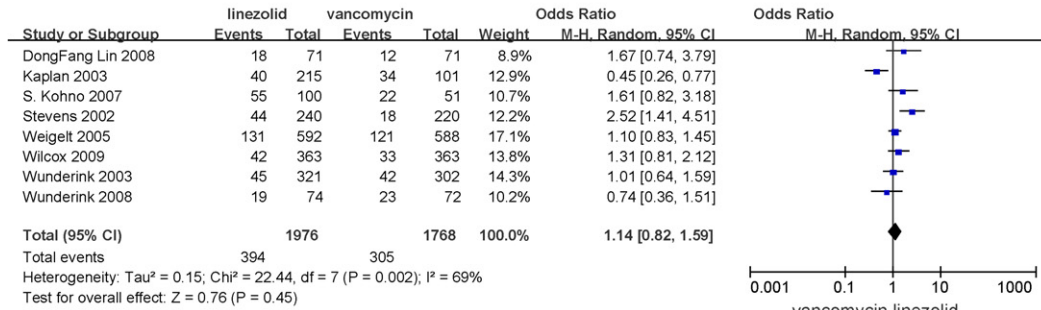
95% CI 0.43–12.84) (Fig. 4) and streptococci species (97 strains, FEM, OR = 0.85, 95% CI 0.25–2.87) (Fig. 4).

3.4. Adverse effects

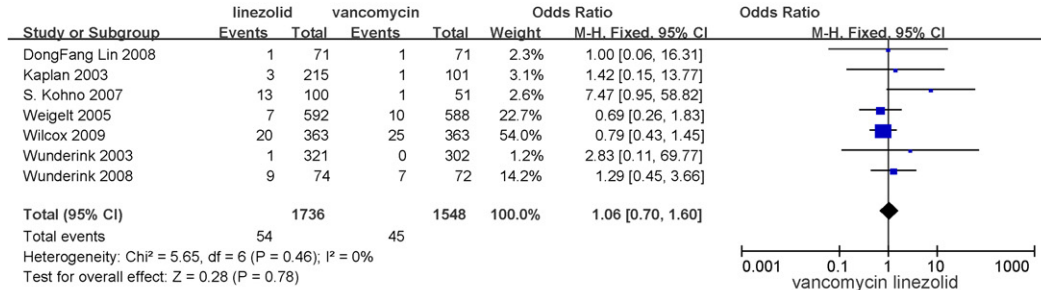
Data on AEs possibly or probably related to the study medications were reported for eight trials (Table 5) [34,36–42]. One trial reported data on AEs of different types but did not report

the total AEs [35] and was therefore excluded from the analysis of AEs. There was no difference in total AEs possibly or probably related to the study drugs (ITT 3744 patients, REM, OR = 1.14, 95% CI 0.82–1.59) (Fig. 5). The majority of drug-related AEs were mild to moderate in severity and were reversible. There was no difference between the compared regimens in the proportion of patients who developed anaemia (ITT 3284 patients, FEM, OR = 1.06, 95% CI 0.70–1.60) (Fig. 5). Although a trend favouring linezolid can be seen,

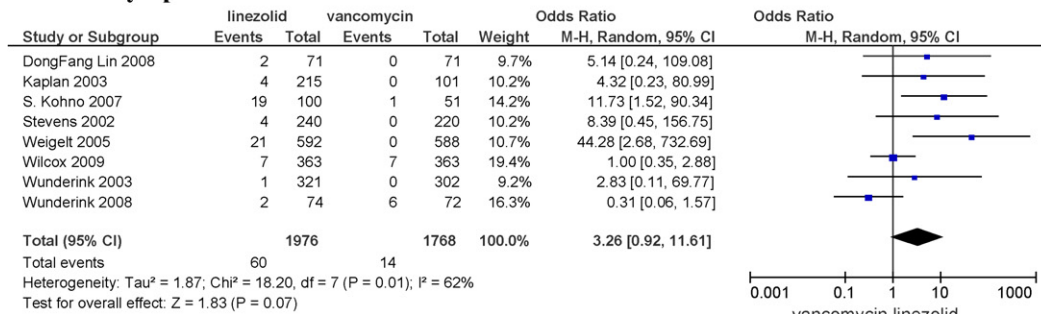
Total adverse effects



Anaemia



Thrombocytopenia



Nephrotoxicity

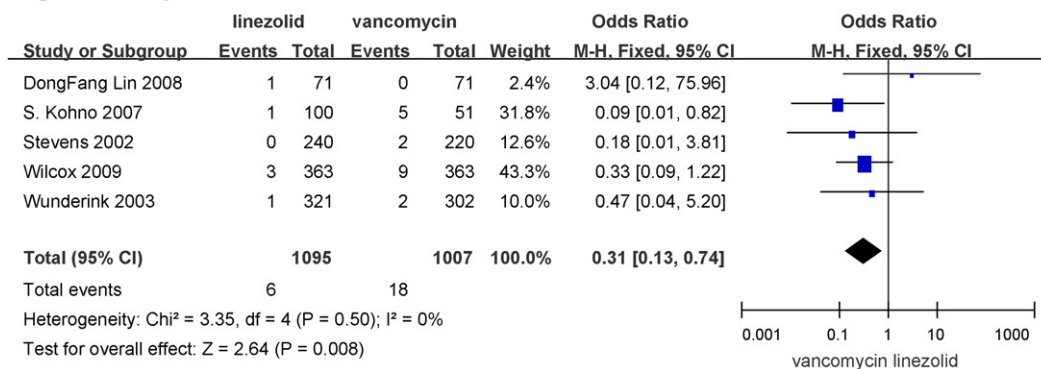


Fig. 5. Meta-analyses of adverse effects probably or possibly related to studied medications. Numbers of events in each study are shown in Table 5.

there was no difference for episodes of thrombocytopenia (ITT 3744 patients, REM, OR = 3.26, 95% CI 0.92–11.61) (Fig. 5; Table 5). However, significantly more episodes of nephrotoxicity were reported in vancomycin-treated patients (ITT 2102 patients, FEM, OR = 0.31, 95% CI 0.13–0.74) (Fig. 5; Table 5).

3.5. Mortality

All-cause mortality during the study period (based on the reported data) was available in eight trials (Table 2) [34–39,41,42]. There was no significant difference in mortality between linezolid

and vancomycin (3414 patients, FEM, OR = 0.99, 95% CI 0.78–1.25) (Fig. 6).

4. Discussion

The results of the current meta-analysis suggest that linezolid is clinically as effective as vancomycin for the treatment of Gram-positive infections for all patients combined (those with SSTIs, pneumonia and bacteraemia). Linezolid was more effective than vancomycin in patients with SSTIs. Empirical linezolid treatment was associated with better

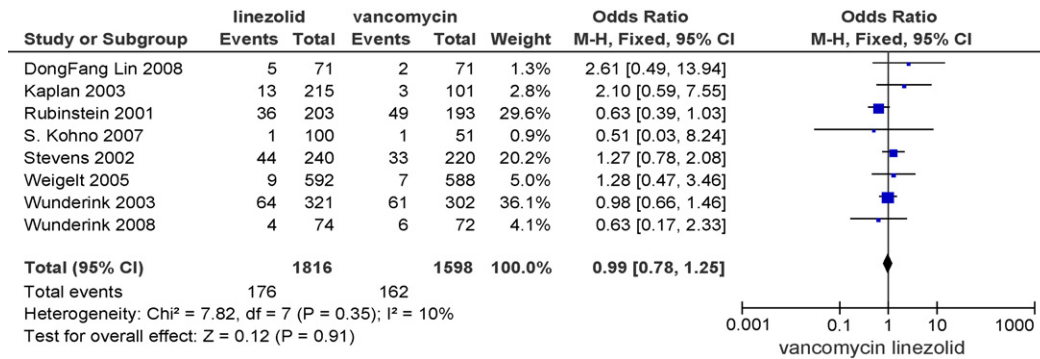


Fig. 6. Meta-analyses of mortality.

eradication rates in all ME patients. Linezolid was more effective for treatment of *S. aureus* infection than vancomycin. Linezolid had similar effectiveness to vancomycin in patients with MRSA, enterococcal and other streptococcal infections. The improved penetration of linezolid into skin compared with vancomycin and the 100% bioavailability for patients receiving oral linezolid may be factors explaining the outcomes seen with linezolid for the treatment of Gram-positive infections.

Mortality was similar between the compared regimens. There was no difference between the studied medications for total AEs possibly or probably related to the study drugs. However, an increased incidence of thrombocytopenia was found in linezolid-treated patients, but this difference was not significant. There was a significantly increased difference in the incidence of nephrotoxicity in vancomycin-treated patients. Previous studies have shown that linezolid can cause mild, reversible, time-dependent myelosuppression, particularly when patients are treated for longer than 14 days [43,44]. The mean duration of linezolid treatment in our meta-analysis was <14 days and therefore may have been too short to affect the probability of thrombocytopenia. Patients with underlying haematological abnormalities or lower baseline values may be at increased risk of thrombocytopenia during treatment with linezolid, as with many antibiotics, and should be monitored, especially when treatment exceeds 14 days.

The findings of the present study must be viewed in the context of potential limitations. First, investigators were not blinded to treatment allocation in five RCTs. This may have introduced bias to the reported outcomes of effectiveness. Second, five RCTs did not routinely measure vancomycin serum concentrations to ensure achievement and maintenance of a therapeutic concentration of the drug. This may have contributed to lower treatment success rates for vancomycin. Third, there were no resistance reports of the treatment in four RCTs [37,39,41,42] and no Gram-positive bacteria developed resistance to either agent during the study in the other five RCTs [34–36,38,40]. Linezolid-resistant MRSA was first reported in 2001 [45]; these linezolid-resistant bacteria typically have a mutation in the 23S ribosome that prevents binding of the drug. The clinical benefits of linezolid must be balanced against the safety profile and the possibility of microbial resistance to linezolid.

In conclusion, despite its limitations, this represents the largest meta-analysis of studies of linezolid and vancomycin for the treatment of Gram-positive infections to date. Linezolid is associated with clinical, microbiological and survival outcomes that are not inferior to those with vancomycin in patients with Gram-positive bacterial infections. However, there is superior clinical and microbiological efficacy with linezolid in complicated SSTIs caused by *S. aureus*. Linezolid was associated with a greater risk of thrombocytopenia compared with vancomycin, and vancomycin with a

greater risk of nephrotoxicity.

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Ethical approval: Not required.

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