Materials and Methods

Search Strategy

The strategy employed for the search in MEDLINE included the terms “daptomycin” and “enterococcus” as medical subject headings (MeSH) and “linezolid” as supplementary term. Similarly, a computerized literature search was performed in EMBASE using the terms “daptomycin”, “linezolid” and “enterococcus” as EMTREE thesaurus terms. To maximize the sensitivity of the search strategy, a number of synonyms of the above terms were entered as free-text terms in the electronic databases CENTRAL, ISI Web of Science and SCOPUS as appropriate (Table S1). No language limitations were applied. The citation lists of the retrieved articles were also hand-searched.

In addition, we screened the abstracts of the following major annual conferences in the field between 01/01/2003 and 31/08/2012: the Annual Meeting of Infectious Diseases Society of America (IDSA), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) and the International Congress on Infectious Diseases (ICID). In order to include results about ongoing, as well as completed, relevant clinical trials, the registry for clinical trials of the United States National Institutes of Health (http://www.clinicaltrials.gov), the European Clinical Trials Register of the European Medicines Agency (https://clinicaltrialsregister.eu), the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au) and the International Clinical Trials Registry Platform Search Portal of the World Health Organization (http://www.who.int/ictrp/en) were also searched, using the terms “enterococcus”, “daptomycin” and “linezolid”.

Data extraction

The following data were extracted from each study: demographic (citation data, country of origin, study period, number of patients in the daptomycin and linezolid groups), methodological (design, number participating centres, inclusion and exclusion criteria, imbalances in potential confounders and method of adjustment for them, covariates included in the model) and procedural (dose, duration of treatment, combination with another anti-VRE agent, adverse events). Any disagreement was resolved by discussion and was referred to the senior investigator (SM).

All authors were contacted in order to further clarify issues regarding the data provided in the studies included in this systematic review. Communication was established with the authors of eight studies (1-8) and answers were provided for three studies (5, 6, 8).

Quantitative data synthesis

The dichotomous data results from each study were expressed as odds ratio (OR) with 95% confidence intervals (CI). These results were combined for meta-analysis using the Mantel/Haenszel model (when using the fixed effects method) and the DerSimonian and Laird method (when using the random effects method).

All results were combined for meta-analysis using the Revman Software (Version 5.1, Copenhagen, The Cochrane Collaboration, 2011). Study-to-study variation was assessed by using the Chi^2 statistic (the hypothesis tested was that the studies were all drawn from populations with the same effect size). A fixed effects model was used when no statistically significant heterogeneity was present, while in the presence of significant heterogeneity ($p<0.05$), a random effects model was applied. A funnel plot analysis and Egger's test were performed, in order to detect the presence of publication bias.

A sensitivity analysis was *a priori* planned to be carried out by combining odds ratios for mortality adjusted for important confounders as identified by the authors of the individual studies through multivariate logistic regression analyses. An additional sensitivity analysis was performed by removing the studies that included patients switched from daptomycin to linezolid or vice-versa (cross-over patients).

References

1. **McKinnell JA, Patel M, Shirley RM, Kunz DF, Moser SA, and Baddley JW.** 2011. Observational study of the epidemiology and outcomes of vancomycin-resistant Enterococcus bacteremia treated with newer antimicrobial agents. Epidemiol. Infect. **139:**1342–1350.
2. **Twilla JD, Finch CK, Usery JB, Gelfand MS, Hudson JQ, and Broyles JE.** 2012. Vancomycin-resistant Enterococcus bacteremia: an evaluation of treatment with linezolid or daptomycin. J. Hosp. Med. **7:**243-248.
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5. **Dubrovskaya Y, Kubin CJ, and Furuya EY.** 2008. Daptomycin (D) Compared to Linezolid (L) for Primary Treatment of Vancomycin-Resistant Enterococcal Bacteremia (VREB). Abstr. Joint 48th Intersci. Conf. Antimicrob. Agents Chemother. and 46th Infectious Diseases Society of America Annual Meeting, abstr K-3443.
6. **Furuya EY, Kubin C, Yin M, Lowy FD, Della-Latta P, and Hammer S.** 2005. Daptomycin Experience and Comparison with Linezolid for the Treatment of Vancomycin-Resistant Enterococcal Bacteremia., Abstr. 45th Intersci. Conf. Antimicrob. Agents Chemother., abstr K-2116.
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9. **El-Lababidi RM, Topal J, and Tsukerman M.** 2007. Daptomycin and Linezolid in the Treatment of Vancomycin-Resistant Enterococcal Bacteremia: A Retrospective Analysis of Treatment Outcomes., Abstr. 45th Annual Meeting of the Infectious Diseases Society of America, abstr 1095.
10. **Kraft S, MacKler E, Schlickman P, Welch K, and Depestel DD.** 2011. Outcomes of therapy: Vancomycin-resistant enterococcal bacteremia in hematology and bone marrow transplant patients. Support. Care Cancer **19:**1969–1974.

Table S1. Search strategy used for the identification of eligible studies in electronic databases that free-text terms were used

	Intervention				**Pathogen**
	daptomycin		**Linezolid**		
Terms	(daptom*) OR (deptom*) OR (cubicin*) OR (cidecin*) OR (dapcin*) OR ('ly 146032') OR (ly146032) OR (ly-146032)	**AND**	(linezolid) OR (zyvox*) OR (linospan) OR ('u 100766') OR (u100766) OR (u-100766) OR ('pnu 100766') OR (pnu100766) OR (pnu-100766)	**AND**	(enterococ*) OR (*e. faecium*) OR (*e. faecalis*) OR (vre)

The asterisk (*) stands for any one or more character and has been used where available to increase the sensitivity of the search.

Table S2. Main characteristics of the studies comparing linezolid to daptomycin for the treatment of VRE bacteremia

Study, country of origin, journal or meeting	Study period	Study design, No of centers	Number of patients (D/L)	Inclusion criteria	Exclusion criteria
Furuya et al, 2005, USA, Abstract 45th ICAAC(6)	2004 – 2005	Retrospective cohort, single center	14/40	Patients with VRE bacteremia Administration of daptomycin for≥48h	Not reported
El-Lababidi et al, 2007, USA, Abstract 45th IDSA Meeting(9)	January 2000 – December 2006	Retrospective cohort, single center	28/28	Patients with VRE bacteremia	Not reported
Dubrovskaya et al, 2008, USA, Abstract 48th ICAAC(5)	January 2005 – December 2007	Retrospective cohort, single center	40/40	Adult patients with VRE bacteremia Daptomycin or Linezolid as initial treatment for≥48h	Not reported
Marion et al, 2008, USA, Abstract 48th ICAAC(7)	June 2005 – July 2007	Retrospective cohort, not reported	21/10	Febrile cancer neutropenic patients with VRE bacteremia	Not reported
Mave et al, 2009, USA, J Antimicrob Chemother(8)	September 2003 – December 2007	Retrospective cohort, multicenter	30/ 68	Patients with VRE bacteremia Age>18 years	VRE BSI susceptible to ampicillin or treatment with other antimicrobial or patient not considered to have true bacteremia
Crank et al, 2010, USA, Clin Ther(4)	September 2003 – June 2007	Retrospective cohort, multicenter	67/34	Hospitalized patients with VRE bacteremia Age≥18years	Patients with polymicrobial bacteremia
McKinnell et al, 2011, USA, Epidemiol Infect(1)	January 2005– July 2008	Retrospective cohort, single center	86/104	All patients with VRE bacteremia Treatment with daptomycin or linezolid for≥3days of the initial 4 days of VRE treatment	Not reported
Kraft et al, 2011, USA, Support Care Cancer(10)	January 2004 – December 2006	Retrospective cohort, single center	43/29	Hematology or bone marrow transplant service patients with VRE bacteremia Age>18 years Daptomycin or Linezolid as initial treatment for≥48h	None reported
Bio et al, 2011, USA Infect Dis Clin Pract(3)	January 2004 – March 2008	Retrospective cohort, single center	37/47	Patients with VRE bacteremia Age>18 years	Follow-up cultures not performed or repeated cultures negative for VRE before the initiation of treatment or concurrent antibiotic active against VRE or treatment for<3 days
Twilla et al, 2012, USA, J Hosp Med(2)	January 2004 – July 2009	Retrospective cohort, single center	63/138	Patients with VRE bacteremia Age≥18 years Daptomycin or Linezolid for≥5days	Simultaneously treated with more than one agent active against VRE

Abbreviations: D, Daptomycin; L: Linezolid; VRE, Vancomycin-resistant Enterococcus.

Table S3. Confounders identified in the studies comparing linezolid versus daptomycin for the treatment of VRE bacteremias and their adjustment

Study	Statistically significant differences in potential confounders		Adjustment for potential confounders	
	Increased in the daptomycin group	Increased in the linezolid group	Method of adjustment	Co-variates included in the model
Furuya et al.(6)	Not reported	Not reported	Logistic regression	Age, immunocompromise, ICU location
El-Lababidi et al.(9)	Patients that received chemotherapy	None	No	n/a
Dubrovskaya et al.(5)	Patients with hematologic malignancies Neutropenic patients within the past 30 days Thrombocytopenic patients Patients in need of renal replacement therapy	None	Logistic regression	Solid malignancy, APACHE II
Marion et al.(7)	Not reported	Not reported	No	n/a
Mave et al.(8)	ICU patients	None	Logistic regression	Age, gender, race, concomitant use of aminoglycosides, CCI, APACHE II
Crank et al.(4)	Patients presenting with shock, Patients having received previous vancomycin or linezolid treatment	None	Logistic regression	Source of infection, enterococcal species, presence of acute renal failure, mechanical ventilation, ICU stay, presence of shock, infective endocarditis, renal replacement therapy, concurrent Tx with gentamicin or rifampin, previous vancomycin or linezolid treatment
McKinnell et al.(1)	Neutropenic patients	None	Logistic regression	Mechanical ventilation, renal insufficiency, timing of antibiotics, transplant
Kraft et al.(10)	Bone marrow transplant patients	Patients with acute myeloid leukemia	No	n/a
Bio et al.(3)	Thrombocytopenic patients	ICU patients	Logistic regression	Age, APACHE II, venous catheter removal, ICU stay
Twilla et al.(2)	Patients with hematologic malignancies and liver transplants	Older patients	No	n/a

Abbreviations: ICU, Intensive Care Unit; n/a, not applicable; APACHE II, Acute Physiology and Chronic Health Evaluation II; CCI, Charlson co-morbidity index; Tx, Therapy.

Table S4. Dosages, treatment durations and adverse events in the studies comparing linezolid versus daptomycin for the treatment of VRE bacteremia

Study	Daptomycin				Linezolid			
	Daily dose (Median; range)	**Duration (Median; range)**	**Combination treatment**	**Adverse Events**	**Daily dose**	**Duration (Median; range)**	**Combination treatment**	**Adverse Events**
Furuya et al.(6)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
El-Lababidi et al.(9)	Not reported	Not reported	Not reported	None	Not reported	Not reported	Not reported	Thrombocytopenia 14% Pancytopenia 7%
Dubrovskaya et al.(5)	6 mg/kg; 4-9	15 days; not reported	Not reported	Thrombocytopenia	Not reported	15 days; not reported	Not reported	Thrombocytopenia
Marion et al.(7)	6 mg/kg; fixed dose	Not reported	Not reported	Not reported	600 mg b.i.d	Not reported	Not reported	Not reported
Mave et al.(8)	6 mg/kg; fixed dose	14 days; 2-42	Aminoglycosides 46.7%	Anaemia 10% Thrombocytopenia 10% Renal insufficiency 10%	600 mg b.i.d.	14 days; 2-42	Aminoglycosides 58.8%	Anaemia 11.8% Thrombocytopenia 11.8% Renal insufficiency 5.9%
Crank et al.(4)	6 mg/kg; 4-8	Not reported	Gentamicin 14.9%	Not reported	600 mg b.i.d.	Not reported	None	Not reported
McKinnell et al.(1)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Kraft et al.(10)	5.5 mg/kg; 4.5-6	13 days; 8.5-14	Not reported	Neutropenia: proportion not reported Thrombocytopenia: proportion not reported Renal insufficiency 9.3% LFTs>2times ULN 14%	600 mg b.i.d	11.5 days; 7-14	Not reported	Neutropenia: proportion not reported Thrombocytopenia: proportion not reported Renal insufficiency 7% LFTs>2times ULN 34.5%
Bio et al.(3)	6 mg/kg; 3.7-8.8 in patients with creatinine clearance <30ml/min administered every 48h	13 days; 3-91	No	Thrombocytopenia during therapy 6·3% CK elevation during therapy 5·4%	600 mg b.i.d	11 days; 3-62	No	Thrombocytopenia during therapy 18.4% CK elevation during therapy 4.3%
Twilla et al.(2)	6 mg/kg; 3.4-10.4	Not reported	No	Not reported	600 mg b.i.d	Not reported	No	Not reported

Abbreviations: b.i.d, twice a day; LFTs, Liver function tests; ULN, Upper limit of normal; CPK: creatine phosphokinase.

Table S5. Pooled analysis of adverse events in patients treated with daptomycin compared to those treated with linezolid for VRE bacteremia

Adverse events	No studies	Sample size	Method applied	Effect size, 95% CI
Anaemia	1	98	Fixed effects model, heterogeneity: n/a	OR: 0.83, (0.20, 3.39)
Thrombocytopenia	3	208	Fixed effects model, heterogeneity: p=0.37	OR: 0.41, (0.14, 1.18)
Pancytopenia	1	56	Fixed effects model, heterogeneity: n/a	OR: 0.19, (0.01, 4.05)
Renal insufficiency	2	170	Fixed effects model, heterogeneity: p=0.84	OR: 1.58, (0.49, 5.15)
Elevated CPK	2	172	Fixed effects model, heterogeneity: n/a	OR: 1.33, (0.18, 10.01)
LFTs > 2 times ULN	1	72	Fixed effects model, heterogeneity: n/a	OR: 0.31, (0.10, 0.98)

Abbreviations: CI, Confidence interval; n/a, not applicable; OR, Odds ratio; CPK: creatine phosphokinase; LFTs, Liver function tests; ULN, Upper limit of normal

Figure S1
PRISMA 2009 Flow Diagram