

# Clinical Outcomes Associated With Linezolid Resistance in Leukemia Patients With Linezolid-Resistant *Staphylococcus epidermidis* Bacteremia

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**Background.** Coagulase-negative staphylococci, including *Staphylococcus epidermidis*, are the most common cause of bloodstream infection in cancer patients. Linezolid resistance is increasingly identified in *S. epidermidis*, but whether such resistance alters the clinical course of *S. epidermidis* infections is unknown. The purpose of this study was to assess the clinical impact of linezolid resistance in leukemia patients with *S. epidermidis* bloodstream infection.

**Methods.** This was a retrospective, single-center cohort study of all adult leukemia patients with *S. epidermidis* bacteremia treated with empiric linezolid between 2012 and 2015. The primary end point was adverse clinical outcome on day 3, defined as a composite of persistent bacteremia, fever, intensive care unit admission, or death. Fourteen- and 30-day mortality were also assessed.

**Results.** Eighty-two unique leukemia patients with *S. epidermidis* were identified. Linezolid resistance was identified in 33/82 (40%). Patients with linezolid-resistant *S. epidermidis* were significantly more likely to have persistent bacteremia (41% vs 7%; adjusted relative risk [aRR], 5.15; 95% confidence interval [CI], 1.63–16.30;  $P = .005$ ); however, adverse short-term clinical outcomes overall were not more common among patients with linezolid-resistant *S. epidermidis* (61% vs 33%; aRR, 1.46; 95% CI, 0.92–2.32;  $P = .108$ ). No differences were observed in 14- or 30-day mortality.

**Conclusions.** Leukemia patients with linezolid-resistant *S. epidermidis* bacteremia who were treated with linezolid were significantly more likely to have persistent bacteremia compared with those with linezolid-sensitive isolates. Interventions to limit the clinical impact of linezolid-resistant *S. epidermidis* are warranted.

**Keywords.** antimicrobial stewardship; catheter-related bloodstream infection; febrile neutropenia; hematologic malignancy; staphylococci.

Coagulase-negative *Staphylococcus* (CoNS), including *Staphylococcus epidermidis*, are the leading cause of catheter-related bloodstream infections (BSIs) in the general hospital population and are responsible for 30% of BSIs in patients with hematologic malignancy [1]. The use of linezolid for infections suspected or known to be caused by Gram-positive bacteria is increasing due to the rise in drug-resistant microorganisms and concerns for nephrotoxicity caused by vancomycin [2, 3]. Globally, approximately 2% of CoNS are resistant to linezolid; however, resistance rates may be higher in institutions with high rates of linezolid usage [4, 5].

Clonal dissemination of linezolid-resistant *S. epidermidis* (LRSE) is increasingly reported in diverse settings worldwide,

although prior studies have not assessed the clinical impact of LRSE [6–11]. At our institution, LRSE occurs nearly exclusively in patients with leukemia and is associated with epidemic spread of a clonal complex 5 (CC5) strain with a *cfr*-harboring plasmid [5, 12]. A case-control study performed in Italy identified higher 30-day mortality in patients with linezolid-resistant compared with linezolid-susceptible staphylococci; however, no information was provided on the antimicrobials used for the treatment of these infections [13]. To our knowledge, no prior studies have examined mortality in relation to linezolid being used as treatment for LRSE BSI. Thus, we sought to test the hypotheses that LRSE bacteremia empirically treated with linezolid would have worse clinical outcomes in comparison with patients infected by linezolid-sensitive strains.

## METHODS

### Study Design

We performed a retrospective cohort study of adult patients (aged  $\geq 18$  years) with leukemia (including acute myeloid leukemia [AML], acute lymphoblastic leukemia [ALL], and others) or myelodysplastic syndrome (MDS) and laboratory-confirmed *S. epidermidis* bacteremia who received empiric

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linezolid treatment at the University of Texas MD Anderson Cancer Center from July 1, 2012, to July 22, 2015. Patients with prior hematopoietic stem cell transplant (HSCT) were included if in relapse at the time of *S. epidermidis* bacteremia. At our institution, CoNS are not routinely identified to the species level unless laboratory-defined criteria suggestive of true infection (ie, culture positivity from more than 1 blood draw site or >10 colony forming units [CFU] from a single site) are met. To further limit the reporting of contaminated blood cultures, cultures positive for <10 CFU of CoNS from a single site are not reported to the treating providers. CoNS that were not identified to the species level or CoNS species other than *S. epidermidis* were not included. Linezolid susceptibility was determined via Vitek 2 (bioMérieux, Marcy-L'Étoile, France) with a minimum inhibitory concentration (MIC) >4 µg/mL considered resistant, per current CLSI standards (<https://clsi.org/standards/products/microbiology/documents/m100/>); resistant isolates were confirmed by Etest (bioMérieux) per standard protocol in the clinical microbiology laboratory. Twelve isolates were missing data for the confirmatory Etest; these isolates were considered resistant based on prior experience demonstrating 100% concordance between Vitek 2 susceptibility testing and laboratory-confirmed resistance [12]. Patients were identified through microbiology laboratory records, and clinical information was collected from the electronic health record. Patients with more than 1 occurrence of *S. epidermidis* bacteremia were included only once.

#### End Points and Study Definitions

The primary end point was a composite of adverse short-term outcomes on day 3 after the index culture, defined as persistent bacteremia (isolation of *S. epidermidis* from blood ≥3 days after the index culture without an intervening negative blood culture), persistent fever (temperature ≥38°C on day 3), intensive care unit (ICU) admission, or death, each by day 3 following the index culture. Day 3 was chosen as this would approximate the time at which organism identification and susceptibility would be available and would therefore more closely reflect the impact of empiric therapy. As mortality due to this organism was expected to be low, 14-day and 30-day mortality were considered secondary outcomes. Other secondary outcomes consisted of individual components of the composite end point and time to blood culture clearance (ie, first recorded negative blood culture) within 7 days. Assessment of persistent bacteremia and time to blood culture clearance was limited to patients in which at least 1 follow-up blood culture was obtained. Empiric treatment with linezolid was defined as at least 1 dose of linezolid within 1 day of the date the positive index blood culture was obtained. Salvage chemotherapy was considered any chemotherapy administered after failed primary induction, relapsed disease, and/or enrollment in a clinical trial for either of these reasons. Severity of illness was assessed at the time of the index

blood culture using the Pitt bacteremia score, a validated scoring system based on mental status, vital signs, requirement for mechanical ventilation, and recent cardiac arrest [14]. This protocol was approved by the Institutional Review Board at MD Anderson Cancer Center with a waiver of informed consent. Data were collected via electronic chart review and stored using Research Electronic Data Capture (Vanderbilt University, Nashville, TN) [15].

#### Statistical Analysis

Baseline characteristics were compared using the Wilcoxon rank-sum and Fisher exact tests, with all comparisons made between patients with linezolid-resistant and linezolid-susceptible isolates. After univariate analysis, multivariate Poisson regression with robust variance estimates, adjusting for clinically relevant confounders, was performed for the primary composite end point and persistent bacteremia. Poisson regression was chosen over logistic regression as the dependent variables of interest had incidence rates greater than 10%, invalidating the assumption that the odds ratio approximates the relative risk [16]. No multivariate analyses were performed for other components of the composite end point as these were infrequent and not amenable to multivariate analysis. Fourteen- and 30-day mortality and time to clearance of bacteremia were assessed using multivariate Cox proportional hazards modeling and Kaplan-Meier curves. As blood cultures were not obtained on a daily basis for most patients, the first date of a documented negative culture was considered the first negative day for the survival analysis. Patients with no follow-up cultures performed were removed from the time-to-event analysis for clearance of bacteremia. Proportional hazards assumptions were verified by visual assessment of scaled Schoenfeld residuals. All multivariate models were constructed using a backwards stepwise approach, incorporating all variables with a univariate *P* value of .2 or less and removing those with the largest *P* value sequentially until only variables with a *P* value of .2 or less remained. Removal of the central venous catheter (CVC) was not included in multivariate models to avoid adjusting for a downstream consequence of persistent bacteremia. Statistical analyses were performed via STATA v14.1 (StataCorp LP, College Station, TX).

## RESULTS

#### Cohort Characteristics

Eighty-two unique patients (median age, 52 years; range, 39–67; 52% male) were included in the study. Overall, 33 (40%) of *S. epidermidis* isolates were LRSE, with an MIC<sub>50</sub> and MIC<sub>90</sub> of 2 mcg/mL and ≥256 µg/mL, respectively. Among the 33 resistant isolates, 30/33 (91%) displayed high-level resistance with MICs of ≥256 µg/mL. There were no statistically significant differences in clinical characteristics between patients with linezolid-resistant and linezolid-susceptible isolates (Table 1), except for neutropenia (absolute neutrophil count <500 cells/

mm<sup>3</sup>), at the time of first positive blood culture (97% vs 67%, respectively;  $P = .001$ ) and nosocomial onset (55% vs 29%, respectively;  $P = .022$ ). The majority of patients had acute myeloid leukemia (62%), followed by acute lymphoblastic leukemia (24%). In general, patients had been extensively treated for their leukemia, with 73% receiving salvage chemotherapy and 29% having previously received an allogeneic hematopoietic stem cell transplant. However, the study population was not acutely ill, as reflected in the low median Pitt bacteremia score (0; interquartile range [IQR], 0–1). Most patients had a CVC (93%), and removal of the CVC within 3 days of bacteremia onset was similarly infrequent among patients with and without linezolid-resistant isolates (17% in each group;  $P = .987$ ).

## Outcomes Assessment

### Composite Outcome

Seventy-four patients (90%) had at least 1 follow-up blood culture. Persistent bacteremia was significantly more common among patients with LRSE (41% vs 7%;  $P = .001$ ) and remained significantly more common after adjustment for confounders (adjusted relative risk [aRR], 3.97; 95% confidence interval [CI], 1.23–12.86;  $P = .021$ ). No significant differences were observed for other components of the composite end point, including persistent fever (27% vs 24%;  $P = .801$ ), ICU admission (15% vs 10%;  $P = .51$ ), and death by day 3 (3% vs 2%;  $P = 1.000$ ). Overall, the composite end point was significantly more frequent in patients with LRSE as compared with those with linezolid-susceptible bacteremia in univariate analysis (61% vs 33%;  $P = .023$ ), however, no significant difference was observed after adjustment for other confounders (aRR, 1.46;

95% CI, 0.92–2.32;  $P = .108$ ). Full Poisson regression models for the composite end point and persistent bacteremia are shown in [Tables 2 and 3](#).

### 14- and 30-Day Mortality

All deaths occurred among patients receiving salvage chemotherapy; therefore, mortality analysis was limited to this subgroup ( $n = 60$ ). A trend toward increased unadjusted and adjusted mortality at day 14 was observed for patients with LRSE vs those without (21% vs 8%; adjusted hazard ratio [aHR], 2.72; 95% CI, 0.43–17.22;  $P = .287$ ). Thirty-day mortality was higher on univariate analysis for patients with LRSE vs those without (33% vs 10%;  $P = .021$ ), although this difference was not significant when adjusted for confounders (aHR, 3.01; 95% CI, 0.72–12.69;  $P = .132$ ). The Kaplan-Meier curve for 30-day mortality is presented in [Figure 1](#), and the final regression models for 14- and 30-day mortality are presented in [Supplementary Tables 1 and 2](#).

### Time to Clearance of Bacteremia

The time to first negative blood culture was significantly longer for patients with LRSE bacteremia compared with those without (median, 5 days vs 3 days; log-rank  $P = .029$ ; hazard ratio [HR], 0.60; 95% CI, 0.41–1.02;  $P = .053$ ). Linezolid resistance was the only term retained in the backwards stepwise Cox model; therefore, no adjusted analyses were performed. The Kaplan-Meier curve for clearance of bacteremia is presented in [Figure 2](#).

## DISCUSSION

Although linezolid has been widely used for nearly 20 years with few reports of resistance in *S. epidermidis*, numerous reports

**Table 1. Cohort Characteristics**

Characteristic	Overall	Linezolid-Resistant	Linezolid-Susceptible	<i>P</i> Value
No. of patients	82 (100)	33 (40)	49 (60)	
Age, median (range), y	60 (39–67)	58 (23–79)	62 (18–87)	.505 <sup>a</sup>
Male gender	43 (52)	16 (48)	27 (55)	.654 <sup>b</sup>
Type of leukemia				.353 <sup>b</sup>
AML	51 (62)	23 (70)	28 (57)	
Other	31 (38)	10 (30)	21 (43)	
Salvage chemotherapy	60 (73)	28 (85)	32 (65)	.075 <sup>b</sup>
Previous HSCT	24 (30)	11 (33)	13 (27)	.622 <sup>b</sup>
ANC < 500 cells/mm <sup>3</sup>	65 (79)	32 (97)	33 (67)	.001 <sup>b</sup>
Pitt bacteremia score, median (IQR)	0 (0–1)	1 (0–2)	0 (0–1)	.053 <sup>a</sup>
Presence of CVC	76 (93)	30 (91)	46 (94)	.681 <sup>b</sup>
Bacterial colony count from CVC, CFU/mL				.707 <sup>b</sup>
<10	7 (9)	2 (6)	5 (10)	
≥10	40 (49)	15 (45)	25 (51)	
Not quantified	35 (43)	16 (48)	19 (39)	
Removal of CVC within 72 h	13 (17)	5 (17)	8 (17)	.987 <sup>b</sup>
Hospital onset	32 (39)	18 (55)	14 (29)	.022 <sup>b</sup>

All values are No. (%) unless otherwise specified.

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; CVC, central venous catheter; HSCT, hematopoietic stem cell transplant; IQR, interquartile range.

<sup>a</sup>Wilcoxon rank-sum test.

<sup>b</sup>Fisher exact test.

**Table 2. Poisson Regression Model for the Composite End Point**

Factor	Unadjusted Model			Adjusted Model		
	RR	95% CI	PValue	aRR	95% CI	PValue
LRSE	1.86	1.14–3.03	.013	1.46	0.92–2.32	.108
Age	1.00	0.99–1.02	.620	–	–	–
Male gender	1.23	0.75–2.02	.407	–	–	–
AML	2.13	1.11–4.08	.023	1.84	0.96–3.49	.064
Salvage chemotherapy	1.10	0.62–1.96	.747	–	–	–
Prior HSCT	1.21	0.73–2.01	.464	–	–	–
Neutropenia	1.74	0.79–3.85	.169	–	–	–
Pitt bacteremia score	1.18	1.10–1.27	<.001	1.09	1.00–1.18	.040
Presence of CVC	0.87	0.37–2.0	.744	–	–	–
Bacterial colony count from CVC				–	–	–
<10 CFU (ref)	–	–	–	–	–	–
>10 CFU	0.88	0.43–1.79	.715	–	–	–
Unknown	0.6	0.27–1.33	.207	–	–	–
Hospital onset	1.95	1.20–3.18	.007	1.49	0.90–2.49	.123

Composite end point: persistent bacteremia, fever, intensive care unit admission, or death within 3 days of index culture.

Abbreviations: AML, acute myeloid leukemia; aRR, adjusted risk ratio; CFU, colony-forming units; CI, confidence interval; CVC, central venous catheter; HSCT, hematopoietic stem cell transplant; LRSE, linezolid-resistant *Staphylococcus epidermidis*; RR, risk ratio.

of increasing numbers of LRSE in diverse clinical settings have recently been published [8–12, 17]. At our hospital, we have found that 40% of *S. epidermidis* strains causing bacteremia in leukemia patients were linezolid-resistant, which is far higher than previously reported rates [18]. Moreover, our data show that leukemia patients with *S. epidermidis* bacteremia treated empirically with linezolid had significantly longer durations of bacteremia without increased rates of ICU admission or short-term death when infected with linezolid-resistant vs linezolid-sensitive strains. Although this result may have been expected, it was not inevitable as in vitro susceptibilities do not always correlate with clinical response and *S. epidermidis* bacteremia may clear in the absence

of specific treatment due to low virulence of the organism [19, 20]. Although complications of *S. epidermidis* bacteremia are relatively rare, *S. epidermidis* is well described to cause metastatic infections such as vertebral osteomyelitis, infective endocarditis, and prosthetic joint infections, and we have observed multiple such complications in our patients [21]. Due to the uncommon nature of metastatic infections in patients with *S. epidermidis*, they were not specifically addressed in this study. Thus, further study is needed to assess the long-term implications of prolonged bacteremia with this organism.

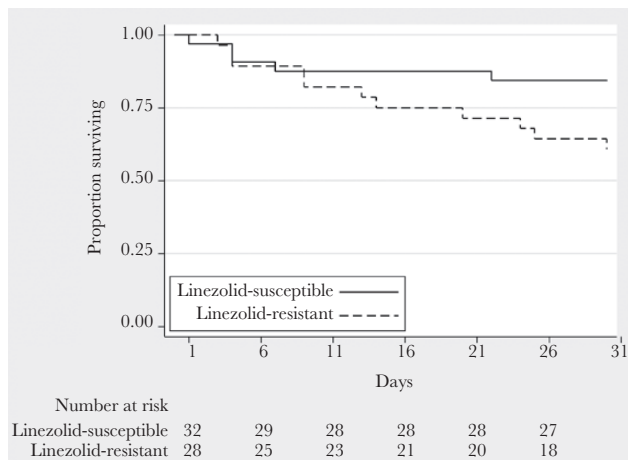
Previous studies have largely been unable to evaluate the significance of linezolid resistance in *S. epidermidis* due to the

**Table 3. Poisson Regression Models for Persistent Bacteremia at Day 3**

Factor	Unadjusted Model			Adjusted Model		
	RR	95% CI	PValue	aRR	95% CI	PValue
LRSE	6.21	1.90–20.28	.003	5.15	1.63–16.30	.005
Age	1.00	0.98–1.02	.924	1.03	1.00–1.05	.021
Male gender	1.14	0.46–2.85	.774	–	–	–
AML	8.52	1.17–62.16	.035	7.17	1.53–33.57	.012
Salvage chemotherapy	1.58	0.49–5.10	.440	–	–	–
Prior HSCT	3.32	1.33–8.30	.010	4.06	1.76–9.36	.001
Neutropenia	3.27	0.46–23.12	.236	–	–	–
Pitt bacteremia score	1.32	1.19–1.52	<.001	–	–	–
Presence of CVC	1.24	0.19–7.95	.824	4.00	0.56–28.49	.167
Bacterial colony count from CVC				–	–	–
<10 CFU (ref)	–	–	–	–	–	–
>10 CFU	1.80	0.27–12.19	.547	–	–	–
Unknown	1.09	0.15–8.07	.930	–	–	–
Hospital onset	1.88	0.76–4.64	.173	–	–	–

Limited to patients with 1 or more follow-up blood cultures (n = 74).

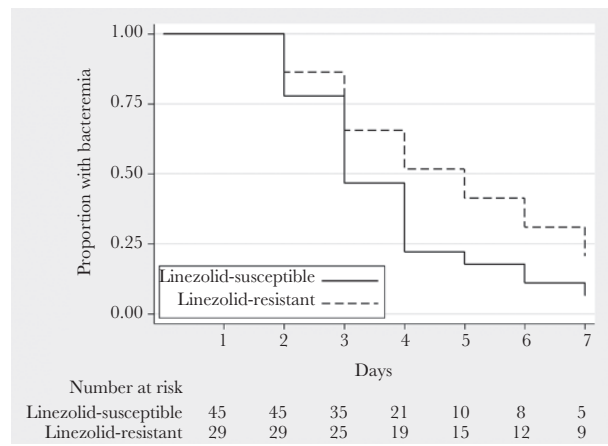
Abbreviations: AML, acute myeloid leukemia; aRR, adjusted risk ratio; CFU, colony-forming units; CI, confidence interval; CVC, central venous catheter; HSCT, hematopoietic stem cell transplant; LRSE, linezolid-resistant *Staphylococcus epidermidis*; RR, risk ratio.



**Figure 1.** Thirty-day mortality stratified by linezolid resistance status.

low incidence of linezolid-resistant isolates. The largest study to date of linezolid resistance in staphylococci, performed in Italy, demonstrated that hospitalized patients with linezolid-resistant isolates were generally more acutely ill and had higher 30-day mortality in comparison with those with linezolid-sensitive strains, although the impact of empiric therapy was not directly assessed [13]. In contrast, patients in our study were relatively homogeneous with regards to both severity of illness and underlying comorbidities, allowing for a direct assessment of linezolid resistance on clinical outcomes in patients treated empirically with linezolid. In our study, both 14- and 30-day mortality were numerically higher among patients with LRSE; however, neither was statistically significant on adjusted analysis. When viewed alongside the persistent bacteremia experienced by patients with LRSE, *S. epidermidis* may have played some role in the observed increase in mortality.

We have previously reported that rates of LRSE at our institution correlate directly with linezolid utilization, with 13 defined daily doses (DDDs) per 100 patient-days serving as a potential threshold for the emergence of resistance, and linezolid use in our leukemia service has consistently exceeded this threshold [5]. Furthermore, our group has recently identified that linezolid resistance in our institution is almost exclusively due to clonal spread of CC5 isolates harboring *cfr* and mutations in the L3 and L4 ribosomal proteins, with selection of linezolid resistance being largely attributable to prior linezolid exposure [12]. Other groups worldwide have also reported the emergence and clonal spread of CC5 isolates in settings where linezolid is commonly used [8, 10, 22, 23]. In light of these data, both infection control and antimicrobial stewardship appear to play an important role in limiting the further spread of LRSE. Thus, given the adverse clinical impact of linezolid resistance in *S. epidermidis* that we have identified and the potential for *S. epidermidis* to serve as a reservoir for dissemination of *cfr* [24], interventions to limit the emergence of LRSE are warranted. Implementation



**Figure 2.** Time to clearance of bacteremia stratified by linezolid resistance status.

of an antimicrobial stewardship program designed to optimize the use of linezolid has been shown to decrease the linezolid resistance rate in CoNS by 63%, with no significant impact on patient safety [25]. Other stewardship interventions and infection control measures are supported by current guidelines and may be similarly effective in reducing the use of linezolid and clonal spread of LRSE [26].

Our study has some limitations, including its retrospective, single-center design. Ideally, prospective studies investigating long-term outcomes in patients with LRSE bacteremia would be performed; however, due to the relative infrequency of these outcomes, such a study is unlikely. As our study was focused on empiric treatment, we did not directly assess the impact of antimicrobial changes or the impact of catheter removal after identification of LRSE. Our inclusion criteria accounted for laboratory-defined criteria for a true infection; however, a full clinical assessment addressing whether these were true *S. epidermidis* infections was not performed, but the high rates of persistent bacteremia that we observed strongly suggest that the majority of cases actually represented *S. epidermidis* bacteremia rather than blood culture contamination. Moreover, as all patients were treated with linezolid empirically, it is likely that any selection bias resulting from this inclusion criteria would be minimal. Lastly, centers do not use linezolid as empiric therapy in leukemia patients due to concerns for cytopenias. However, as linezolid resistance is being increasingly reported worldwide, these findings are likely to be applicable to any center with high rates of empiric linezolid use.

## CONCLUSIONS

Patients with LRSE bacteremia treated empirically with linezolid have persistent bacteremia and numerically increased mortality when compared with patients with linezolid-susceptible infections. Implementation of an antimicrobial stewardship program to optimize linezolid usage may contribute



to reducing the negative clinical impact of linezolid resistance among *S. epidermidis*.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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### References

1. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. *Clin Infect Dis* **2003**; 36:1103–10.
2. Lahoti A, Kantarjian H, Salahudeen AK, et al. Predictors and outcome of acute kidney injury in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome. *Cancer* **2010**; 116:4063–8.
3. Jaksic B, Martinelli G, Perez-Oteyza J, et al. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. *Clin Infect Dis* **2006**; 42:597–607.
4. Farrell DJ, Mendes RE, Ross JE, Jones RN. Linezolid surveillance program results for 2008 (LEADER Program for 2008). *Diagn Microbiol Infect Dis* **2009**; 65:392–403.
5. Mulanovich VE, Huband MD, McCurdy SP, et al. Emergence of linezolid-resistant coagulase-negative *Staphylococcus* in a cancer centre linked to increased linezolid utilization. *J Antimicrob Chemother* **2010**; 65:2001–4.
6. Lazaris A, Coleman DC, Kearns AM, et al. Novel multiresistance cfr plasmids in linezolid-resistant methicillin-resistant *Staphylococcus epidermidis* and vancomycin-resistant *Enterococcus faecium* (VRE) from a hospital outbreak: co-location of cfr and optrA in VRE. *J Antimicrob Chemother* **2017**; 72:3252–7.
7. Morroni G, Brenciani A, Vincenzi C, et al. A clone of linezolid-resistant *Staphylococcus epidermidis* bearing the G2576T mutation is endemic in an Italian hospital. *J Hosp Infect* **2016**; 94:203–6.
8. Rodriguez-Lucas C, Fernandez J, Boga JA, et al. Nosocomial ventriculitis caused by a methicillin- and linezolid-resistant clone of *Staphylococcus epidermidis* in neurosurgical patients. *J Hosp Infect.* **2018** Feb 16; [Epub ahead of print]. doi:10.1016/j.jhin.2018.02.011.
9. Freitas AR, Dilek AR, Peixe L, Novais C. Dissemination of *Staphylococcus epidermidis* ST22 with stable, high-level resistance to linezolid and tedizolid in the Greek-Turkish region (2008–2016). *Infect Control Hosp Epidemiol* **2018**; 39:492–4.
10. Dortet L, Glaser P, Kassis-Chikhani N, et al. Long-lasting successful dissemination of resistance to oxazolidinones in MDR *Staphylococcus epidermidis* clinical isolates in a tertiary care hospital in France. *J Antimicrob Chemother* **2018**; 73:41–51.
11. Weßels C, Strommenger B, Klare I, et al. Emergence and control of linezolid-resistant *Staphylococcus epidermidis* in an ICU of a German hospital. *J Antimicrob Chemother* **2018**; 73:1185–93.
12. Li X, Arias CA, Aitken SL, et al. Clonal emergence of invasive multidrug-resistant *Staphylococcus epidermidis* deconvoluted via a combination of whole-genome sequencing and microbiome analyses. *Clin Infect Dis.* **2018**; 67:398–406.
13. Russo A, Campanile F, Falcone M, et al. Linezolid-resistant staphylococcal bacteraemia: a multicentre case-case-control study in Italy. *Int J Antimicrob Agents* **2015**; 45:255–61.
14. Hill PC, Birch M, Chambers S, et al. Prospective study of 424 cases of *Staphylococcus aureus* bacteraemia: determination of factors affecting incidence and mortality. *Intern Med J* **2001**; 31:97–103.
15. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* **2009**; 42:377–81.
16. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* **2004**; 159:702–6.
17. Layer F, Vourli S, Karavasilis V, et al. Dissemination of linezolid-dependent, linezolid-resistant *Staphylococcus epidermidis* clinical isolates belonging to CC5 in German hospitals. *J Antimicrob Chemother* **2018**; 73:1181–4.
18. Flamm RK, Mendes RE, Hogan PA, et al. Linezolid surveillance results for the United States (LEADER Surveillance Program 2014). *Antimicrob Agents Chemother* **2016**; 60:2273–80.
19. Rogers KL, Fey PD, Rupp ME. Coagulase-negative staphylococcal infections. *Infect Dis Clin North Am* **2009**; 23:73–98.
20. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* **2006**; 42(Suppl 2):S82–9.
21. Otto M. *Staphylococcus epidermidis*—the ‘accidental’ pathogen. *Nat Rev Microbiol* **2009**; 7:555–67.
22. Weßels C, Strommenger B, Klare I, et al. Emergence and control of linezolid-resistant *Staphylococcus epidermidis* in an ICU of a German hospital. *J Antimicrob Chemother* **2018**; 73:1185–93.
23. Layer F, Vourli S, Karavasilis V, et al. Dissemination of linezolid-dependent, linezolid-resistant *Staphylococcus epidermidis* clinical isolates belonging to CC5 in German hospitals. *J Antimicrob Chemother* **2018**; 73:1181–4.
24. Cafini F, Nguyen le TT, Higashide M, et al. Horizontal gene transmission of the cfr gene to MRSA and *Enterococcus*: role of *Staphylococcus epidermidis* as a reservoir and alternative pathway for the spread of linezolid resistance. *J Antimicrob Chemother* **2016**; 71:587–92.
25. García-Martínez L, Gracia-Ahulfinger I, Machuca I, et al. Impact of the PROVAUR stewardship programme on linezolid resistance in a tertiary university hospital: a before-and-after interventional study. *J Antimicrob Chemother* **2016**; 71:2606–11.
26. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* **2016**; 62:e51–77.