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ORIGINAL ARTICLE

Spread of clonal linezolid-resistant *Staphylococcus epidermidis* in an intensive care unit associated with linezolid exposure

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Abstract

The aim of the study was to determine factors associated with spread of linezolid (LNZ)-resistant *Staphylococcus epidermidis* isolates in a surgical intensive care unit (ICU). A case-control study was conducted in one French adult surgical ICU. From January 2012 to December 2016, patients with at least a single positive LNZ-resistant *S. epidermidis* blood culture were matched to control with LNZ-susceptible *S. epidermidis* blood culture in a 1:4 manner. Cases were compared to controls regarding baseline clinical characteristics and LNZ exposure before positive blood culture. Bacterial isolates were genotyped by using pulsed-field gel electrophoresis (PFGE) and MLST. We identified 13 LNZ-resistant *S. epidermidis* isolates, 1 in 2012, 3 in 2014, 6 in 2015, and 3 in 2016. LNZ use increased steadily from 8 DDDs/100 patient days in 2010 to 19 in 2013 and further decrease by more of 50% in 2015 and 2016. The only independent risk factors associated to LNZ-resistant *S. epidermidis* isolation were length of stay in ICU before infection (OR 1.45; 95% CI 1.07–1.98), prior exposure to LNZ (OR 109; 95% CI 3.9–3034), and Charlson comorbidities score (OR 3.19; 95% CI 1.11–9.14). PFGE typing showed that all LNZ-resistant isolates were clonal belonging to ST2 and that LNZ-susceptible isolates were highly diverse. We report herein that previous exposure to LNZ substantially increased the risk of occurrence of LNZ resistance in *S. epidermidis* even in the case of clonal spread of LNZ-resistant isolates. These findings highlight the need for reducing the use of LNZ to preserve its efficacy in the future.

Keywords Linezolid · Antibiotic resistance · Risk factors · Genotyping · *Staphylococcus epidermidis*

Introduction

Coagulase-negative staphylococci (CoNS) are among the most important pathogens involved in hospital associated with bloodstream infections and infections related to vascular prosthetic devices [1]. A large proportion of nosocomial strains of CoNS are resistant to most of the available antibiotics [2]. Linezolid (LNZ) short-term safety, pharmacokinetics/pharmacodynamics profile, and clinical effectiveness as well could make it more attractive than vancomycin, especially in the ICU setting. However, three LNZ resistance mechanisms have been characterized so far: mutations in the domain V region of 23S rRNA genes, particularly a G2576T substitution; acquisition of the ribosomal methyltransferase gene *cfr*; and mutations in the ribosomal proteins L3 and L4 [3]. Both vertical and horizontal transmission of LNZ resistance may occur. LNZ-resistant CoNS are increasingly reported worldwide [4–8] .

We therefore conducted a case control study for a 5-year period in the surgical ICU of a French University Hospital to identify risk factors associated with LNZ-resistant *S. epidermidis*. We also characterized the molecular epidemiology of LNZ-resistant *S. epidermidis*.

Materials and methods

The study was performed in the surgical ICU of the University Hospital of Besancon. To identify risk factors, a case control

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study was performed. All patients, in whom LNZ-resistant *S. epidermidis* had been recovered in blood sample between 1 January 2012 and 31 December 2016, were included as case patients. If several episodes occurred, only the isolate from the first episode was considered. They were matched 1:4 with controls that had LNZ-susceptible *S. epidermidis* in blood sample. For each case, eligible controls were randomly selected.

Infection caused by *S. epidermidis* was defined when isolates were recovered from multiple blood cultures meeting criteria from the Centers for Disease Control and Prevention for significant bacteremia [9].

Staphylococcus epidermidis isolates were cultured and identified according to routine diagnostic procedures. Antimicrobial susceptibility testing was performed using disk diffusion methods according to EUCAST recommendations and LNZ MIC of LNZ-resistant isolates was determined using Etest®. A MIC > 4 mg/L defined LNZ resistance according to EUCAST guidelines [10].

Demographic and clinical data were collected retrospectively by reviewing the medical charts Administration of antibiotics in the month before admission was also documented. Global LNZ use in the surgical ICU was collected from the pharmacy database and expressed in defined daily doses (DDDs) per 100 patient days.

Bacterial isolates were genotyped by using pulsed-field gel electrophoresis (PFGE) as previously described [11] and clustered in pulsotypes according to international recommendations [12]. LNZ-resistant isolates were further characterized using the MLST scheme developed by Thomas et al. [13].

All variables were examined by univariate analysis using the chi-square or Fisher's exact test, as appropriate. Continuous variables were analyzed by Student's *t* test. All statistical tests were two-tails, and $P < 0.05$ was considered to be statistically significant. Multivariate analysis was performed by conditional logistic regression. Stepwise selection with an entry and stay level of $P = 0.1$ was used to build the final multivariate logistic regression model. The adjusted odds ratio (OR) and 95% confidence interval (CI) for the variables selected in the final model are reported. Statistical analyses were computed using the SPSS program version 24 (SPSS Inc., Chicago, USA).

Results

Patient characteristics

During the study period, 13 patients had positive blood cultures with LNZ-resistant *S. epidermidis* (1 in 2012, 3 in 2014, 6 in 2015, and 3 in 2016). The mean age was 65.7 ± 11 years, 10 (77%) were male, and all patients had received antibiotics within the previous month. Recent exposure to LNZ was reported in 12 (92.3%) patients (Table 1).

Antimicrobial susceptibility

All isolates had a LNZ MIC > 256 mg/L and were co-resistant to methicillin. Co-resistance was also observed with gentamicin (100% of isolates), ofloxacin (100%), rifampicin (31%), and teicoplanin (23%). No vancomycin resistance was observed.

Risk factors and outcome

In multivariate analysis (Table 1), length of stay in ICU before infection (OR 1.45; 95% CI 1.07–1.98), prior exposure to LNZ (OR 109; 95% CI 3.9–3034), and Charlson comorbidities score (OR 3.19; 95% CI 1.11–9.14) were associated with LNZ-resistant *S. epidermidis*.

There is no difference in mortality in ICU between the 2 groups ($p = 0.68$), even in the group of patients with blood stream infection (2/9 (22%) for cases vs 3/30 (30%) for controls, $p = 0.66$).

Linezolid use

The number of LNZ DDDs/100 patient days was 8 in 2010 and increased steadily until it more than doubled to 19 in 2013. LNZ consumption fell by more 50% to 8 DDDs/100 patient days in 2015 and 2016 (Fig. 1).

Molecular typing of bacterial strains

Sixty five isolates of *S. epidermidis* were genotyped: the 13 LNZ-resistant isolates shared the same PFGE pattern and the 52 LNZ-susceptible isolates showed different PFGE patterns than resistant ones. Globally, LNZ-susceptible isolates displayed a high genomic diversity when considering PFGE results. All LNZ-resistant isolates belonged to ST2.

Discussion

The effectiveness of LNZ against Gram-positive cocci and its favorable short-term safety profile have promoted its widespread use, leading in turn theoretically to the emergence and dissemination of LNZ resistance. In most of published surveillance studies, LNZ-resistant isolates were rare (< 1% in the LEADER surveillance program and 0.4% in the ZAAPS program) [14, 15].

Gu et al. reported a total of 351 LNZ-resistant CoNS cases and the majority from patients in North America (30.8%) and Europe (20%) [16]. LNZ administration is reported to be one of the most important risk factors for LNZ-resistant Gram-

Table 1 Univariate and multivariate analysis of risk factors for linezolid-resistant coagulase-negative *Staphylococcus* in intensive care unit patients

Variables	Cases ($n = 13$)	Controls ($n = 52$)	Univariate p value	Multivariate	
Age (years), mean ± SD	65.7 ± 118	57.9 ± 16.5	0.14	P	OR (IC 95%)
Male sex, *n* (%)	10 (77)	36 (69)	0.74		
Body mass index (kg/m^2), mean	27.6 ± 7.0	27.2 ± 5.45	0.77		
SAPSII score upon admission, mean	57.8 ± 19	51.9 ± 19.5	0.24		
Charlson score, mean ± SD	2.55 ± 1.97)	1.35 ± 1.9	0.012	0.031	3.19 (1.11–9.14)
Hospital admission cause*,					
Acute respiratory disease, *n* (%)	2 (15)	9 (17)	1		
Acute cardiovascular disease, *n* (%)	1 (7.7)	7 (13)	1		
Acute neurologic disease, *n* (%)	2 (15)	19 (37)	0.19		
Infectious disease, *n* (%)	3 (23)	11 (21)	1		
Other, *n* (%)	5 (38)	20 (38)	1		
Surgery, *n* (%)	12 (92.3)	24 (46)	0.02	NT	
Length of stay in ICU before H+, dy mean ± SD	21.8 ± 8	10.7 ± 6.9	< 0.01	0.018	1.45 (1.07–1.98)
Recent exposure to					
Any antibiotic, *n* (%)	13 (100)	44 (85)	0.34		
Linezolid, *n* (%)	12 (92.3)	8 (15)	< 0.01	0.006	109 (3.9–3034)
Length of use, dy mean ± SD	10.3 ± 7.7	4.13 ± 3.1	< 0.01	NT	
Presence of:					
Central venous catheter, *n* (%)	13 (100)	52 (100)	1		
Arterial catheter, *n* (%)	12 (92.3)	52 (100)	0.2		
Dialysis catheter, *n* (%)	10 (77)	18 (35)	0.02	NT	
Surgical drain, *n* (%)	11 (85)	38 (73)	0.49		
Blood stream infection, *n* (%)	9 (69)	30 (58)	0.66		
Length of stay in ICU after H+, dy mean ± SD	19.4 ± 11	19.2 ± 16.1	0.58		
Death in ICU, *n* (%)	3 (25)	9 (17)	0.68		

H+ positive hemoculture

*not exclusive

NT not included in the final model

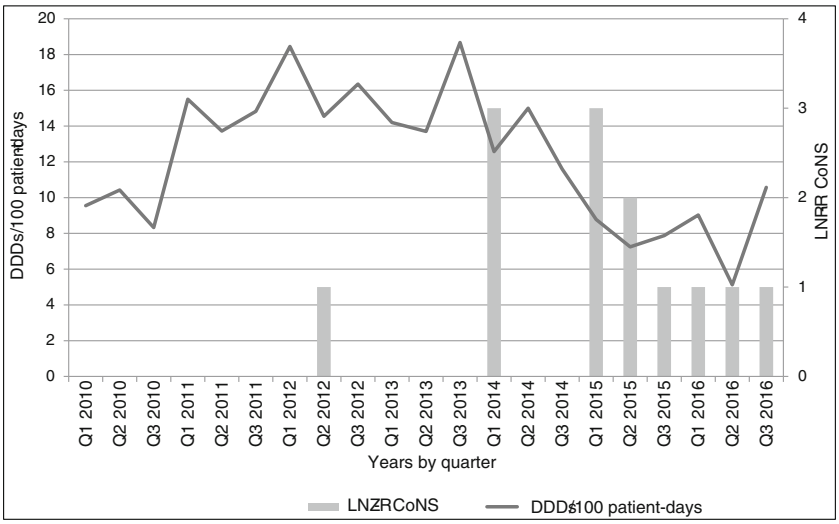

Fig. 1 Yearly hospital linezolid use in DDDs per 100 patient days and number of events from January 2010 until December 2016

positive cocci isolation in hospital outbreaks [17–22]. A review of studies that have identified risk factors associated with the isolation of LNZ-resistant CoNS was reported in Table 2.

The emergence of LNZ resistance in *S. epidermidis* in our ICU was associated with usage of LNZ, which has exerted a high selective pressure. However, it is worth noting that one out of 13 patients did not receive LNZ before resistant *S. epidermidis* isolated [23]. Other studies showed that being hospitalized near an already colonized patient increased the chances of acquiring such resistant microorganism [24, 25].

PFGE typing showed that all LNZ-resistant isolates belonged to the same pulsotype and that LNZ-susceptible isolates were highly diverse. These findings showed the emergence of a clonal spread of LNZ-resistant *S. epidermidis* in the ICU that persisted despite a decreased of LNZ consumption.

Beside previous exposure to the drug, we identified the Charlson comorbidities score elevation as an independent risk factor for the isolation of LNZ-resistant *S. epidermidis*, suggesting that patients with comorbidities were likely to acquire such difficult-to-treat bacteria. One explanation of this finding is that patients with comorbidities require more care, more admission in hospitals, so more opportunities to acquire resistant bacteria. Moreover, increased length of stay was also found to be an important risk factor for LNZ-resistant strains isolated, which confirms our hypothesis. LNZ exposure was probably a factor permitting the emergence of the clone and participate of these diffusion with cross transmission.

Treatment options for LNZ-resistant CoNS are limited and are based on current in vitro susceptibility data. LNZ-resistant CoNS remain universally susceptible to vancomycin, daptomycin, and tigecycline.

Density of LNZ exposure also plays a key role in the emergence of resistance, and it has been suggested that defined daily dose (DDD) longer than 13–15 days generate enough selective pressure to trigger outbreaks [18, 26]. According to our data, the average number of days treated with LNZ was 10.3, and 8 patients (60%) had been treated with LNZ for at least 13 days. Previous use of LNZ before isolation of resistant strain and LNZ DDDs consumption in different studies were reported in Table 3. In France, in 2016, the median [min-max]

Table 2 Studies that have identified risk factors with the isolation of linezolid resistant coagulase-negative staphylococci

Authors	Years	Country	Ward of occurrence	Number of isolates	Study design	Factors associated with LNZ-resistant strain
Our study	2019	France	ICU	13	Case control study (1:4)	- Charlson score OR 3.19 (1.11–9.14) - Length of stay in ICU before H+ OR 1.45 (1.07–1.98) - Recent exposure to LNZ OR 109 (3.9–3034)
Balandin et al.	2015	Spain	ICU	49	Retrospective study	Correlation between LNZ consumption and the prevalence of LNZ resistant strain ($p < 0{,}005$)
Bouiller et al.	2017	France	ICU	66	Case control study (1:2)	- SOFA score OR 1.17 (1.06–1.29) - LNZ OR 9.71 (4.29–21.74)
Papadimitriou-Olivgeris et al.	2013	Greece	ICU	33	Case-case control study	- Days at risk OR 1.2 (1.1–1.3) - Use of linezolid OR 27.2 (5.3–138.8) - Resistant strain in patients in nearby beds per day OR 32.6 (2.3–472.5)
Potoski et al.	2005	Hungary	University hospital	25	Case-case control study	- Receipt of LNZ OR 20.6 (5.8–73) - Location in ward C OR 12.4 (3.4–45.5)
Ramirez et al.	2013	Spain	Single tertiary referral center	NA	Prospective observational/interventional study	- Correlation between LNZ consumption and the prevalence of LNZ resistant strain ($p < 0{,}005$) - Correlation was more important with inadequate use of LNZ
Russo et al.	2015	Italy		38	Case-case control study	- Previous LNZ therapy OR 4.5 (2.89–7.12) - LNZ therapy > 14 days OR 5.9 (3.91–9.23) Antibiotic therapy > 14 days OR 4.4 (2.76–6.12) - Previous use of at least two antibiotics OR 3.1 (1.93–5.12) - Hospitalization in previous 90 days OR 2.1 (1.87–2.95) - Antibiotic therapy in previous 30 days OR 3.1 (1.45–6.23)

LNZ linezolid, *ICU* intensive care unit, *H+* positive hemoculture, *NA* not available

Table 3 Previous use of LNZ before isolation of resistant strain and LNZ DDDs consumption in different studies

Authors	Years	Country	Ward of occurrence	Number of isolates	Previous LNZ use	Duration, days	LNZ DDDs/100 patients day, median [min-max]
Our study	2019	France	ICU	13	92.3%	Mean (SD) 10.3 (7.7)	14 (5–19)
Balandin et al.	2015	Spain	ICU	49	87.7%	Median (IQR) 11 (7–15)	13 [8–14]
Baos et al.	2013	Spain	ICU	Infection ($n = 52$) colonization ($n = 48$)	Infection 90% colonization 58.3%	> 10 days: 89% (infection) 78.5% (colonization)	NA
Bouiller et al.	2017	France	ICU	66	74.2%	mean (range) 7.2 (2–18)	9.9 [5.9–9.9]
Dortet et al.	2017	France	ICU and surgical unit	168	100%*	Median (IQR)* 18 (13–27)	14 [0–35]
Kelly et al.	2008	Ireland	ICU	16	62.5%	Mean (range) 24.5 (4–83)	NA
Li et al.	2018	USA	Cancer center	39	79%	Median (range) 12 (3–22)	17 (2–14)
Liakopoulos et al.	2010	Greece	3 hospitals	26	46%	Range (< 14–84)	NA
Mihaila et al.	2012	France	ICU	18	100%	Mean (range) 18.7 (6–59)	> 13
Mulanovich et al.	2010	USA	Cancer center	27	100%	Median (range) 16 (8–37)	5.2 (3.7–7) 13.3 in leukemia service
Papadimitriou et al.	2013	Greece	ICU	33	76%	NA	NA
Potoski et al.	2005	Hungary	University hospital	25	80%	Mean (range) 10.3 (3–44)	13.6 in ICU A 1.11 (0.61–1.74) in all hospital
Pournaras et al.	2013	Greece	University hospital	27	92.6%	Mean (SD) 12.9 ± 7.4	NA
Russo et al.	2015	Italy	3 university hospital	38	44.7%	Mean (SD) 21.4 (4.2)	NA
Seral et al.	2011	Spain	ICU	27	71%	Mean (range) 12.9 (7–22)	NA
WeBels et al.	2017	Germany	ICU	14	93%	Mean (range) 15 (6–32)	13 (2.02–20.4)

*Analysis of 23 patients

LNZ linezolid, *ICU* intensive care unit, *DDD* defined daily dose

of LNZ use in 29 intensive care units was 3.2 DDJ/100 patient days [0.1–16.6] (ATB-Raisin surveillance network) [27]. These results showed an important disparity of LNZ use in French ICUs and confirmed a high consumption of these in our hospital.

Taken together our findings suggest that increasing LNZ use produced selective pressure likely to promote resistant strain selection. Patient's cross-transmission has contributed to the outbreak since patients without prior exposure required a longer time in the ICU before isolation of LNZ-resistant CoNS.

Of note all isolates tested in the present study were clonal by PFGE and belonged to ST2, which is a common *S. epidermidis* lineage in Europe [17, 28]. There are nine main clonal lineages composing the nosocomial *S. epidermidis* population worldwide. Also, strains of ST2, ST5, and ST22 are clustered into CC5 which is the most prevalent clonal complex regarding the nosocomial *S. epidermidis* population [13]. Mihaila et al. reported an outbreak of bloodstream infections with LNZ-resistant *S. epidermidis* and *Staphylococcus pettenkoferi* in an ICU in Paris [29]. Their analysis revealed that cross-infection was responsible of the acquisition of the LNZ-resistant CoNS, and they concluded that the emergence of these strains was rather the result of transmission of clonal strains than the selection of resistant mutants under therapeutic treatment. In our study, an overlapping hospital stays were present for 7 patients (54%), which confirm the important role of cross-transmission in the emergence of this clone.

Our study has limitations. Data were collected retrospectively, and the control group was chosen from among patients with non-LNZ-resistant *S. epidermidis*. However, this design may bias results and lead to an overestimation of the OR, particularly with regard to previous exposure to antibiotics [30].

Author contributions K.B. analyzed the data, K.B. wrote the manuscript with support from X.B and C.C. X.B., P.H.W, and C.C conceived the study, P.C performed bacteriological analysis. D.I. and P.H.W collected data. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

Compliance with ethical standards

Ethics approval and consent to participate Not applicable. According to French legislation in this period, and because no intervention was performed on patients, no written informed consent was given by the patients.

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