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Impact of the PROVAUR stewardship programme on linezolid resistance in a tertiary university hospital: a before-and-after interventional study

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Background: There is little evidence of the impact of antimicrobial stewardship programmes on antimicrobial resistance.

Objectives: To study the efficacy and safety of a package of educational and interventional measures to optimize linezolid use and its impact on bacterial resistance.

Methods: A quasi-experimental study was designed and carried out before and after implementation of a stewardship programme in hospitalized patients with Gram-positive infections treated with linezolid.

Results: The intervention reduced linezolid consumption by 76%. The risk of linezolid-resistant CoNS isolates (OR=0.37; 95% CI=0.27–0.49; $P<0.001$) and *Enterococcus faecalis* (OR=0.44; 95% CI=0.21–0.90; $P=0.03$) during the intervention period was lower than in the pre-intervention period.

Conclusions: A programme to optimize linezolid use can contribute to reducing the resistance rate of CoNS and *E. faecalis* to this antibiotic.

Introduction

Inadequate antimicrobial treatment favours the development of antimicrobial resistance and increases morbidity, mortality and costs.[1–3] The emergence of linezolid-resistant strains is a growing problem.[4] To combat this problem, the development of programmes to enhance antimicrobial stewardship is recommended. Some educational and interventional measures have proven effective.[5–7]

In this work, we studied the efficacy and safety of a package of educational and interventional measures to optimize the use of linezolid and its impact on *Staphylococcus* spp. and *Enterococcus* spp. resistance to linezolid.

Methods

Review of guidelines

Guidelines for linezolid use were established institutionally by the Pharmacy and Therapeutics Committee of the Hospital Universitario Reina Sofía (HURS), in Córdoba, Spain, following a systematic review of the literature by infectious diseases specialists (C. N., E. V. and J. T.-C.). The studies were retrieved from the PubMed database using the following search terms: linezolid AND outcome OR efficacy OR mortality OR death. Observational or randomized studies that examined the following efficacy parameters were selected: clinical cure, microbiological cure, mortality, complications and recurrence. Only observational studies using accepted methods for controlling confounding variables (controlled designs and multivariate or stratified analyses) were selected. The guidelines chosen from among those established in the literature were discussed and finally adopted as an institutional antibiotics policy.

Setting

HURS is a 1200 bed tertiary university hospital, which has an institutional programme to optimize antimicrobial use [*Programa Institucional de Optimización del Uso de Antimicrobianos* (PROA)] and an antimicrobial stewardship team consisting of specialists in antimicrobial use from different units co-ordinated by infectious diseases specialists. The activities of PROA follow recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology. PROVAUR, the Programme for the Validation of Guidelines for Restricted-Use Antibiotics (*Programa de Validación de la Indicación de Antibióticos de Uso Restringido*) was set up within the framework of PROA.

Study design

To assess the utility of the PROVAUR programme, a quasi-experimental study was designed before (November 2011–October 2012) and during

Table 1. Measures in the pre-intervention and intervention periods of the PROVAUR programme

Period	Activity
Pre-intervention	(1) Linezolid was dispensed after non-standardized written justification of the indication for which it was prescribed. (2) The pharmacy issued a quarterly report of global pharmaceutical expenditure for each department. (3) Active 'bacteraemia programme' consisting of an unrequested consultation with an infectious disease specialist for all cases of bacteraemia. This included non-structured recommendations for patient management and targeted treatment. (4) Consultant infectious disease specialists were available. (5) Request for help from specialists in dosing and monitoring vancomycin pharmacokinetics. (6) Non-structured meetings to analyse expenditure on medicines in the hospital and in each unit.
Intervention	(1) The intervention was authorized by the institution. (2) The intervention was explained to all department heads, who accepted the intervention in writing and appointed a departmental-level programme manager. (3) The intervention was explained to each department in educational clinical sessions. (4) The pharmacy and therapeutics committee updated guidelines for linezolid use and informed all prescribing services. (5) A standardized prescription form was developed by selecting the approved indication for which the drug was prescribed. (6) The prescription was validated on the next working day by a member of the antimicrobial stewardship team. (7) The pharmacy issued a quarterly report on the global pharmaceutical expenditure of each department. (8) A report on the DDD per 1000 patient-days, global expenditure and antimicrobial expenditure was presented twice yearly at a meeting attended by the HURS medical director, clinical unit directors and the antimicrobial stewardship team. (9) The bacteraemia programme and consultation with infectious diseases specialists was maintained. (10) Request for help by specialists for pharmacokinetic dosing and monitoring of vancomycin was maintained. In patients with non-validated linezolid prescriptions, unrequested assessment of vancomycin dosing and monitoring was performed when indicated.

the intervention (November 2012–October 2014). This study was carried out in all wards. Patients prescribed linezolid (in addition to the rest of the listed restricted-use antimicrobials) were identified daily through the prescription drugs computer system (Farmatools®). The antimicrobial stewardship team was provided daily with a standardized list of all patients prescribed linezolid (name, clinical history number, bed, dose and day of prescription), which was prepared by the pharmacy.

The activities carried out before the intervention and the package of interventional measures are summarized in Table 1. The core activity of the intervention consisted of a personal interview between the patient's attending physician and the specialist from the antimicrobial stewardship team, who jointly reviewed the case and analysed the appropriateness of the prescription and therapeutic alternatives [prescription validation interview (PVI)]. Consensus did not have to be reached between the attending physician and the prescribing physician. For the specialist to validate the prescription, it had to comply with the institutionally approved guidelines. The pharmacy was informed by telephone or e-mail of the validation to continue dispensing the drug. Non-validated antibiotics were substituted for alternative treatments upon recommendation by the specialist. All patients were followed up until discharge or death and survival was evaluated at 14 and 30 days by telephone. The data were collected by non-blinded researchers.

In the 6 months prior to the intervention, non-structured activities were carried out to reduce overall spending in the hospital, including high-cost antibiotics such as linezolid (meetings to review overall spending per unit, personal interviews on spending with directors of units and prescribing physicians). Other concurrent interventions in the community or hospital setting that could affect the level of resistance of the studied microorganism were not performed.

Ethics

The study was approved by the HURS Ethics Committee (approval number 3130), which waived the need to obtain written informed consent. All data collected were anonymized. The analysis is presented following the STROBE recommendations (Table S1, available as Supplementary data at *JAC* Online).[8]

Variables and definitions

The primary variable of the quasi-experimental study was the risk of MRSA, CoNS and *Enterococcus* spp. resistant to linezolid. The secondary variables included: (i) risk of resistance to vancomycin and daptomycin; (ii) appropriateness of prescribing linezolid; (iii) crude mortality at 14 and 30 days of sentinel events [bacteraemia due to MRSA, ventilator-associated pneumonia (VAP) caused by any bacteria and VAP due to MRSA]; (iv) linezolid, vancomycin and daptomycin consumption (DDD/1000 patient-days); and (v) degree of acceptance of the programme. Teicoplanin was not included in the study due to very low consumption of this antibiotic in our institution. In our hospital, tigecycline was not used for resistant Gram-positive infections. Ceftaroline was not marketed in Spain at the time of the study.

Only one isolate per patient was considered. We examined all clinical specimens and tested the first isolate obtained from each microorganism. Identification and susceptibility testing was performed by microdilution (Dade MicroScan, Sacramento, CA, USA). MICs were classified according to the EUCAST breakpoints.

Prescription of linezolid was considered appropriate when it complied with the institutionally approved guidelines and was subsequently validated. In the pre-intervention period, the appropriateness of the prescription was assessed by a retrospective chart review using the indications accepted in the pre-intervention period. The DDD per 1000 patient-days was calculated following the methodology of the Anatomical Therapeutic Chemical (ATC)/DDD system 2014 developed by the Drug Utilization Research Group and the Nordic Council of Medicines, which is periodically revised and updated by the WHO International Working Group for Drug Statistics Methodology (available at http://www.whocc.no).

Acceptance of the programme was evaluated by means of an anonymous and voluntary questionnaire in which the respondents were asked to state their opinion about the utility of the programme. The questionnaire is provided in Table S2.

Statistics

The results are presented using the mean, standard deviation (descriptive data) or standard error (estimations) and 95% CI for quantitative data. Qualitative data are summarized using frequency and percentages. Logistic regression models considering the binomial distribution were fitted to the data on occurrence of antimicrobial resistance to determine significant changes in the risk of resistance from pre- to post-intervention. OR measures were obtained. Furthermore, where possible, joint-point log linear regression was used to estimate the trend over time. The analysis was performed in SPSS version 19. Statistical tests were carried out at the 5% significance level.

Results

Systematic review and definition of guidelines

The search yielded 67 articles for review. The institutionally approved guidelines in each period are provided in Table 2.

Analysis of the impact of the intervention on antimicrobial use and prescription appropriateness

The intervention period was 2 years. No significant difference in the number of patient-days during the periods was found.

The average monthly consumption of linezolid and other complementary antibiotics is shown in Table 3. The proportion of inadequate treatments decreased from 64.4% to 39.9% ($P<0.001$).

Impact of the intervention on antimicrobial resistance (Table 4 and Figure 1)

CoNS

The odds of resistance to linezolid during the pre-intervention period were 2.70 times higher than in the post-intervention period. In fact, the lower risk of linezolid resistance was associated with the reduction in linezolid consumption, since a model adjusted by DDD per 1000 patient-days of linezolid consumption showed a change in the OR. The change was explained by the quantity of linezolid consumed (OR 1.07 per unit increase of DDD per 1000 patient-days of linezolid consumption; $P<0.001$; 95% CI = 1.03–1.11).

Segmented regression analyses were performed to check the trend of linezolid resistance and detect a change point during the study period. The incidence of linezolid-resistant CoNS in the intervention period decreased over time. Segmented regression analysis applied to the monthly percentage of linezolid-resistant CoNS showed a 2.37% reduction 6 months prior to the intervention and a progressive, average monthly reduction of 0.10% ($P<0.001$) (Figure 1).

The risk of vancomycin-resistant isolates was not significantly different during the pre- and post-intervention periods.

Staphylococcus aureus

The risk of resistance to linezolid or vancomycin was not significantly different during the pre- and post-intervention periods. Resistance to daptomycin was not observed.

Table 2. Institutionally approved guidelines for linezolid use in the pre-intervention and post-intervention periods

Period	Authorized guidelines
Pre-intervention	- Treatment of nosocomial pneumonia when vancomycin is not indicated.
Post-intervention	- Nosocomial pneumonia caused by methicillin-resistant *Staphylococcus* spp. (including VAP) with microbiological evidence. - CNS infections due to *Staphylococcus* spp. - Severe infections caused by *Staphylococcus* spp. or *Enterococcus* spp. with a vancomycin MIC >1.5 mg/L. - Vancomycin intolerance or toxicity. - Treatment of severe methicillin-resistant Gram-positive infections in patients with renal impairment (creatinine clearance of <50 mL/min/m^2 or patients undergoing renal replacement therapy). - Second-line treatment of MDR-TB when no other alternative therapies exist. - Second-line treatment of rare MDR infections such as nocardiosis when no other alternative therapies exist.

Table 3. Impact of the intervention on antimicrobial consumption

	Antimicrobial consumption	
	monthly DDD/1000 patient-days, mean (SD)	*P*
Linezolid		
pre-intervention	19.44 (5.55)	<0.001
intervention	4.57 (1.78)	
Daptomycin		
pre-intervention	5.4 (1.80)	0.289
intervention	2.0 (0.64)	
Vancomycin		
pre-intervention	18.0 (4.97)	0.441
intervention	23.1 (5.92)	

P values were determined using Student's *t*-test or the Mann–Whitney test as appropriate. Level of statistical significance was set at $P \leq 0.05$.

Enterococcus faecalis

The odds of resistance to linezolid during the pre-intervention period were 2.27 times higher than during the post-intervention period. In fact, the reduction in the risk of linezolid resistance was related to the reduction in linezolid consumption, since a model adjusted by DDD per 1000 patient-days of linezolid consumption showed a change in the OR explained by the quantity of linezolid consumed (OR 1.06 per unit increase of DDD per 1000 patient-days of linezolid consumption; $P<0.001$; 95% CI = 1.05–1.08). Segmented regression analyses were performed for the incidence

Table 4. Risk of drug resistance during intervention

	Resistance, *n*/*N* (%)		Non-adjusted model OR (95% CI); *P*	Model adjusted by DDD/1000 patient-days OR (95% CI); *P*
	pre-intervention	intervention		
CoNS				
linezolid	108/2707 (4)	76/5050 (1.5)	0.37 (0.27–0.49); <0.001	1.05 (0.53–2.08); 0.88
vancomycin	4/2707 (0.15)	9/5050 (0.18)	1.21 (0.37–3.39); 0.75	0.46 (0.04–5.10); 0.53
S. aureus				
linezolid	8/1872 (0.43)	16/4137 (0.39)	0.90 (0.39–2.12); 0.82	0.99 (0.13–7.74); 0.99
vancomycin	1/1872 (0.05)	9/4137 (0.22)	4.08 (0.51–32.22); 0.18	13.20 (0.10–1823.39); 0.30
E. faecalis				
linezolid	17/1791 (0.94)	13/3118 (0.42)	0.44 (0.21–0.90); 0.03	1.80 (0.27–12.17); 0.55
vancomycin	8/1791 (0.45)	8/3118 (0.26)	0.57 (0.21–1.53); 0.27	6.20 (0.33–116.47); 0.22
daptomycin	2/1791 (0.11)	2/3118 (0.06)	0.57 (0.08–4.08); 0.58	1.90 (0.01–382.42); 0.81
E. faecium				
linezolid	7/294 (2.38)	0/456 (0)	NA	NA
vancomycin	0/294 (0)	3/456 (0.66)	NA	NA
daptomycin	1/294 (0.34)	4/456 (0.88)	2.59 (0.29–23.31); 0.40	1.28 (0.01; 144.76); 0.92

N, total isolates; *n*, resistant isolates; NA, not applicable.
CoNS or daptomycin-resistant *S. aureus* isolates were not observed.

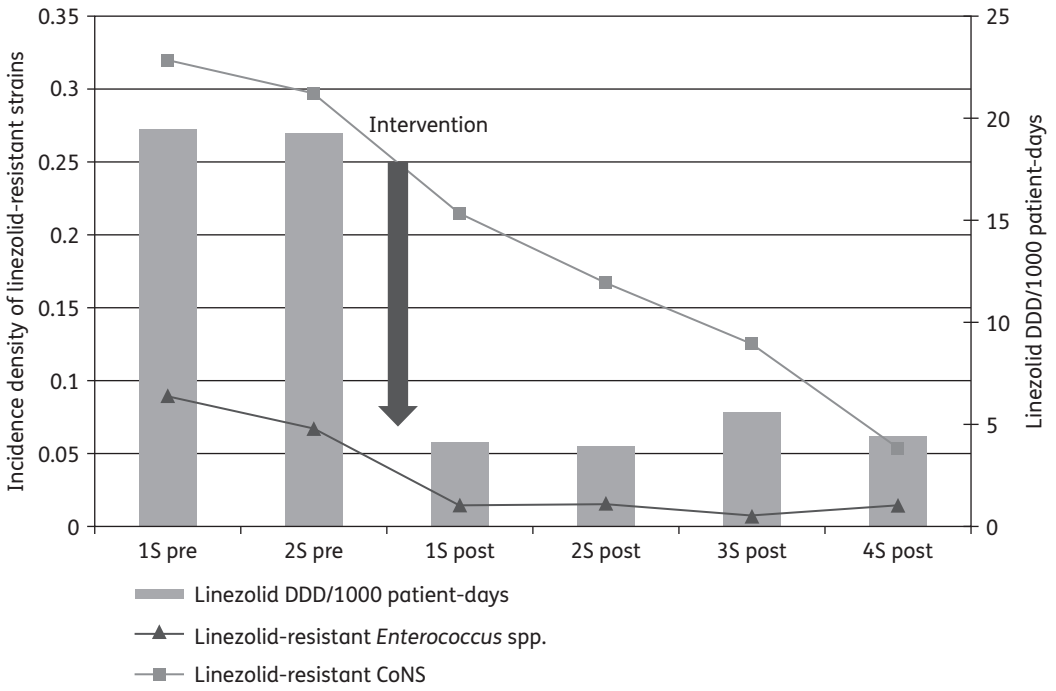

Figure 1. DDD of linezolid per 1000 patient-days versus the incidence density of linezolid-resistant strains, by semester, from November 2011 to October 2014. Arrow indicates time of the intervention. 1S pre, first semester pre-intervention; 2S pre, second semester pre-intervention; 1S post, first semester post-intervention; 2S post, second semester post-intervention; 3S post, third semester post-intervention; 4S post, fourth semester post-intervention.

of linezolid resistance. No change in the slope of resistance to linezolid was observed ($P=0.229$).

The risk of resistance to vancomycin and daptomycin was similar during the pre- and post-intervention periods.

Enterococcus faecium

No significant differences were found for the risk of antimicrobial resistance during the pre- and post-intervention periods.

Table 5. Impact of the intervention on sentinel event survival

	Survival at 14 days			Survival at 30 days		
	yes	no	*P*	yes	no	*P*
MRSA bacteraemia, *n* (%)						
pre-intervention (*N*=29)	22 (75.9)	7 (24.1)		19 (65.5)	10 (34.5)	
intervention (*N*=50)	39 (78.0)	11 (22.0)	0.827[a]	34 (68.0)	16 (32.0)	0.821[a]
VAP, *n* (%)						
pre-intervention (*N*=68)	56 (82.3)	12 (17.6)		42 (61.7)	26 (38.2)	
intervention (*N*=117)	94 (80.3)	23 (19.6)	0.736[a]	74 (63.2)	43 (36.7)	0.841[a]
VAP caused by MRSA, *n* (%)						
pre-intervention (*N*=8)	4 (50.0)	4 (50.0)		2 (25.0)	6 (75.0)	
intervention (*N*=14)	12 (85.7)	2 (14.3)	0.192[b]	10 (71.4)	4 (28.6)	0.096[b]

n, patients with event who are alive at the end of the period; *N*, total patients with event.
[a]χ^2 test.
[b]Fisher's test.

Impact of the intervention on sentinel event survival rate

Table 5 shows the impact of the intervention on certain events defined as sentinel. MRSA bacteraemia and VAP (global and MRSA) survival rates did not increase because of the intervention.

Acceptance of the PROVAUR programme

Two hundred and fifty questionnaires were distributed to the prescribers, of which 228 (91.2%) were completed. Of these, 201 physicians (88.2%) responded they were familiar with the programme, 226 (99.1%) stated that the programme was useful and 215 (94.3%) said they were satisfied with its implementation.

Discussion

Our study shows a temporal relationship between the overall intervention programme (including educational activities) and reduction in the resistance of CoNS and *E. faecalis* to linezolid associated with the reduction in the consumption of this antibiotic. Nevertheless, in the case of CoNS, the segmented regression analysis showed that the change in the trend began to be observed 6 months prior to the intervention. The most interesting finding of our study is that the reduction in linezolid use had an immediate ecological impact on linezolid resistance. Another previous experience using a non-educational strategy has also associated linezolid resistance with the appropriate use of this antibiotic.[9]

There is abundant evidence that different institutional strategies to optimize antimicrobial use have an immediate impact on the appropriateness of the prescription and consumption.[7,10] These effects have also been found in our study. It is generally accepted that restrictive interventions have an immediate effect but are poorly accepted and difficult to maintain over time.

However, other programmes based on non-restrictive educational strategies may be as effective and more widely accepted when they are not limited to a single group of antibiotics.[10] For this reason, the intervention strategy used in our programme was 2-fold. Given the overuse of linezolid (19.38 DDD/1000 patient-days and 64.4% of inappropriate prescriptions), the scientific information was reviewed and a restrictive programme based on a standardized prescription following the approved guidelines was established. This restrictive measure was complemented by a PVI conducted by a specialist from the antimicrobial stewardship team. The PVI had a fundamentally educational objective, as it consisted of a review of the guidelines between the attending physician and the specialist, who discussed the appropriateness of prescribing linezolid and possible therapeutic alternatives. The PVI formed part of a broader programme that affected other restricted antibiotics. This explains that the reduction in linezolid use did not result in an increase in daptomycin use. The strategy has proved useful and safe. It was also well accepted, as 94.3% of prescribers who were familiar with the programme stated that they were also satisfied with it.

The rapid and positive impact of the programme on the percentage of linezolid-resistant CoNS and *E. faecalis* strains was striking. There is evidence that prior use of linezolid is a risk factor for infection by a resistant strain.[4,11,12] As regards hospital ecology, there is evidence that the overuse of linezolid is associated with an increase in the resistance of Gram-positive bacteria to the antibiotic.[4,11–13] It is therefore reasonable to consider optimizing the use of linezolid within the framework of measures to control resistance. Some limited experiences have corroborated the usefulness of this recommendation.[9,14] The *Zyvox Annual Appraisal of Potency and Spectrum* report estimated linezolid resistance to be 0.9% for CoNS, 0.8% for *Enterococcus* spp. and <0.1% for MRSA in 2012.[15] At our centre, the percentage of resistance to linezolid was much higher, thus indicating that the problem may be underestimated. Following implementation of the programme, a significant reduction in linezolid-resistant CoNS and linezolid-resistant *E. faecalis* was achieved. In the case of CoNS, the trend began in the second semester of the pre-intervention period parallel to a reduction in the consumption explained by the impact of non-structured control measures in a period of economic crisis. No significant reduction was observed for *E. faecium* and MRSA. Thus, our data confirm the importance of optimizing the overuse of linezolid to control the emergence of resistant strains. Obviously, the reduction in linezolid use led to an increase in vancomycin use. This did not result in increased

resistance to vancomycin of CoNS, *Enterococcus* spp. or MRSA during the study period.

One of the unknown factors of any restrictive antimicrobial stewardship programme is its safety. In theory, if the approved guidelines are based on robust scientific evidence and they improve the appropriateness of the prescription, mortality should not increase. This aspect has not been sufficiently studied in many publications demonstrating the effectiveness of optimization programmes. To study this aspect, we used several events considered 'sentinel' as they are related to significant mortality (MRSA bacteraemia, VAP) and because in some of them, such as MRSA nosocomial pneumonia, the use of linezolid has been associated with reduced mortality. Given that our intervention did not affect the mortality of these events, we consider it a safe strategy.

Our study has some limitations, such as the fact it is a retrospective study, which was carried out in the pre-intervention period at a single centre. Some measures of economic control were implemented in the second semester of this pre-intervention period. Another limitation of our study is that the mechanisms of linezolid resistance were not studied. Therefore, we cannot relate the ecological impact of the programme to a particular mechanism of linezolid resistance. In addition, it is not possible to determine whether the low impact of the programme on linezolid-resistant MRSA is related to different resistance mechanisms. A discussion on this aspect would therefore be purely speculative. Assuming this limitation, the linezolid resistance mechanism most frequently associated with antibiotic pressure in Spain is the acquisition of the *crf* gene or the G2576T mutation. It is known that this resistance mechanism may be preceded by an increase in linezolid consumption.[16] It is reasonable to think that our results can be explained by the fact that the reduction in linezolid consumption is beneficial in limiting the expression of these resistance mechanisms.

In conclusion, our linezolid optimization strategy based on the validation of prescriptions reduced linezolid consumption and the resistance rate of CoNS and *E. faecalis* to linezolid without producing undesirable, adverse clinical outcomes.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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