*This is a pre-copyedited, author-produced version of an article accepted for publication in J Antimicrob Chemother following peer review. The version of record Lloréns-Villar Y, Tusell F, Canut A, Barrasa H, Corral E, Martín A, Rodríguez-Gascón A. Antibiotic susceptibility trend before and after long-term use of selective digestive decontamination: a 16 year ecological study**. J Antimicrob Chemother**. 2019 Aug 1;74(8):2289-2294. doi: 10.1093/jac/dkz186. PMID: 31065685 is available online at: https://academic.oup.com/jac/article/74/8/2289/5486502?login=false*

Antibiotic susceptibility trend before and after long-term use of selective digestive decontamination: a 16-year ecological study

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Running title: Antibiotic susceptibility before and after long-term use of SDD

Synopsis

Objectives: To compare the antimicrobial susceptibility rate in an Spanish ICU before and after the introduction of selective digestive decontamination (SDD), and also to compare with susceptibility data from other Spanish ICUs without SDD.

Methods: We performed a retrospective study in the ICU of the University Hospital of Alava, where SDD was implemented in 2002. SDD protocol consisted of a 2% mixture of gentamycin, colistin and amphotericin B applied on the buccal mucosa, and a suspension of the same drugs in the gastrointestinal; additionally, for the first 3 days, systemic ceftriaxone was administered. From 1998 to 2013 we analyzed the antimicrobial susceptibility rates in 48 antimicrobial/organism combinations. Interrupted time series using a linear dynamic model with the SDD as an intervention was used. Data from other ICUs were obtained from the ENVIN-HELICS national registry.

Results: Only *E. coli* and *P. mirabilis* against amoxicillin/clavulanate, and *E. faecali*s against high concentration of gentamycin, resulted in a significant decrease of the susceptibility rate after the implementation of the SDD, with a drop of 20%, 27% and 32%, respectively. Compared to other Spanish ICUs without SDD, susceptibility rate was higher in the ICU of our hospital in most cases. When it was lower, differences were less than 10%, except for *E. faecium* against high concentration of streptomycin, in which the difference was 19%.

Conclusions: No relevant changes in the overall susceptibility rate after the implantation of the SDD was detected. Susceptibility rates were not lower than the media in the Spanish ICUs without SDD.

Introduction

Selective digestive decontamination (SDD) consists of the topical application of non-absorbable antimicrobial agents in the oropharynx and gut,[1] and has been associated with better patient outcome.[2,3] Although high-quality evidence supports the use of SDD, it is not widely used in clinical practice,[4] The predominant concern seems to be the development of antimicrobial-resistant pathogens. However, in a meta-analysis,[5] no relation between the use of SDD and the development of antimicrobial resistance was detected. Several reasons justify the limited evidence of the lack of the SDD effect on antimicrobial resistance, including relatively few studies, most of which assessed the effects of SDD at the patient (treated with SDD) level rather than at ICU (ecologic) level, and with limited follow-up time. In addition, there are few studies assessing long-term effects of SDD on multidrug-resistant bacteria in settings of high rates of resistance.[6] The aim of the present work was to evaluate the antimicrobial susceptibility rates before and after the introduction of the SDD in an ICU of Spain, a country with high level of resistance. A second objective was to compare the susceptibility rates with those reported in other Spanish ICUs without SDD.

Methods

The study was performed in a ICU of the University Hospital of Alava (Spain), a 800-bed tertiary care teaching facility. This 13-bed ICU cares for surgical, neurosurgical and medical patients. SDD consisted of a 2% mixture gentamycin, colistin and amphotericin B applied on the buccal mucosa, and a suspension of the same drugs (respective doses of 80, 100 and 500 mg) provided in the gastrointestinal tract at 6-h intervals. In addition, for the first 3 days, intravenous ceftriaxone (2 g a day) was administered to all SDD patients. SDD was implanted in 2002 (third quarter), and there were no relevant changes

either in the occupancy rates or in the characteristics of the patients admitted in the ICU before and after the implantation of the SDD.

Bacterial isolates and antimicrobial susceptibility

From 1998 to 2013 we analyzed the bacterial susceptibility rate in 48 antimicrobial/organism combinations (Tables S1 to S11). We also calculated the rate of resistant microorganism acquisition, expressed per 100 patients-day. We included isolates taken for clinical or surveillance purposes, and only the first isolate per patient.

Data of antimicrobial susceptibility from the ENVIN-HELICS national registry[7] were obtained (report of 2014, corresponding to susceptibility data of 2013). It includes a total of 22,064 patients and 192 ICUs. Less than 5% of these ICUs have implanted the SDD; therefore, these data were used as control (susceptibility rates in absence SDD).

Antibiotic use

Antibacterial consumption, expressed as DDD/100 patient-days, was calculated according to the 2014 version of the ATC/DDD classification.[8] Prophylactic and therapeutic medication were not distinguished.

Statistical analysis

We developed a statistical model of interrupted time series in which the introduction of the SDD was considered as the intervention. The susceptibility rate λ_t was assumed to be linearly as follows:

$$\log \lambda_t = x_{1t} + x_{2t}(\text{DDD/100 patient-days})_t + x_{3t}\text{SDD}_t$$

$$x_t = Tx_{t-1} + w_t$$

where T is a fixed matrix and w_t a vector of random noise. The components of the vector are the (unknown) trend of the susceptibility rate of the organism against a given

antimicrobial, $x_{1t,}$ as well as the unknown coefficient x_{2t} of the variable DDDs/100 patient-days, and the coefficient x_{3t} of a 0-1 step variable SDD_t designed to capture the effect of SDD.

The total number of isolates (whose distribution given N_t is assumed Poisson $N_t\lambda_t$) determines how much each observation in the data set influences the susceptibility rate. To apply this model, the statistical package R version 3.3.1 and in particular package FAS[9] was used. A significant level of 5% was considered.

On the other hand, trends in the number of isolates, in the rate of resistant microorganism acquisition, and in the antimicrobial consumption were analyzed in the pre- and post-SDD period with linear correlation. An appropriate degree of fit was considered when the correlation coefficient was ≥0.7.[10] A p value <0.05 was considered statistically significant. IBM® SPSS® Statistics v. 24 was used.

Results

Out all the combinations studied, only the difference in the susceptibility rate before and after the SDD of *E. coli* and *P. mirabilis* against amoxicillin/clavulanic acid, and *E. faecali*s against high concentration of gentamycin turned out to be significant ($p<0.05$), the susceptibility rate being lower in the post-SDD period (Table S12). Figure 1 shows the predicted and observed values for these three combinations. The change in the susceptibility of *E. coli* and *P. mirabilis* against amoxicillin/clavulananic acid before and after the implantation of the SDD was 20% and 27%, respectively. In the case of *E. faecalis* against high concentration of gentamycin, the reduction of the susceptibility was 32%. The difference in the susceptibility rate of *E. coli* and *P. mirabilis* against amoxicillin/clavulanic acid before and after the implementation of SDD was significant even after the inclusion of all beta-lactam consumption in the statistical model (Table

S13). The difference in the susceptibility rate of *E. coli* was also significant with the introduction in the model of the consumption of piperacillin-tazobactam.

For most microorganisms (Figure S1), the number of isolates was constant over the period of study. Data of antibiotic consumption are presenting in Figure S2 and Table S14. No trend in the consumption of all beta-lactam and all antibiotics was detected either in the pre-SDD or in the post-SDD. No increase in the rate of resistant microorganism acquisition was detected in the post-SDD period (Table S15).

Table 1 shows the susceptibility rate of all antibiotic-organism combinations in 2013 (mean value of the four trimesters) and those from the ENVIN-HELICS report for 2013. In most cases, the susceptibility rate is higher in the ICU of our hospital than those reported for the Spanish ICUs.

Discussion

In this ecological study, we detected evidence of decreasing susceptibility trends after the introduction of the SDD only for *E. coli* and *P. mirabilis* against amoxicillin/clavulanic acid, and *E. faecalis* to high concentration of gentamycin. It is widely assumed that SDD facilitates the selection of enterococci and transmission of hospital-adapted strains,[11,12] and this may justify the decrease in the susceptibility of *E. faecalis* against high level gentamycin; in fact, a dominant and epidemic *E. faecalis* clone (ST6) was recently detected in the ICU of our hospital, which was related to the use of SDD.[13] Over the last years, an increase in the rate of resistance to amoxicillin/clavulanic acid among *E. coli* isolates in Europe[14] has been noted, including Spain[15], which has been related to an increase in the consumption of this antibiotic. Therefore, the decrease in the susceptibility of *E.coli* against amoxicillin/clavulanic acid may be explained by the increase in the use of this antibiotic in the community, and not only by the introduction of the SDD. Since the overall consumption of beta-lactams in our ICU was lower in the post-

SDD period, the decrease in the susceptibility of *E. coli* cannot be explained by the use of beta-lactams. The reduction of the susceptibility of *P. mirabilis* to amoxicillin/clavulanic acid in the post-SDD period should be taken with caution, since the level of significance was lower but very close to 0.05, and because the number of isolates was very low (Table S4). It is important to take into account that beta-lactam resistance of *P. mirabilis* has increased in recent years in several countries.[16]

For the rest of microorganism-antibiotic combinations, changes in the susceptibility after the introduction of the SDD were not detected. Additionally, no trends in rate of resistant microorganism acquisition in the post-SDD period were found, which confirms that SDD does not contribute to the spread of resistant isolates. It is important to take into account that, in the post-SDD period, other interventions that may have conditioned the susceptibility rates were introduced, such as the International Standard ISO 9001:2000 guidance in 2005, the Bacteremia Zero program in 2009[17], and the "Zero-ventilator-associated pneumonia (VAP)" bundle in 2011[18].

Contrary to that reported in other studies,[6] no trends in the number of isolates in the post-SDD period were detected. The overall use of antibiotics in our ICU was lower in the post-SDD period, and it did not increase over time. These results are in agreement with Daneman,[5] which postulates that the use of prophylactic selective decontamination could even lead to reductions in the need for therapeutic antimicrobials.

We also compared the susceptibility rates of our ICU with those reported in the ENVIN-HELICS national registry (most of the ICUs without SDD).[7] The susceptibility rate in our hospital was of the same order or even higher that the media in the Spanish ICUs. Only the susceptibility rate of *E. faec*ium against high concentration of streptomycin was lower in our hospital (50% versus 69%).

In conclusion, our study reveals no relevant changes in the overall susceptibility rate after the implantation of the SDD. Additionally, susceptibility rates were not lower than

the media in the Spanish ICUs without SDD. One important shortcoming of our study is that it is retrospective in nature and based on a single institution.

Funding

This work was supported by the University of the Basque Country UPV/EHU (GIU17/32, PPG17/65).

Transparency declarations

None to declare.

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Figure 1. Predicted and observed susceptibility values of *E. coli* and *P. mirabilis* against amoxicillin/clavulanic acid, and *E. faecalis* against high concentration of gentamycin.

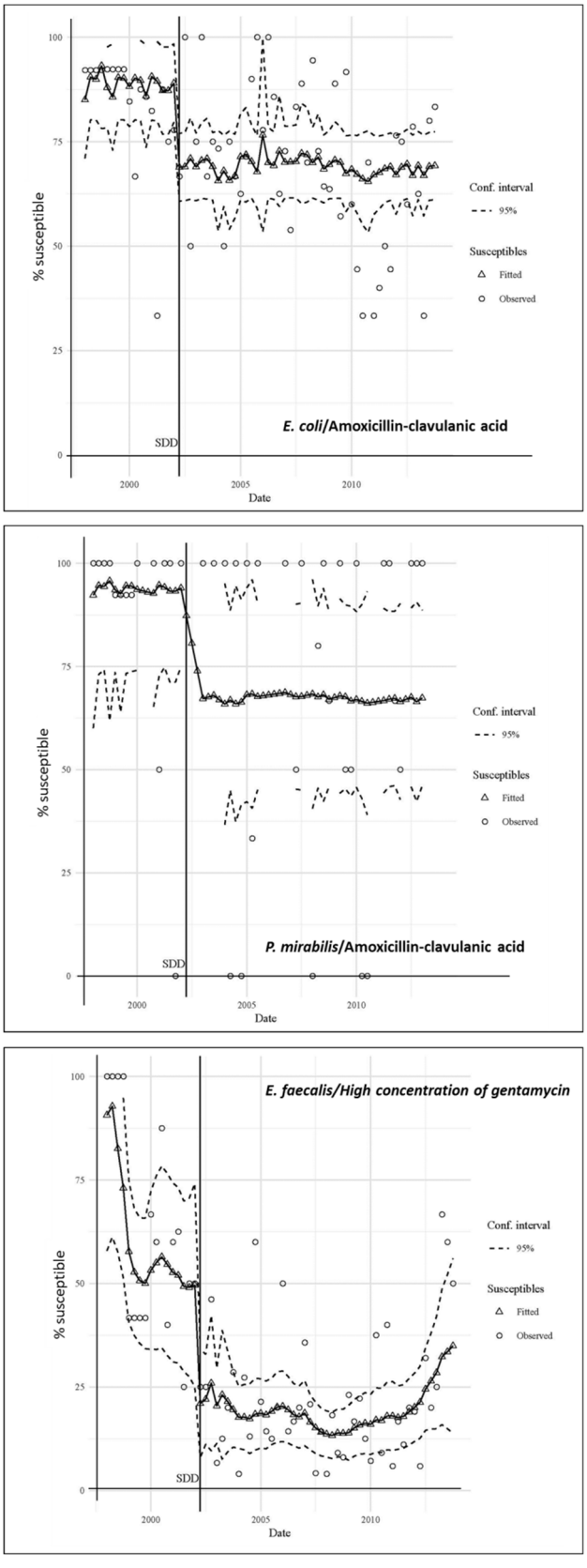

Table 1.Compared values of susceptibility rate between the ICU of the HUA and data in the ENVIN-HELICS report.[7]

Microorganism	Antimicrobial agent	Susceptibility rate in 2013 (%)	
Gram-negative organisms			
Enterobacterales		**HUA***	**ENVIN-HELICS**
Enterobacter spp.	Cefotaxime	80	50
	Imipenem	100	89
E. coli	Amoxicillin/clavulanicacid	64	66
	Cefepime	88	85
	Cefotaxime	77	83
	Ceftazidime	88	84
	Ciprofloxacin	59	67
	Gentamycin	78	85
	Levofloxacin	87	77
	Piperacillin/tazobactam	93	85
Klebsiella pneumoniae	Cefotaxime	100	62
	Ceftazidime	83	60
P. mirabilis	Amoxicillin/clavulanicacid	100	76
	Cefepime	100	94
	Cefotaxime	100	98
	Ceftazidime	100	100
	Ciprofloxacin	100	82
	Gentamycin	100	82
	Levofloxacin	100	100
	Piperacillin/tazobactam	100	100
Serratia spp.	Cefepime	100	100
	Cefotaxime	100	77
	Ceftazidime	100	85
	Ciprofloxacin	100	78
	Gentamycin	100	95
	Levofloxacin	100	91
	Piperacillin/tazobactam	100	80
Non-fermenters			
Acinetobacter spp	Imipenem	0	15
P. aeruginosa	Amikacin	86	82
	Cefepime	88	61
	Ceftazidime	88	67
	Ciprofloxacin	61	47
	Colistin	90	94
	Imipenem	67	49
	Levofloxacin	67	41
	Meropenem	67	51
	Piperacillin/tazobactam	67	66
	Tobramycin	56	n.a.
Gram-positive organisms			
E. faecalis	High concentration of gentamycin (500 mg/L)	51	44[1]
	High concentration of streptomycin (1,000 mg/L)	57	42[1]
	Vancomycin	100	98
	Daptomycin	96	97
	Linezolid	96	99
	Tigecycline	-	-
E. faecium	High concentration of gentamycin (500 mg/L)	53	54[2]
	High concentration of streptomycin (1,000 mg/L)	50	69[2]
	Vancomycin	100	100
	Daptomycin	83	90
	Linezolid	92	97
	Tigecycline	-	-
S. aureus	Cloxacillin	92	100
	Vancomycin	100	97
	Daptomycin	100	100
	Linezolid	100	100
	Tigecycline	92	100
CoNS	Cloxacillin	12	15
	Vancomycin	100	97
	Daptomycin	96	100
	Linezolid	96	95
	Tigecycline	92	100

*HUA: mean value of the four quarters
n.a.: not available
[1]Not available in the ENVIN-HELICS report. Obtained from Kuch*et al*[19]. 2012. Data from 2006-2009
[2]Not available in the ENVIN-HELICS report. Obtained from García-Vázquez *et al*[20].