Impact of a Change in Antibiotic Prophylaxis on Total Antibiotic Use in a Surgical Intensive Care Unit

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Abstract

Objective: The aim of this study was to evaluate the impact of reducing the length of antibiotic prophylaxis for cerebrospinal shunts on total antibiotic use and key resistant pathogens.

Methods: In January 2004, the use of antibiotic prophylaxis was reduced to a single shot dose with cefuroxime in an intensive care unit (ICU). Prior to this intervention, prophylaxis with second-generation cephalosporins was administered during the entire period of external cerebrospinal fluid (CSF) drainage. The effect on the antibiotic use density (AD: DDD [defined daily doses] per 1,000 patient-days [pd]) was calculated prior to (January 2002–December 2003) and following implementation of the intervention (January 2004–December 2006) by segmented regression analysis of an interrupted time series. Resistance proportions (RP) and resistance densities (RD), defined as resistant pathogen/1,000 pd of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* or *E. faecium*, third-generation-resistant (3GC) *Escherichia coli* and *Kebsiella pneumoniae*, and imipenem-resistant *Pseudomonas aeruginosa*, were compared by the Fisher's exact test before and after the intervention.

Results: Total antibiotic use by 147 DDD/1,000 pd decreased after the intervention when pre-operative prophylaxis was changed into single shot prophylaxis, from an estimated mean of 1,036 DDD/1,000 pd before the intervention to 887 DDD/1,000 pd post-intervention. This decrease was primarily due to a significant reduction in the amount of cefuroxime used for prophylaxis. The reduction in total antibiotic consumption was sustainable, and it did not increase again during the next 36 months. The RR and RD of third-generation cephalosporin-resistant *E. coli* increased after January 2004, whereas the percentage of MRSA significantly decreased.

Conclusion: Change to single shot prophylaxis along with an ongoing antibiotic stewardship program resulted in a cut-back in total antibiotic use amounting to as much as 15%. It would therefore appear that targeting interventions aimed at reducing antibiotic prophylaxis in surgical ICUs may be very worthwhile.

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Introduction

In recent years, there has been increasing public awareness of the need to limit antibiotic use and, concomitantly, increasing efforts to control antibiotic use and promote the prudent use of antibiotics [1]. There are two reasons. The first is ecological: antibiotics induce and select for bacterial resistance, and resistance is viewed as a global threat to health and welfare of the general population; as such, areas where pathogens are susceptible are considered to be a social good [2]. The second is economical: antibiotics represent a large portion of the pharmacy budget of hospitals and are, therefore, a main target for cost-savings measures.

It is estimated that up to 50% of antibiotic prescribing for therapy and prophylaxis is inappropriate [3]. Intensive care units (ICU) as high consumers of antibiotics adopt a large variety of strategies to control antibiotic use and the spread of bacterial resistance. Antibiotic management strategies include formal protocols and guidelines, the use of narrow-spectrum antibiotics, and shorter courses of antibiotic treatment, among others [4]. One approach to improving antibiotic use, particularly in surgical ICUs, is to analyze how antibiotics are used for the prevention of postoperative infections.

A Cochrane report that was published in 2006 arrived at the conclusion that antibiotic prophylaxis for the surgical introduction of intracranial ventricular shunts is

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beneficial in preventing shunt infections. However, this benefit was not shown for a prophylaxis for a prolonged period of time (> 24 h) [5].

The aim of this study was to evaluate the impact of a reduced duration of antibiotic prophylaxis for cerebrospinal shunts on total antibiotic use in the ICU and key resistant pathogens. Our study design is that of an interrupted time series analysis in which a series of observations over time is interrupted by one or more interventions [6].

Methods

Setting

The surgical ICU is a 24-bed unit within the Katharinenhospital in Stuttgart, a 900-bed tertiary care teaching hospital mainly for patients with head injuries, intracranial hemorrhages, multiple trauma, and multiple organ failure. Characteristics of the ICU are shown in Table 1. Between 2002 and 2006, the ICU had annually 15, 20, 20, 19, and 20% neurosurgical patients, respectively. An admission screening for methicillin-resistant *Staphylococcus aureus* (MRSA) for all surgical patients was introduced in October 2003.

Intervention

In autumn 2003, a comprehensive teaching session on antibiotic prophylaxis in cerebrospinal shunts was organized by the infection control and neurosurgery teams. This resulted in a revised recommendation of single shot prophylaxis with cefuroxime for shunt catheters, beginning in January 2004. Prior to implementation of this recommendation, cefuroxime was administered for the whole duration of external CSF drainage, which could be up to 2–3 weeks. Compliance with the new recommendation was 100%.

We analyzed the 24-month time period prior to implementation of the intervention (January 2002 to December 2003) and the 36-month period post-intervention (January 2004 to December 2006).

Data Collection

Monthly data on antimicrobial use were obtained from the computerized pharmacy database. Antimicrobial use was reported not only for neurosurgical patients but for all patients in the ICU. Consumption, i.e., antimicrobial usage density (AD), was expressed as daily defined doses (DDD) and normalized per 1,000 patient-days (pd). One DDD is the standard adult daily dose of an antimicrobial agent for a 1 day's treatment, as defined by the World Health Organization (WHO; ATC/DDD index 2006; http://www.whocc.no).

Monthly resistance data were collected from the microbiology laboratory. Only samples taken in the ICU were considered. These were specified as resistant by the clinical laboratory on the basis of interpretive criteria recommended by the German Institute for Standardization (DIN) [7]. Copy strains – defined as an isolate of the same species showing the same susceptibility pattern throughout a 1-month period in the same patient, no matter what the site of isolation – were excluded. The proportion of resistant isolates (RP) was calculated by dividing the number of resistant isolates by the total number of isolates of this species tested against this antibiotic multiplied by 100. The incidence density of resistant isolates (RD) was defined as the number of resistant isolates per 1,000 patient-days.

Data Analysis

We used an interrupted time series analysis to evaluate the longitudinal effects of the change in antibiotic prescribing. Segmented regression analysis of interrupted time series is a robust modeling technique that enables dynamic changes in various outcomes to be analyzed.

Level and slope are the two parameters which define each segment of a time series. The level is the value of the series at the beginning of a given time interval, and the slope is the change in the measure during a time step (1 month). An abrupt intervention effect constitutes a drop or jump in the level of the outcome after the intervention. A change in slope is defined by an increase or decrease in the slope of the time step after the intervention, as compared with the time step preceding the intervention. It represents a gradual change of the outcome parameter during a time step. The method is described in greater detail by *Wagner* et al. and *Ansari* et al. [6, 8].

For the statistical analysis of monthly antibiotic consumption, we looked at 24 time points before the intervention and 36 thereafter (single shot prophylaxis). All antibiotic groups with an AD > 30 were considered in the regression analysis. The analysis of antibiotic use was performed stepwise backward: use was tested for normal distribution by Shapiro-Wilk test and for autocorrelation by the Durbin-Watson test. The p-value for removing a variable from the model was p = 0.06.

We calculated three-monthly intervals of resistance data if at least ten isolates per 3-month period were available, i.e., RP and RD of MRSA, vancomycin-resistant *Enterococcus faecalis* or *E. faecium* (VRE), imipenem-resistant *Pseudomonus*

Table 1
Characteristics of the ICU.

Parameter	Before intervention January 2002–December 2003	After intervention January 2004–December 2006	Total
Months	24	36	60
Patient (days)	13,502	21,420	34,922
Patients (n)	4,684	7,203	11,887
Mean age of patients (years)	62.6	63.2	
Number of patients died (%)	246 (5.3%)	326 (4.5%)	572 (4.8%)
Mean length of stay (days)	2.88	2.74	2.80
Device utilization use (device days/100 patient days)			
Urinary catheter use	88.14	84.10	85.74
Central venous catheter use	75.12	71.82	73.16
Ventilator use	49.60	42.79	45.56

aeruginosa, and third-generation-resistant *Escherichia coli* and *Klebsiella pneumoniae.* For these data we could not use segmented regression analysis of interrupted time series because there were too few resistant isolates to be reasonably calculated on a monthly basis. Therefore, resistance data are not an outcome parameter. For the resistance data, the relative risks (RR) with 95% confidence intervals (CI) were calculated between the two time periods. All analyses were performed using SPSS ver. 12.0 (SPSS, Chicago, IL) and EpiInfo ver. 6.04 (CDC, Atlanta, GA).

Results

Total antibiotic use decreased (–147.3 DDD/1,000 pd, p = 0.052) after the intervention when pre-operative prophylaxis for shunt catheters was changed into single shot prophylaxis (Figure 1). This corresponds to a decrease of 15% and was mainly due to a significant reduction in the use of cefuroxime, which was the only second-generation cephalosporin used in the ICU (Table 2). The reduction in total antibiotic consumption was sustainable and did not increase over the next 36 months.

The RR and RD of third-generation resistant *E. coli* increased after January 2004 (Table 3).

Discussion

Our segmented regression analysis of a 60-month period showed that a change to single shot antibiotic prophylaxis together with an antibiotic stewardship program was associated with a surprisingly high 15% reduction in total antibiotic use.

In surgical ICUs, the use of antibiotics not only for therapy but also for prophylaxis contribute to total antibiotic consumption, to the selective pressure by antibiotics, and to the pharmaceutical budget. Shunt infections, which are dreaded as a major complication of shunt implantations in neurosurgical patients, can be prevented by antibiotic prophylaxis [9]. Prior to January 2004, the standard practice of the surgical ICU of the Katharinenhospital was to administer cefuroxime for the whole duration of external CSF drainage, which could be up to 2–3 weeks. There was no evidence supporting this regimen, but it remained common practice for years. Although there was ample evidence that single shot preoperative prophylaxis is safe and effective, it took time and effort to convince the neurosurgeons in this particular ICU to switch to a single dose prophylaxis with cefuroxime [10]. The subsequent 15% decrease in total antibiotic use is noteworthy because antibiotic use in the studied ICU was already low in comparison to that of other German surgical ICUs (mean antibiotic use 1104 DDD/1000 pd; data January 2002–December 2006) [11].

In terms of antibiotic resistance, one might expect that a significant reduction in antibiotic use would have a positive impact on the susceptibility of pathogens. However, although there was a possibility that the total amount of ecological pressure by antibiotics would be diminished, this was not the case. There are several possible explanations for this lack of effect. Firstly, the mean duration of ICU stay was 2.8 days. The effects of restricting the use of antibiotics was therefore likely not reflected in the ICU but in wards to which the patients were transferred. Secondly, not all groups of antibiotics equally affect the selection of drug-resistant organisms. Some groups of antibiotics seem to have a higher risk of causing collateral damage than others. Quinolones, for example, are linked with isolation and infection with MRSA and Gram-negative bacilli [12–14]. Thirdly, confounding factors could act in both directions and also mask a positive effect of antibiotic restriction even in an unadjusted before–after comparison.

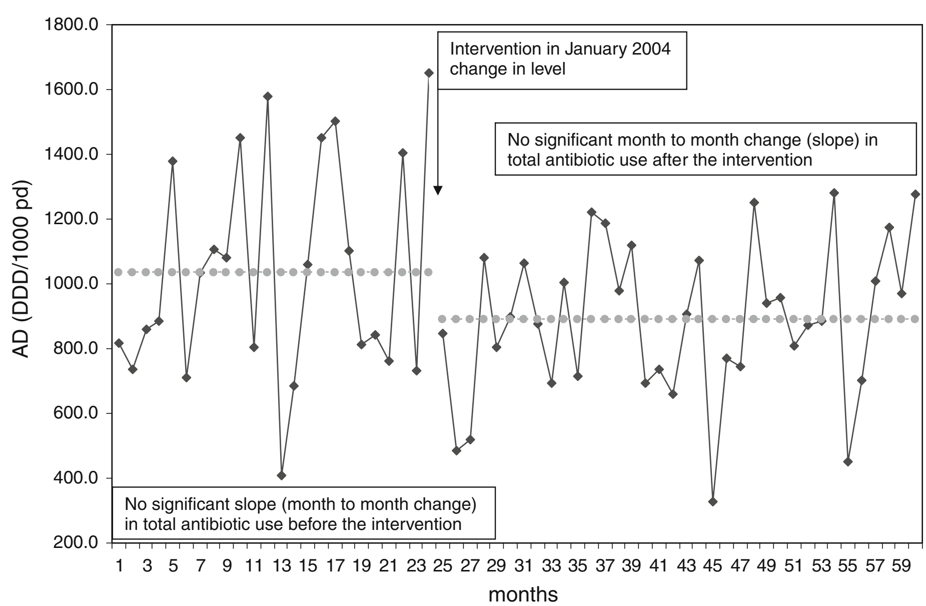

Figure 1. Changes in antibiotic use density (AD: defined daily doses [DDD]/1,000 person-days) of total antibiotic use 24 months before and 36 months after the intervention (January 2002 to December 2006). The estimated (*grey dotted line*) mean pre-intervention use (AD) is 1,036, the mean estimated post-intervention use is 887, and the estimated change in level is –147.

Table 2
Mean antimicrobial use density (AD) of antibiotic groups with an AD > 30 before and after the intervention and interrupted time series analysis.

Intervention	Level pre-intervention	Slope pre-intervention	Change in level post-intervention	Change in slope post-intervention
Intervention ICU				
Total antibiotic use	1035.9 (920.6–1151.2)	NS	–147.3 (–296.1–1.6)	NS
Combination of penicillins with BLI	129.5 (110.3–148.7)	NS	NS	NS
Piperacillin–tazobactam	58.2 (49–67.5)	NS	NS	NS
Amoxicillin–clavulanic acid	129.8 (83.1–176.4)	–3.6 (–6.3 to –0.9)	NS	4.6 (0.8–8.4)
Cephalosporins	423.5 (366.4–480.5)	NS	–90.5 (–164.1 to –16.8)	NS
First-generation cephalosporins	94.6 (81.3–107.9)	NS	NS	NS
Second-generation cephalosporins	164.1 (128.3–199.8)	NS	–84.4 (–130.6 to –38.3)	NS
Third-generation cephalosporins	143.5 (130.9–156)	NS	NS	NS
Carbapenems	75.8 (63.4–88.2)	NS	NS	NS
Quinolones	129.2 (106.4–152)	NS	NS	NS
Sulfonamides and trimethoprim	46.9 (31.9–61.8)	NS	–27.5 (–46.8 to –8.2)	NS
Imidazoles	72.3 (66.3–78.3)	NS	NS	NS

Pre-intervention: January 2002 to December 2003; post-intervention: January 2004 to December 2006; ICU: intensive care unit; NS: not significant; 95% CI: 95% confidence interval; BLI: beta lactamase inhibitor; segmented regression models with estimated antibiotic use density before the intervention and estimated change in level from the most parsimonious (significant) models; 95% CI is given in parenthesis

Table 3
Resistance proportions (RP, %) and resistance densities (RD, resistant pathogens/1,000 person-days) 24 months pre- (January 2002 to December 2003) and 36 months post-intervention (January 2004 to December 2006).

Resistance proportions	Before intervention (January 2002 to December 2003)		Post-intervention (January 2004 to December 2006)		Relative risk (January 2002 to December 2003 vs January 2004 to December 2006)
	Tested	RP	Tested	RP	
3GC-resistant ECO (%)	186	0.5	326	5.2	9.70 (1.30–72.30)
3GC-resistant KLE (%)	102	10.8	141	7.1	0.66 (0.29–1.49)
Imipenem-resistant PSEU (%)	161	21.1	214	15.4	0.73 (0.47–1.23)
MRSA (%)	558	22.8	1,870	10.1	0.44 (0.36–0.54)
VRE (%)	118	1.7	193	3.6	2.14 (0.45–10.13)
Resistance densities	**Before intervention (January 2002 to December 2003)**		**Post- intervention (January 2004 to December 2006)**		**Relative risk (January 2002 to December 2003 vs January 2004 to December 2006)**
	Resistant	**RD**	**Resistant**	**RD**	
3GC-resistant ECO	1	0.07	17	0.79	10.72 (1.43–80.52)
3GC-resistant KLE	11	0.81	10	0.47	0.57 (0.24–1.35)
Imipenem-resistant PSEU	34	2.52	33	1.54	0.61 (0.38–0.99)
MRSA	127	9.41	189	8.82	0.94 (0.75–1.17)
VRE	2	0.15	7	0.33	2.21 (0.46–10.62)

3GC: Third-generation cephalosporin; ECO: *E. coli*; KLE: *K. pneumoniae*; PSEU: *P. aeruginosa*; VRE: vancomycin-resistant *E. faecalis* or *E. faecium*; MRSA: methicillin-resistant *Staphylococcus aureus*; 95% CI is given in parenthesis

The significant decrease in the use of cefuroxime use in January 2004 was not associated with a decrease in third-generation cephalosporin-resistant *E. coli*. In contrast, the RR and RD of the third-generation cephalosporin-resistant *E. coli* even increased in the ICU, paralleling a nationwide trend [15, 16]. With respect to antibiotic use, most studies have found that third-generation cephalosporin use is risk factor for extended-spectrum beta lactamase (ESBL)-producing organisms; to a lesser account, this is also true for the use of quinolones, trimethoprim–sulfamethoxazole, and metronidazole – but not for second-generation cephalsoporins [17].

One may hypothesize that decreased selection pressure through the reduced use of second-generation cephalosporins would result in more frequent isolation of methicillin-susceptible *S. aureus* in comparison to MRSA.

However, we hold that the reduction in the percentage of MRSA was primarily achieved by enforced infection control and by the introduction of the admission screening in the ICU [18, 19]. Enforced infection control may have also affected the transmission of other resistant pathogens.

The study has some limitations that must be taken into account. Firstly, we can not provide valid data on shunt-associated infection rates. However, this study was not designed to prove that single dose prophylaxis is safe, as this is already accepted. Secondly, we cannot provide the exact numbers of shunt operations or the number of purchased shunts due to a change in the hospital's computer system. However, there was no change in the number of neurosurgical beds, in the type of surgery performed, or in the patients during the study period. Although we do not have the proportion of patients with shunts, the results of the regression analysis clearly show that antibiotic use was reduced immediately following the implementation of the intervention and that the reduction was sustainable, thereby supporting our statement that there was a nearly constant proportion of stunted patients during the study. Thirdly, we could not apply segmented regression analysis on the resistance data. This means that the changes could have occurred for reasons unrelated to the intervention. However, because we could not claim a success with respect to an improved resistance situation – not even with an uncontrolled before-and-after comparison of means – we consider a positive impact unlikely to have occurred. Fourthly, the study design does not control for other changes over time that could have contributed to a decreased use of antibiotics, such as the ongoing antibiotic stewardship program by the infection control team. Lastly, the study was performed in a specific setting. This could hinder generalizations to other ICUs.

In conclusion, the change from prophylaxis during the whole duration of external CSF drainage to a single shot treatment along with an ongoing antibiotic stewardship program resulted in a cut-back of up to 15% of total antibiotic use. Therefore, targeting measures aimed at reducing antibiotic prophylaxis in surgical ICUs may be a worthwhile objective. However, we were unable to provide evidence of a positive impact of our intervention on the resistance situation in the ICU.

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Transparency declaration. None to declare.

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