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The impact of antimicrobial drug consumption and alcohol-based hand rub use on the emergence and spread of extended-spectrum β-lactamase-producing strains: a time-series analysis

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***Background*: The aim of this study was to explore the temporal relationship between the consumption of different antibiotics, alcohol-based hand disinfection and the incidence of nosocomial bacterial strains producing extended-spectrum β-lactamases (ESBLs).**

***Methods*: Time-series analysis was performed based on monthly data available from January 2005 to October 2007. The incidence of nosocomial ESBL (cases/1000 patient-days) was regressed on the different antibiotic agents and the volume of alcohol-based hand rub orders. Antibiotic consumption was defined as monthly defined daily doses (DDD)/1000 patient-days, while alcohol-based hand rub was quantified in litres/1000 patient-days.**

***Results*: The multivariate analysis showed that using alcohol-based hand rub for hand disinfection had a significant influence on the ESBL incidence (*P* = 0.002). A higher volume of alcohol-based hand rub use was subsequently associated with a lower incidence of ESBL-producing strains. Additionally, the model showed that temporal increase in the use of third-generation cephalosporins (*P* = 0.022) and fluoroquinolones (*P* = 0.001) is, after a time lag of up to 3 months, followed by temporal variations in the incidence of nosocomial ESBLs. Furthermore, the incidence of patients admitted with ESBL was also shown to have an influence on the incidence of nosocomial ESBLs (*P* < 0.001). The final model explained 75% of the monthly variations in the incidence of nosocomial ESBLs.**

***Conclusions*: The analysis identifies selective pressure caused by the use of different antimicrobial agents as a driving factor in the emergence and spread of ESBLs. Furthermore, the study confirms that hand disinfection is key to the prevention of nosocomial ESBLs.**

Keywords: antibiotic use, hand disinfection, antibiotic resistance, ESBLs

Introduction

The emergence and spread of extended-spectrum β-lactamase (ESBL)-producing strains is still an unresolved problem both in Germany and worldwide.[1–3]

During the past two decades, consumption of broad-spectrum cephalosporins has increased worldwide and a large number of ESBL-positive strains have emerged since the initial description of ESBL production by *Klebsiella pneumoniae* isolates in Germany in 1983.[4] Generally, seriously ill patients with prolonged hospital stay and invasive devices are at risk for acquisition of ESBL-producing pathogens.[5]

Antibiotic consumption is also a well-known risk factor, and several studies have found a positive relationship between third-generation cephalosporin, other β-lactam or fluoroquinolone use and the acquisition of ESBL-producing organisms.[6–8]

The epidemiology of ESBLs has changed dramatically since the year 2000.[9] Until recently, most infections caused by ESBL-producing bacteria have mostly been described as nosocomially acquired, often in specialist units. The enzyme variants found were mostly TEM or SHV. Now the CTX-M enzymes have replaced these. Infections due to ESBL producers are increasingly being found in non-hospitalized patients, but the

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mode of transmission is not exactly clear.[10,11] Livermore *et al*.[9] conclude that at present 'the opportunities for control (of ESBLs) are disturbingly small'.

The statistical technique of time-series analysis has proved to be a powerful tool to determine the relationship between antibiotic use and the occurrence and spread of methicillin-resistant *Staphylococcus aureus* (MRSA).[12–14] Two recent studies included the use of antiseptic hand rub in their analysis.[15,16] This gives a more complete picture of the dynamics of resistance, since the influence of both selective pressure and the transmission of resistant strains is analysed.

A major aim of the analysis presented here was to apply the methodology used in these recent analyses on the incidence of ESBLs. Thus, the temporal relationship is shown between the incidence of nosocomial ESBLs, in-hospital consumption of different antimicrobial agents, the amount of alcohol-based hand rub used and the incidence of patients admitted with ESBL-producing organisms.

Methods

Setting

The analysis took place at the University Medical Center Freiburg, a 1600 bed tertiary care hospital with ~54 000 inpatient admissions annually (Figure 1).

Data collection

For the study period (January 2005–October 2007), monthly quantities of all antimicrobial drugs delivered to each hospital unit were exported from the pharmacy information system. Antimicrobial use was expressed in defined daily doses (DDD) following the definition of the WHO ATC index, in order to allow a comparison of the different antimicrobial agents used. Data on the use of alcohol-based hand rub were derived from the orders placed by each hospital unit, expressed in litres. The non-duplicate number of monthly nosocomial ESBL cases was exported from an existing database at the Department for Infection Control. For ESBL status, agar diffusion test with clavulanic acid plus or minus cefotaxime and ceftazidime was used. An ESBL case was defined as nosocomial if detected more than 48 h after admission. Infected and colonized cases were included. Data on ESBLs were only available from 2005, whereas all the other parameters were available from the beginning of 2003 and were integrated in conformance with the lagged structure of the model from August 2004 through October 2007. All the variables were normalized in values/1000 patient-days.

Statistical analysis

A two-step time-series approach was carried out to explore the influence of antimicrobial use and hand disinfection on the incidence of nosocomial ESBL. All the variables were logarithmically transformed. All of the observed series were highly volatile. Carbapenems were not included in the analysis, because their application may be a result rather than a cause of ESBL-producing organisms.[17]

Setting: 1600 bed tertiary care teaching hospital in Southern Germany with approximately 54 000 inpatient admissions annually. Infection control department with four hospital epidemiologists and three full-time infection control nurses.
Dates: January 2005 to October 2007.
Population: A monthly average of 35 898 (range 30 063–39 781) patient-days were documented. Endemic ESBL (a mean of 0.135 nosocomial ESBL cases/1000 patient-days) with clones of *E. coli, Enterobacter cloacae, Klebsiella* species, *Acinetobacter* and *Citrobacter*.
Infection control changes: The monthly use of alcohol-based hand rub for hand disinfection was highly variable during the study period.
Antibiotic policy: Hospital guidelines for antibiotic use. However, no restriction policy.
Isolation policy: Besides standard precautions, contact precautions are recommended for all patients colonized or infected with ESBL-positive bacteria. Barrier precautions include single-room placement or cohorting. Staff wear gloves and gowns while treating the patient. Furthermore, roommates are screened. No admission screening. Electronic flagging of patients identified in the past with ESBL who are readmitted to the hospital was in place for the whole study period.
Definition of ESBL incidence: Number of nosocomial cases of ESBL (both colonizations and infections)/1000 patient-days.

Figure 1. Setting, dates, population, infection control changes, antibiotic policy, isolation policy and definitions; summary table according to the ORION statement.[29]

Table 1. Characteristics of the explanatory variables at the Freiburg University Medical Center (August 2004–October 2007)[a]

Possible explanatory variable	Average monthly use[b]	Trend[c]	*P* value[c]
All antimicrobials	631.8 (560.1–714.6)	upward	0.02
Second-generation cephalosporins	176.1 (113.1–205)	no	0.76
Fluoroquinolones	70.7 (51.4–92.4)	upward	<0.001
Penicillins with extended spectrum	67.4 (30.5–98.1)	downward	<0.001
Macrolides	49.6 (36.1–73.8)	upward	0.025
Third-generation cephalosporins	47.3 (11.1–67.6)	upward	0.025
Combinations of penicillins with β-lactamase inhibitors	45.4 (27.8–56.7)	no	0.369
β-lactamase-sensitive penicillins	40.3 (28.7–56.7)	no	0.164
Imidazoles	30.7 (22–68.2)	upward	<0.001
Lincosamides	24.8 (10.6–41.8)	no	0.246
Carbapenems	20.8 (12.6–47.2)	upward	<0.001
Combinations of sulphonamides and trimethoprim	21.5 (0–56.7)	upward	<0.001
Glycopeptides	13.5 (7.8–21.2)	no	0.059
Tetracyclines	11 (1.6–31.3)	no	0.796
Aminoglycosides	9.8 (4.5–15.3)	downward	0.007
Other antimicrobials[d]	2.5 (0–7.7)	upward	0.001
Alcohol-based hand rub	59.8 (50.3–73.8)	upward	0.01

[a]Data on ESBLs were only available from January 2005, whereas all other parameters were available from the beginning of 2003. According to the lagged structure of the model, all possible explanatory variables were integrated in the model from August 2004.
[b]Quantities of antimicrobials are expressed in DDD/1000 patient-days, those of alcohol-based hand rub in litres/1000 patient-days.
[c]Based on regressions of the series on time.
[d]Including the sparse use of linezolid, daptomycin, tigecycline and fosfomycin.

In the first step, the relationship between each explanatory variable (the different antimicrobial drug consumption and the alcohol-based hand rub series) and the explained variable (the ESBL series) was explored by separately running simple ordinary least squares regressions for each independent variable. The purpose of these univariate regressions was to quantify the relationship between the independent variables and ESBL, and to identify lag structures for the final multivariate regression model.[18] Furthermore, we tested for stationarity with the augmented Dickey–Fuller test, which is provided by the Eviews statistical package with which the whole analysis was conducted (Eviews 5.0, Quantitative Micro Software, Irvine, CA, USA). All the relevant variables (the explained variable and explanatory variables) are stationary at the 10% level.

In the second step, a multivariate model to explain the correlation between ESBL incidence, consumption of the different antimicrobials and the use of alcohol-based hand rub was built. The final models were arrived at by the econometric ‘general-to-specific’ approach that has been used previously under connatural circumstances.[14,19] Altogether, 17 variables were tested for inclusion in the multivariate model (all listed in Table 1), but only four remained in the final model. Furthermore, we integrated the incidence of patients admitted with ESBL as an additional explanatory variable in the multivariate model. To address the fact that for the series of alcohol-based hand rub use more than one lag was identified as being statistically significant, a polynomial distributed lag modelling approach was used for the multivariate regression analysis.

The Akaike Information criterion was estimated to inform about the optimal lag length and the goodness of the overall analysis, as well as the determination coefficient, R^2, which informs about what percentage of variance of the ESBL series is explained by the model.

Results

Incidence of ESBL

From January 2005 to October 2007, a total of 167 nosocomial ESBL cases (mean 4.91 cases per month) and 143 admitted cases (mean: 4.21 cases per month) were documented at the University Medical Center Freiburg. These values were transformed into an incidence of 0.135 nosocomial ESBL cases/1000 patient-days and a mean incidence of patients admitted with ESBL of 0.116 cases/1000 patient-days. Overall, 54% of all the ESBL cases were nosocomial and the biggest proportion (78%) of these nosocomial cases were infections. A peak for the nosocomial cases was observed in late summer 2007, while in two periods (April 2005 and January 2007), no cases of nosocomial ESBL were observed at all (Figure 2).

There was an increasing trend in the incidence of nosocomial ESBL (based on regressions of the series on time, $P<0.001$) and in the incidence of patients admitted with ESBL-producing organisms ($P<0.001$).

Antibiotic use and the use of alcohol-based hand rub

Trends in the use of each class of antimicrobials and in alcohol-based hand rub are presented in Table 1. The overall monthly use of antimicrobials was 631.8 DDD/1000 patient-days and showed a significant ascending trend ($P=0.02$). Also, consumption of some antibiotic classes remained constant, and significant ($P<0.05$) increasing trends were observed in the use of fluoroquinolones, macrolides, third-generation cephalosporins, imidazoles, carbapenems, combinations of sulphonamides and trimethoprim, and other antimicrobials as well as in alcohol-based

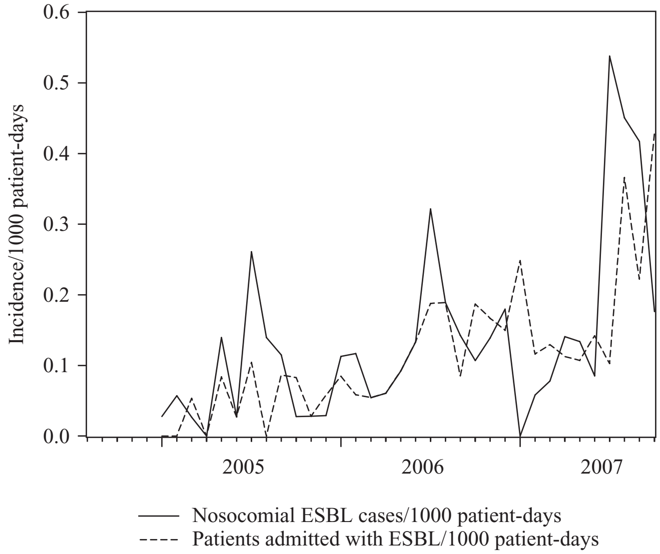

Figure 2. The number of nosocomial ESBL cases/1000 patient-days and number of patients admitted with ESBL/1000 patient-days at the Freiburg University Medical Center, January 2005–October 2007.

hand rub. Descending trends were observed in the use of extended-spectrum penicillins and aminoglycosides.

Final model

For the incidence of nosocomial ESBL, a multivariate model was estimated including four explanatory variables. Consumption of fluoroquinolones and third-generation cephalosporins was identified as having a statistically significant influence on the incidence of nosocomial ESBL. Accordingly, temporal variations in the use of fluoroquinolones or third-generation cephalosporins are followed by temporal variations in the incidence of nosocomial ESBL. Positive coefficients were estimated for both fluoroquinolone and third-generation cephalosporin use, which shows a positive relationship between these variables and the incidence of nosocomial ESBL. Furthermore, since all the variables were normalized due to logarithmical transformation, a 1% increase in fluoroquinolone consumption is, according to the estimated coefficient in Table 2, followed by a 4.43% increase in the incidence of nosocomial ESBL after a time lag of 1 month. Correspondingly, a reduction in fluoroquinolone use is followed by a decline in the incidence of nosocomial ESBL. A 1% increase in the use of third-generation cephalosporins is followed by a 1.98% rise in the incidence of nosocomial ESBL after a time lag of 3 months.

Conversely, the use of alcohol-based hand rub was shown to have a negative influence on the incidence of nosocomial ESBL. A 1% increase in the use of alcohol-based hand rub is thus able to cause a decrease in the incidence of nosocomial ESBL of 6.73% after a time lag of up to 4 months.

Also, the incidence of patients admitted with ESBL-producing organisms (both colonized and infected) was included in the model, showing that every 1% change in the incidence of patients admitted with ESBL was followed by a 0.9% change in the incidence of nosocomial ESBL. Graphical representations between the monthly use of explanatory variables and the monthly incidence of ESBL are displayed in Figure 3.

Additionally, the model included an autoregressive term of order (lag) 1 and had an R^2 of 0.75 and an adjusted R^2 of 0.69, which means that up to 75% of the monthly variations in the ESBL incidence can be explained by the included variables. Also, the F-statistic showed significance ($F=11.54$). We can reject the null hypothesis of serial correlation with the Breusch–Godfrey test and the null hypothesis of heteroskedacity with the White heteroskedacity test. Figure 4 compares the logarithmically transformed incidence of nosocomial ESBL with the weighted sum of all lagged variables used in the final model, which were logarithmically transformed as well.

Discussion

The main aim of this study was to investigate the temporal relationship between certain classes of antimicrobials, hand disinfection and the incidence of ESBLs. The final model demonstrates the efficiency of hand disinfection and has allowed us to quantify the impact of antimicrobial use on the incidence of ESBLs. Consumption of third-generation cephalosporins and fluoroquinolones was positively correlated with ESBL incidence; the use of these antibiotics appears to have a stimulating effect on the emergence and spread of ESBLs in hospital settings. In contrast, the use of alcohol-based hand rub had a negative impact on ESBLs, presumably by preventing ESBL transmission in the hospital setting.

The method chosen in this study, time-series analysis, establishes a time-dependent relationship and allows forecasting of

Table 2. Multivariate model to explain the monthly number of nosocomial ESBL cases/1000 patient-days ($R^2=0.75$)

Explanatory variable	Lag (months)	Coefficient	T-statistic	P value
Third-generation cephalosporins[a]	3	1.98	2.5	0.022
Fluoroquinolones[a]	1	4.43	3.82	0.001
Alcohol-based hand rub[b]	3–4	−6.73	−3.47	0.002
Patients admitted with ESBL[c]	0	0.90	4.35	<0.001
Autoregressive term[d]	1	0.63	3.48	0.003

[a]In DDD/1000 patient-days.
[b]In litres/1000 patient-days.
[c]Patients admitted with ESBL infections or colonizations/1000 patient-days.
[d]The autoregressive term represents the past incidence of ESBL.

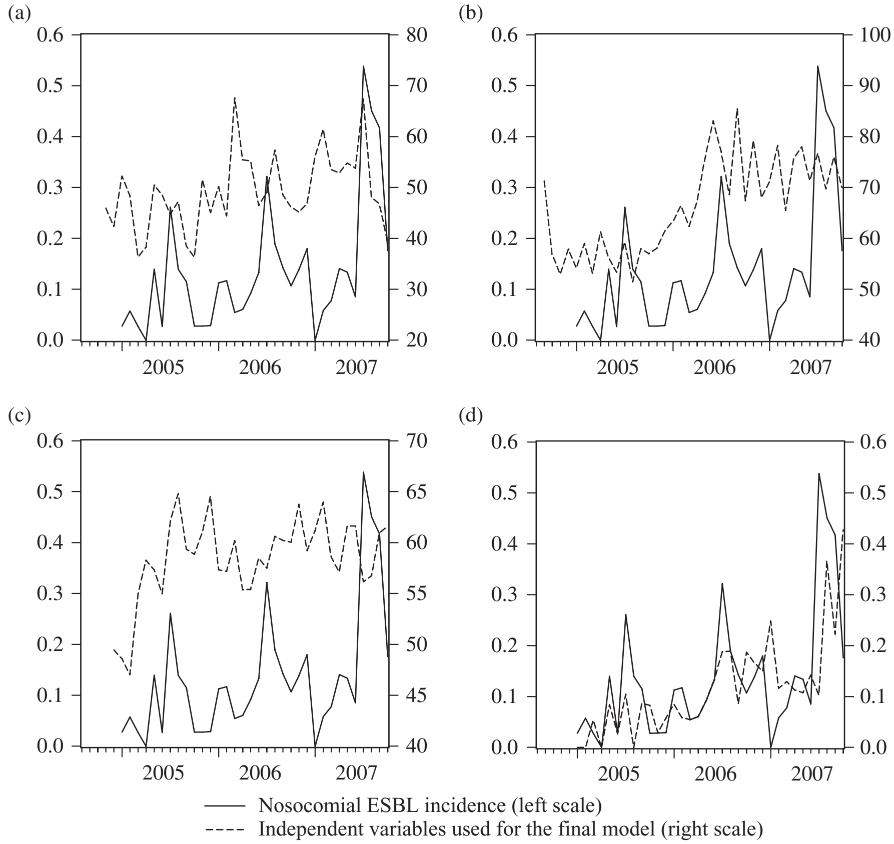

Figure 3. Graphical explorations of the monthly number of nosocomial ESBL cases/1000 patient-days and lagged values of explanatory variables. (a) Third-generation cephalosporin use (in DDD/1000 patient-days, lag 3 months); (b) fluoroquinolone use (in DDD/1000 patient-days, lag 1 month); (c) alcohol-based hand rub use (in litres/1000 patient-days, cumulated lags 3–4 months); (d) patients admitted with ESBL.

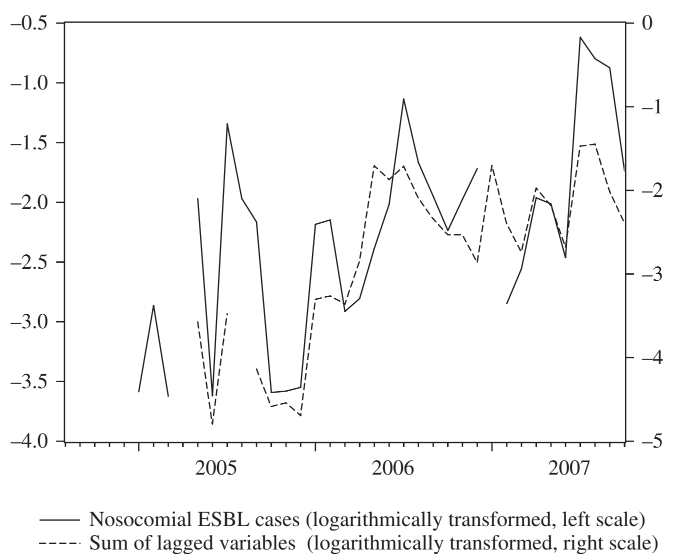

Figure 4. The monthly incidence of nosocomial ESBL/1000 patient-days and monthly sums of lagged independent variables as identified in the model, both logarithmically transformed.

future trends and consequences. The approach has already been used to study the cause–effect relationship between antibiotic use, hand disinfection and MRSA,[13–16,20] but not yet for ESBL.

In previous studies, consumption of fluoroquinolones and third-generation cephalosporins was identified as constituting a risk factor for the selection of ESBLs.[21–23] Our results are also in line with the only study so far to employ time-series analysis for ESBL resistance and antibiotic use: Hay and Pettitt[24] showed that the incidence of ESBL-producing *Klebsiella* spp. in an Australian hospital followed the amount of third-generation cephalosporin use but lagged by 3 months.

The negative impact of hand disinfection on the spread of ESBL-producing organisms in the hospital setting might be small.[9] In our study, however, hand disinfection proved to be an effective measure to control ESBL.[25] This relationship underlines the importance of infection control practices at hospital admission, including screening and isolation.[26]

The limitations of the study must be considered. No admission screening programme was in place for ESBL. Therefore, it is not possible to state the exact number of imported and nosocomially acquired resistant pathogens. Second, aggregated data may be distorted by ecological fallacy. The data were produced at a large teaching university hospital (1600 beds), which might not be representative. Furthermore, there were no reliable data on other ESBL-specific infection control interventions. Also, there was no validation regarding the distribution of alcohol-based hand rub in the hospital or compliance with hand hygiene, but the correlation between consumption and effectiveness has been described previously by others.[27,28]

In conclusion, the driving factors of ESBL resistance were the number of ESBL cases imported to the hospital and the extensive use of fluoroquinolones and third-generation cephalosporins. An easy-to-implement measure for the prevention of ESBL transmission, however, appears to be the use of alcohol-based hand rub.

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Transparency declarations

None to declare.

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