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REVIEW

Impact of Ceftriaxone De-restriction on the Occurrence of ESBL-Positive Bacterial Strains and Antibiotic Consumption

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Summary

As a cost-saving measure, the Drug and Therapeutics Committee (DTC) removed ceftriaxone from the list of restricted antibiotics in May, 2008, which permitted its use as a first-line antibiotic. To evaluate the impact of this change, the occurrence of extended-spectrum beta-lactamase (ESBL)-positive bacterial strains and antibiotic consumption were monitored for 2 years before and after the intervention. In the post-intervention period, ceftriaxone utilization increased, while total antibiotic utilization did not change significantly. The utilization of all restricted antibiotics decreased (p <0.05) in the post-intervention period. Utilization of carbapenems increased (p <0.05), while utilization of quinolones increased nonsignificantly. The density of resistant ESBLs increased (p = 0.001) from 0.99 to 1.34 per 1000 bed-days from the pre- to the post-intervention period. Ceftriaxone use was significantly correlated with ESBL occurrence (p <0.005). It can be concluded that ceftriaxone de-restriction increased the occurrence of ESBLs and the utilization of carbapemens.

Key words: **Antibiotic policy, antibiotic use, cephalosporins, ceftriaxone, ESBLs, resistance.**

INTRODUCTION

In recent years, there have been increasing efforts to control antibiotic use and to promote the rational use of antibiotics [1]. The two main reasons for these activities are the global increases in bacterial resistance and in treatment costs due to the overuse of antibiotics [2]. Antibiotic management strategies include therapeutic guidelines and hospital formal protocols, such as a list of antibiotics with restricted use to control bacterial resistance.

The production of extended-spectrum beta-lactamases (ESBLs) is one of the most important resistance mechanisms that hamper the antimicrobial treatment of infections caused by *Enterobacteriaceae*. ESBLs are classified into several groups according to their amino-acid sequence homology [3]. Antibiotic choices for infections caused by ESBL-producing organisms are limited [4,5]. Treatment of these infections with cephalosporins has been associated with poor clinical outcome, even if the causative organisms appeared to be susceptible to the antibiotics *in vitro* [6]. Furthermore, ESBL-producing isolates tend to show a high rate of resistance to various other classes of antibiotics, such as fluoroquinolones and aminoglycosides [7,8].

Carbapenems (e.g., imipenem, meropenem, and ertapenem) are regarded as the drugs of choice for treating serious infections caused by ESBL-producing organisms. They are stable against the hydrolytic activity of ESBLs, and treatment with carbapenems produces a significantly better clinical outcome than treatment with other antibiotics [9,10]. Most studies have found that third-generation cephalosporin use is a risk factor for ESBL-producing organisms [11].

Because antibiotics represent a large portion of the hospital pharmacy budget, they are usually a main target for cost-saving measures. Cefuroxime is the only second-generation cephalosporin available in Croatia. As a first-line antibiotic, cefuroxime is responsible for the largest share of antibiotics cost at the University Hospital Dubrava. The market price of ceftriaxone, which is included in the list of antibiotics with restricted use at the hospital, is about 40% lower than the market price of cefuroxime. As a cost-saving measure, the DTC decided to remove ceftriaxone from its list of restricted-use antibiotics in May, 2008. This action permitted the use of ceftriaxone as a first-line antibiotic. The goal of this study was to evaluate the impact of this change in the antibiotic use protocol on the occurrence of ESBL-positive bacterial strains and antibiotic consumption at the University Hospital Dubrava.

METHODS

Settings: University Hospital Dubrava is a 600-bed teaching hospital with a medical and a surgical clinic. The DTC monitors and controls the consumption of all drugs, including antimicrobials, and updates the list of restricted antibiotics. Restricted-release antibiotics can only be prescribed when susceptibility is microbiologically proven and/or a drug is approved by the physician, a DTC member.

Data on antibiotic use: Data on antibiotic use were obtained monthly from the computerized hospital pharmacy database. These data are expressed as the number of defined daily doses (DDDs) per 1000 bed-days (b.d.), as defined by the World Health Organization [12]. The observed period was 2 years before (May, 2006 to April, 2008) and 2 years after (May, 2008 to April, 2010) the de-restriction of ceftriaxone.

Microbial resistance data: Resistance density data were collected monthly during the study period from the hospital microbiological laboratory. These data are expressed as the number of ESBL-positive bacterial strain isolates per 1000 bed-days. Microbiology reports included all samples (blood, urine, sputum, wound, cerebrospinal fluid, etc.) taken from hospitalized patients according to clinical indications. 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. Species were identified on the basis of interpretive criteria recommended by the *Clinical Microbiology Procedures Hand-*

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book of the American Society for Microbiology [13].

The antibiotic susceptibility of each isolate was determined by the disc diffusion method of the Clinical and Laboratory Standards Institute (CLSI) [14,15]. Clavulanic acid screening/confirmatory tests were used for ESBL-producing strains [16]. When suspected according to CLSI screening criteria, ESBL production was confirmed by phenotypic CLSI confirmatory double disc synergy test in *Escherichia coli, Klebsiella* spp and *Proteus mirabilis* [14,15]. ESBLs in the other members of the *Enterobacteriaceae* family were detected by minimum inhibitory concentration (MIC) method using the Etest (AB Biodisk, Solna, Sweden) or modified double disc synergy test [17].

ESBL-resistant strains included: *Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp./*cloacae, Proteus mirabilis/vulgaris, Serratia marcescens, Providencia* spp., and *Morganella morganii*. The hospital infection control process, including the isolation policy, did not change during the entire study period. Standard measures for the prevention of hospital infection were consistently implemented.

Statistical analysis: For the statistical analysis of monthly antibiotic consumption and resistance density, 24 time points pre- and 24 time points post-intervention were examined. The statistical analysis mainly consisted of typical descriptive statistics. The significance of the obtained results was determined by Student's *t*-test. The correlation between variables was analyzed by means of the correlation coefficient. Statistical significance was set at $p < 0.05$. All analyses were performed by using MedCalc ver. 11.5 (Mariakerke, Belgium).

RESULTS

The utilization of cefuroxime and ceftriaxone showed the expected changes (*Figure 1*). From the pre- to the post-intervention period, average ceftriaxone use increased from 11.1 to 46.7 DDD/1000 b.d., respectively, and average cefuroxime use decreased from 36.8 to 14.3 DDD/1000 b.d., respectively. Total antibiotic use in the pre- and post-intervention periods was 818.9 and 808.3 DDD/1000 b.d., respectively ($p > 0.05$) (*Table 1*). The use of restricted antibiotics decreased from 104.9 to 95.5 DDD/1000 b.d., respectively, from the pre- to the post-intervention period ($p < 0.05$) (*Table 1*). The average carbapenem use increased from the pre- to the post-intervention period from 15.7 to 18.7 DDD/1000 b.d., respectively ($p < 0.05$) (*Table 1*). Although quinolone use also increased (from 41.7 to 44.0 DDD/1000 b.d., respectively), this change was not significant (*Table 1*).

The proportions of ESBL-positive strains determined did not change significantly during the study period. The predominant ESBL-positive strains were *K. pneumoniae* (62%) and *E. coli* (23%), with all other strains accounting for 15% (*Figure 2*). The

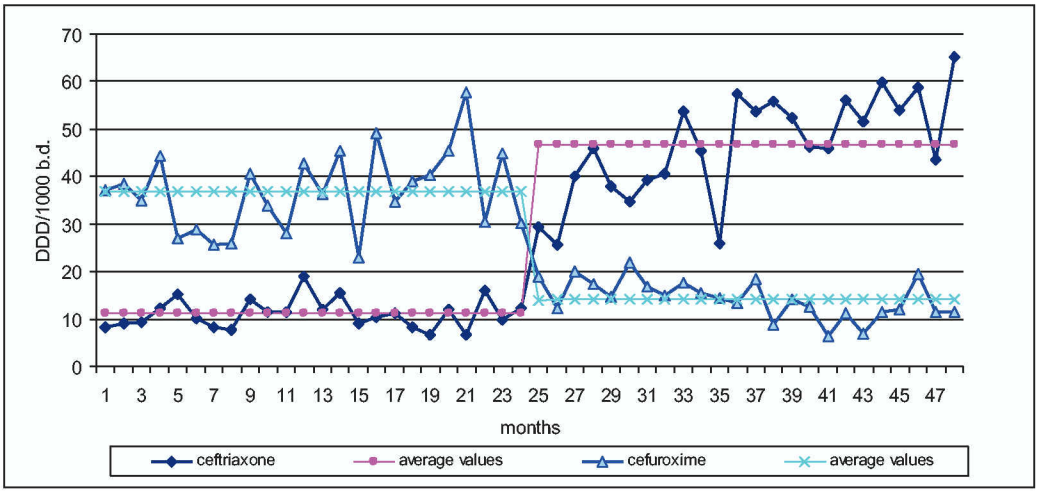

FIGURE 1 - Cefuroxime and ceftriaxone use (DDD/1000 b.d.) in the 24-month pre- (May, 2006 to April, 2008) and 24-month post- (May, 2008 to April, 2010) intervention period. Significance of the changes in utilization ($p < 0.0001$).

TABLE 1 - *Antibiotic use in the pre- (May, 2006 to April, 2008) and post- (May, 2008 to April, 2010) intervention period*

	Pre-intervention period	Post-intervention period	Significance of change
Total antibiotics	818.9 (± 57.1)	808.3 (±77.5)	NS
Restricted antibiotics	104.9 (± 18.2)	95.5 (± 24.8)	p = 0.0297
Carbapenems	15.7 (± 6.2)	18.7 (± 4.9)	p = 0.0372
Quinolones	41.7 (± 9.5)	44.0 (± 9.4)	NS

Data are shown as the mean (± SD) antibiotic usage in DDD/1000 b.d. Significance is defined as $p < 0.05$.

TABLE 2 - *Resistance densities in the pre- and post-intervention periods.*

	Pre-intervention period resistance density	Post-intervention period resistance density	Significance of change
ESBL-positive strains	0.99 (± 0.41)	1.34 (± 0.40)	p = 0.001

Data are shown as the mean (± SD) resistance density per 1000 b.d. Significance is defined as $p < 0.05$.

density of resistant ESBL-positive bacterial strain isolates increased from 0.99 to 1.34 per 1000 b.d., respectively from the pre- to the post-intervention period (*Figure 3, Table 2*) (p = 0.001). A significant correlation (p = 0.002) was observed between ceftriaxone use and the occurrence of ESBL-positive bacterial strains during the study period (*Table 3*).

TABLE 3 - *Correlation between ceftriaxone use (DDD/1000 b.d.) and resistance density (ESBL-positive isolates/1000 b.d.) during the study period.*

Correlation coefficient r	0.4358
95% Confidence interval for r	0.1731 - 0.6406
Significance level	p = 0.0020

DISCUSSION

During the study period there were between 27,000 – 29,000 hospital admissions per year. No variation in the incidence of ESBL-producing bacteria was noted in the admitted population. In the pre-intervention period, ceftriaxone represented 1.3% of total antibiotic consumption. Its share in the post-intervention period increased 4.5-fold, as the antibiotic was substituted for the more expensive cefuroxime as a first-line antibiotic. Ceftriaxone was mainly used for the treatment of respiratory and urinary tract infections, skin and soft tissue infections and infections associated with surgery. During this period, total antibiotic use did not change significantly. The hospital list of restricted antibiotics contained 17 antibiotics in the pre- and 16 antibiotics in the post-intervention period, including carbapenems and quinolones, and did not change during the 4-year period, except for the removal of ceftriaxone. The utilization of antibiotics with restrictive use significantly decreased, due to the de-restriction of ceftriaxone.

Carbapenem use was significantly increased in the post-intervention period. The share of carbapenems among all of the restricted antibiotics utilized increased from 15% in the pre- to almost 20% in the post-intervention period. The higher carbapenem (imipenem, meropenem, and ertapenem) use, which are the drugs of choice for treating serious infections caused by ESBL-producing organisms, corresponded with a significantly increased density of resistant ESBL-positive bacterial isolates in the post-intervention period. The increase in quinolone use, although not significant, was probably related to the increased resistance density.

Quinolones also are used to treat nosocomial infections caused by ESBL-producing organisms based on acceptable susceptibility testing, according to the report of Committee for Antibiotic Resistance Surveillance in Croatia [18], which is a part of the European Antimicrobial Resistance Surveillance System (EARSS). The increased use of ceftriaxone, a third-generation cephalosporin, was associated with a significant increase in the occurrence of ESBL-positive bacterial strains isolates. Other

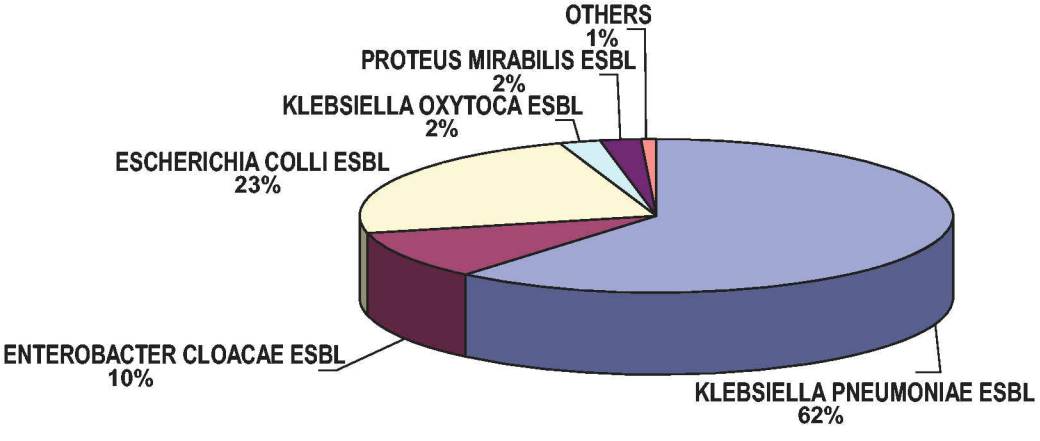

FIGURE 2 - Proportions of determined ESBL-positive strains during the study period.

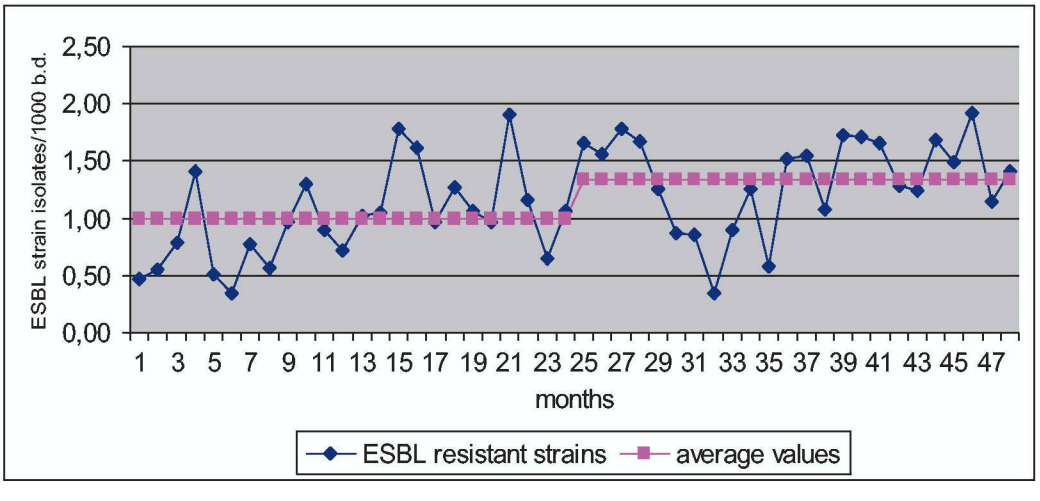

FIGURE 3 - Resistance density (ESBL-positive strains isolates/1000 b.d.) in the 24-month pre- (May, 2006 to April, 2008) and 24-month post- (May, 2008 to April, 2010) intervention period.

studies also document the adverse influence of the frequent use of third-generation cephalosporins on the spread of ESBL-positive bacterial pathogens. Their extensive use is considered to be an independent risk factor [19-21]. According to the previous report, high utilization of third-generation cephalosporins was associated with an increase in frequency of ESBL-positive *K. pneumoniae* strains of 10-24% [22,23]. The results of our study are consistent with these previous findings.

The correlation between increased antibiotic use and subsequently increased resistance is not simple and is influenced by many confounding factors. In general, inpatients are exposed to infection caused by ESBL-positive pathogens during prolonged hospitalization and because of invasive entry, through the insertion of endotracheal, urinary, or central venous catheters [24,25]. Another important risk factor is previous antibiotic treatment. Cephalosporins are popular as effective and safe antibiotics, but their increasing use has a negative epidemiological impact. Therefore, a reduction in the use of third-generation cephalosporins and their replacement with different types of antibiotics seems necessary.

This study suggests that the de-restriction of ceftriaxone and its wide use as a first-line antibiotic result in the significantly increased occurrence of ESBL-positive bacterial strains and consequently increased carbapenem use. Thus, this intervention cannot be considered as a cost-saving measure; only consistent drug policies and continuous rational drug-prescribing programs can be effective in the long-term. Otherwise, after a short-term cost improvement, deterioration of bacterial susceptibility can be expected. Based on the changes in resistance rates, the antibiotic policy was adapted.

Study limitations

The increase in ESBL infections may have been related to a difference in case-mix or admission types. Although such differences were not noted during the study period, they cannot be completely ruled out.

CONFLICT OF INTEREST: The authors have no conflicts of interest to declare.

ETHICAL APPROVAL: Not required; this study did not include individual patient data and, as a part of a hospital quality assurance program, did not require ethics committee approval.

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