Switching From Ceftriaxone to Cefotaxime Significantly Contributes to Reducing the Burden of Clostridioides difficile Infections

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We analyzed Clostridioides difficile infection (CDI) rates and various antimicrobials’ application densities from 2013 to 2019 at Leipzig University Hospital, Germany, by using multivariate linear regression. Ceftriaxone application was the only independent predictor of CDI incidence. Thus, antimicrobials’ specific pharmacokinetic and pharmacodynamic properties such as biliary excretion of ceftriaxone in its active form should be considered when determining their potential to cause CDI.

Keywords. antimicrobial stewardship; cephalosporines; biliary excretion; Clostridioides difficile; PK/PD.

Clostridioides difficile infections (CDIs) are a global health threat [1]. Since 2003, an increase in the incidence and severity of the disease has been reported worldwide [2, 3]. While CDI cases increased dramatically between 2000 and 2011 in the United States [4, 5], there was a total decrease of 24% from 2011 to 2017 in health care–associated cases [5]. Interestingly, infections and community-associated CDIs remained almost unchanged during this period; the latter even increased in recent years [5, 6].

For Germany, an analysis of discharge diagnoses in 2000 to 2004 showed a significant increase in CDIs from 7 to 39 cases per 100,000 inpatients, which doubled between 2004 and 2006 [3, 7]. Even if the overall prevalence rates decreased slightly since 2013 (from 0.52 cases per 100 patients in 2013 to 0.37 cases per 100 patients in 2018), the number of severe or lethal cases in Germany continued to increase (from 0.03 cases per 1000 patient bed days [PBDs] in 2013 to 0.05 cases per 1000 PBDs in 2018) [8, 9].

In addition to patient age and comorbidities, the application densities of broad-spectrum antibiotics have been postulated by various studies to be the main risk factors for CDIs [5, 6, 10, 11]. However, the specific antibiotic agents that have the greatest impact on CDI rates in hospital settings remain unclear. To explore this question, we analyzed the CDI rates and application densities of various antibiotics from 2013 to 2019 at a large university hospital in Leipzig, Germany.

METHODS

Hospital Setting

The Leipzig University Hospital (UKL) is a tertiary care provider with 1451 beds and 29 clinics of all specialties located in the state of Saxony in the eastern part of Germany.

Antimicrobial Stewardship Intervention

An interdisciplinary antimicrobial stewardship (AMS) program has been established at the UKL since 2012, with subsequent implementation of various measures to optimize antibiotic prescriptions [12]. This includes regular ward visits by an interdisciplinary and trained AMS team, implementation of annually updated institution-specific antibiotic guidelines, AMS training of staff, restriction of selected antibiotics, and surveillance of hospital-associated infection rates, bacterial resistance, and antibiotic use. From the beginning, these AMS interventions aimed to optimize the use of broad-spectrum antibiotics, especially fluoroquinolones, broad-spectrum cephalosporins, and carbapenems.

Data Collection

The application densities of selected antibiotics were recorded by the hospital pharmacy and presented as recommended daily doses (RDDs) [13] per 100 PBDs for the years 2013 to 2019 (Table 1).

CDI rates were monitored by the Institute of Medical Microbiology and Epidemiology of Infectious Diseases and presented as relative values per 1000 PBDs. Case-related CDI data included C. difficile cultures, positive enzyme immunoassays (EIAs) detecting glutamate dehydrogenase (GDH) and toxins A and B, and nucleic acid amplification tests (NAAT) of a stool sample. Samples without free toxin detected by toxins A and B EIA but with positive GDH, EIA, NAAT, or toxigenic culture were recorded as asymptomatic carriage and were not counted as CDI cases in our
evaluation. The method of detection was not changed during the investigation period.

To identify possible confounders, information was also collected on the patients’ mean age, mean disease severity using the case mix index (CMI), mean length of hospital stay (LOS), and the application densities of proton pump inhibitors (PPIs).

Statistics
A multivariate linear regression model was used to estimate the influence of 16 independent x variables on 1 dependent y variable (y = CDI/1000 PBDs) per year. Other variables that are not explicitly listed in Table 1 were not considered. The regression coefficients (R) were calculated step by step and in the reverse direction starting with all independent variables. These calculations were carried out using SPSS, version 24.0 (IBM, Armonk, NY, USA). The aim was to identify the x variable with the greatest significant influence on CDI incidence.

RESULTS
All original data and results of multiple regression are shown in Table 1. Multicollinearity was excluded in advance (tolerance, 1.0; variance influence factor, 1.0). Ceftriaxone turned out to be the only independent predictor of CDI incidence: R = .673; 95% CI, 0.411–0.935; P < .001; SEM, 0.102.

DISCUSSION
The risk of CDIs is essentially determined by the use of certain antibiotic groups and the overall consumption rate of antibiotics [11]. In particular, restricting the use of cephalosporins is generally proposed to reduce CDI rates. However, despite a reduction in overall cephalosporin consumption, the CDI incidence could not be reduced in many countries [11]. There is no clear association between prescribing cephalosporins and CDIs when looking at specific categories or overall consumption rates. Assessing which individual substances are the main CDI drivers seems important. Obviously, factors such as...
pharmacokinetic and pharmacodynamic parameters (PK/PD) have an explanatory potential for the development of CDI. CDI risk and antibiotic usage are much more complicated than simply correlating the risk with the drug type.

At our institution, we observed a sharp decline of CDI rates by 68% from 2013 to 2019, even though the overall prescription of cephalosporins remained more or less unchanged in the same time period, and the application density of third-generation cephalosporins as a whole increased. Thus, taking a closer look at the systemic and molecular behavior of single substances is important. Most cephalosporins, such as cefotaxime, cefadroxil, cefalexin, cefuroxime, ceftazidime, and ceftobiprol, are excreted primarily via the kidneys through glomerular filtration. By contrast, a few cephalosporins such as ceftriaxone are biliary-excreted to a large extent (30%-40% of its active form) [11]. However, this means that a substantial amount of the antibiotic substance can also be found in the intestines, having a lasting effect on the gut microbiota. The human intestinal microbiome provides an important host defense factor against C. difficile. Disruption of the gut microbiota helps create favorable conditions for CDI development. In general, cephalosporins have poor in vitro activity against C. difficile [11]. If large amounts of ceftriaxone are in contact with the intestinal microbiota, C. difficile may be selected. Moreover, ceftriaxone promotes spore germination and toxin production [14]. Both properties contribute to a higher CDI incidence.

In this study, the influence of ceftriaxone on the CDI rate can even be interpreted as strong and significant (R = .673; P < .001). The concentrations and activity of cephalosporins in the gut can also be affected by the presence of β-lactamases expressed by commensal bacteria. However, this topic has not been sufficiently investigated. By contrast, in our analysis, the antibiotic tigecycline did not appear to be an independent predictor of CDI, although it is excreted in large amounts via the bile. The best way to explain this is that tigecycline itself has a bacteriostatic effect on clostridia [15]. Although tigecycline has comparable pharmacokinetic properties to ceftriaxone, their pharmacodynamic effects are completely different.

Use of third-generation cephalosporins at our institution includes ceftriaxone, ceftazidime ± β-lactamase inhibitors, cefixime, and mainly cefotaxime. Ceftriaxone and cefotaxime have a comparable spectrum of antimicrobial activity (ie, the same pharmacodynamic properties), but they are different in terms of pharmacokinetics. In our AMS program, we have largely replaced ceftriaxone (64% reduction in application density from 2013 to 2019) with cefotaxime. This important goal was mainly achieved by establishing cefotaxime instead of ceftriaxone in our institution-specific antibiotic guidelines.

Interestingly, clindamycin was not a significant influencing variable in this analysis. Its application density even increased from 2013 to 2019, while CDI incidence decreased. In some studies, the importance of clindamycin with regard to the CDI incidence in the hospital setting may have been overestimated. However, our analysis cannot adequately explain this finding.

This study has several limitations. First, it is a monocentric retrospective observational analysis and not a multicentric prospective intervention study. Naturally, no causality between the variables can be proven. Possible confounding factors include the presence of comorbidities, polypharmacy, C. difficile outbreak events, dose and duration of the antibiotic treatments, and use of multiple substances. Moreover, our analysis may be subject to the choice of potential predictors for CDI incidence. The focus was just on antibiotics, but our AMS program contains a bundle of different measures.

Future investigations should examine other potential factors that could affect CDI incidence. Determining whether other hospitals can show a comparable relationship between ceftriaxone and CDIs would also be interesting. To our knowledge, there is currently no prospective study that answers this question. However, we interpret the application density of ceftriaxone as at least one important factor for CDI. Nevertheless, many other important AMS and hospital epidemiology tools and strategies must be considered.

CONCLUSIONS

CDI incidence seems to be sustainably reduced by choosing appropriate antibiotics in combination with other established AMS interventions. Thus, considering the pharmacokinetic and pharmacodynamic properties of individual substances is important. As a biliary-excreted antibiotic, ceftriaxone appears to have a significant influence on CDI incidence.

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