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

Sebastian Wendt,[1,2,3] Donald Ranft,[3,4] Arne C. Rodloff,[2,3] Norman Lippmann,[2,3] and Christoph Lübbert[1,3,5]

[1]Division of Infectious Diseases and Tropical Medicine, Department of Medicine II, Leipzig University Hospital, Leipzig, Germany, [2]Institute for Medical Microbiology and Epidemiology of Infectious Diseases, Leipzig University Hospital, Leipzig, Germany, [3]Interdisciplinary Center for Infectious Diseases, Leipzig University Hospital, Leipzig, Germany, [4]Hospital Pharmacy, Leipzig University Hospital, Leipzig, Germany, and [5]Department of Infectious Diseases/Tropical Medicine, Nephrology and Rheumatology, Hospital St. Georg, Leipzig, Germany

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, antibiotics' 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, reinfections 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

Table 1. Overview of All Data From 2013 to 2019 for CDI Rates With Reference to the Application Densities of Various Antimicrobial Agents, Occupancy Data Including Case Mix Index and Mean Age of Patients, and Consumption of PPIs

Year	2013	2014	2015	2016	2017	2018	2019		
Number of CDIs	523	279	290	265	207	168	169		
CDI per 1000 PBDs	1.48	0.77	0.82	0.67	0.52	0.48	0.47		
PBDs	354 148	361 814	353 027	394 110	394 732	351 173	358 578		
								R	*P* Value
Mean case mix index	1.493	1.450	1.53	1.533	1.528	1.529	1.498	.246	.157
Patients' mean age, y	47.7	47.9	48.8	48.9	49.1	49.5	49.8	.380	.393
Mean length of hospital stay, d	7.85	7.54	7.44	7.55	7.49	7.4	7.37	.425	.143
Antibiotic agents in RDDs per 100 PBDs									
Systemic antibiotics (total)	48.29	43.63	47.3	42.83	41.63	49.21	47	.053	.761
Cephalosporins (total)	8.38	7.68	8.65	7.55	7.84	8.87	9.35	.081	.639
First-generation cephalosporins	0.12	0.14	0.14	0.1	0.17	0.21	0.27	−.006	.978
Second-generation cephalosporins	4.57	4.07	4.47	3.73	3.85	3.84	3.53	.136	.658
Third-generation cephalosporins	3.69	3.47	4.04	3.72	3.82	4.82	5.55	.074	.725
Ceftriaxone	1.88	1.35	1.08	0.82	0.55	0.67	0.51	.673	<.001***
Cefotaxime	0.65	0.96	1.78	2.02	2.62	3.66	4.58	.139	.671
Carbapenems	4.44	4.33	4.65	4.04	4.22	5.13	4.45	−.053	.754
Clindamycin	2.28	2.76	2.72	2.68	2.6	3.12	3.72	−.103	.647
Fluoroquinolones	10.84	8.54	8.98	8.25	7.64	8.26	5.05	.091	.763
Tetracyclines (total)	1.17	1.31	1.32	1.42	1.2	1.27	1.14	−.127	.436
Doxycycline	0.71	0.83	0.86	0.90	0.85	0.85	0.87	−.276	.331
Tigecycline	0.46	0.47	0.46	0.52	0.34	0.42	0.27	−.112	.583
Nonantibiotic agents in DDDs per 100 PBDs									
PPIs	123.26	147.61	150.8	133.91	130.77	146.65	148.18	−.238	.132

The results of the multiple regression are shown in the columns on the far right. ***Indicates *P* < .001.

Abbreviations: CDI, *Clostridioides difficile* infection; DDDs, defined daily doses; PBDs, patient bed days; PPIs, proton pump inhibitors; RDDs, recommended daily doses.

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. Other antibiotics (especially fluoroquinolones, all cephalosporins, carbapenems, tigecycline, and clindamycin), the total consumption of antibiotics as well as the application density of PPIs, the mean CMI, the mean LOS, and the mean age of patients did not have a significant influence. Statistical calculations using defined daily doses (DDDs) instead of recommended daily doses (RDDs) gave comparable results.

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, cafalexin, 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 $\pm \beta$-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.

References

1. Czepiel J, Dróżdż M, Pituch H, et al. *Clostridium difficile* infection: review. Eur J Clin Microbiol Infect Dis **2019**; 38:1211–21.
2. Seugendo M, Janssen I, Lang V, et al. Prevalence and strain characterization of *Clostridioides* (*Clostridium*) *difficile* in representative regions of Germany, Ghana, Tanzania and Indonesia - a comparative multi-center cross-sectional study. Front Microbiol **2018**; 9:1843.
3. Robert Koch-Institut. *Clostridioides* (früher *Clostridium*) *difficile* 2018. Available at: https://www.rki.de/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber_Clostridium.html. Accessed 7 August 2020.
4. Centers for Disease Control and Prevention. *Clostridioides difficile* (*C. diff*) 2018. Available at: https://www.cdc.gov/cdiff/index.html. Accessed 7 August 2020.

5. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. burden of *Clostridioides difficile* infection and outcomes. N Engl J Med **2020**; 382:1320–30.

6. Roo AC de, Regenbogen SE. *Clostridium difficile* infection: an epidemiology update. Clin Colon Rectal Surg **2020**; 33:49–57.

7. Vonberg RP, Schwab F, Gastmeier P. *Clostridium difficile* in discharged inpatients, Germany. Emerg Infect Dis **2007**; 13:179–80.

8. Nationales Referenzzentrum für Surveillance von Nosokomialen Infektionen. KISS Krankenhaus-Infektions-Surveillance-System. Modul CDAD-KISS Referenzdaten 2019. Available at: https://www.nrz-hygiene.de/fileadmin/nrz/module/cdad/201801_201812_CDAD_Ref.pdf. Accessed 7 August 2020.

9. Robert Koch-Institut. Infektionsepidemiologisches Jahrbuch meldepflichtiger Krankheiten für 2018. Available at: https://www.rki.de/DE/Content/Infekt/Jahrbuch/Jahrbuch_2018.pdf?__blob=publicationFile. Accessed 7 August 2020.

10. Eze P, Balsells E, Kyaw MH, Nair H. Risk factors for *Clostridium difficile* infections - an overview of the evidence base and challenges in data synthesis. J Glob Health **2017**; 7:010417.

11. Wilcox MH, Chalmers JD, Nord CE, et al. Role of cephalosporins in the era of *Clostridium difficile* infection. J Antimicrob Chemother **2017**; 72:1–18.

12. Deutsche Gesellschaft für Infektiologie (DGI). S3-Leitlinie Strategien zur Sicherung rationaler Antibiotikaanwendung im Krankenhaus 2018. Available at: https://www.antibiotic-stewardship.de/fileadmin/media/initiative/Langfassung_der_Leitlinie_Strategien_zur_Sicherung_rationaler_Antibiotika-Anwendung_im_Krankenhaus.pdf. Accessed 7 August 2020.

13. Först G, de With K, Weber N, et al; ABS-QI Study Group. Validation of adapted daily dose definitions for hospital antibacterial drug use evaluation: a multicentre study. J Antimicrob Chemother **2017**; 72:2931–7.

14. Baines SD, Chilton CH, Crowther GS, et al. Evaluation of antimicrobial activity of ceftaroline against *Clostridium difficile* and propensity to induce *C. difficile* infection in an in vitro human gut model. J Antimicrob Chemother **2013**; 68:1842–9.

15. Kechagias KS, Chorepsima S, Triarides NA, Falagas ME. Tigecycline for the treatment of patients with *Clostridium difficile* infection: an update of the clinical evidence. Eur J Clin Microbiol Infect Dis **2020**; 39:1053–8.