

Interprofessional Antimicrobial Stewardship Influencing *Clostridioides difficile* Infection: An 8-Year Study Using Antimicrobial Use Density

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Purpose: To reduce *Clostridioides difficile* infection (CDI), we implemented interprofessional antimicrobial, infection control, and diagnostic stewardship (ipAS) conducted by physicians/pharmacists, infection control nurses, and medical technologists, respectively. As a numerical indicator for ipAS, we used antimicrobial use density (AUD) in an 8-year study to validate its efficacy in CDI reduction.

Patients and methods: This was an observational study. CDI was defined as stool samples or *C. difficile* isolates containing toxin A and/or B from a patient with diarrhea occurring three or more times per day. From 2011–2018 at a 10-ward single site the subjects were in-patients with CDI, and the following data were collected: AUDs for 23 antibiotics, and antimicrobial test results. By 2015, we had established ipAS, consisting of culture submission before the administration of broad-spectrum antimicrobials, the promotion of point-of-care testing for diagnosis-based antimicrobials, perioperative prophylactic antibiotics, intervention at positive diagnosis of blood culture, team round for diarrhea, and inspection on contact precautions and disinfection in CDI cases. The study outcomes included annual numbers of CDI patients and blood culture sets. We compared annual AUDs between former (2011–14) and latter (2015–18) periods using Kruskal–Wallis tests and examined the correlation between AUDs and CDI numbers.

Results: Of a total 50,970 patients, 1,750 patients underwent *C. difficile* toxin tests, of whom 171 patients (9.8%) were positive for CDI. Between the former and latter periods, AUDs for flomoxef (11.96 to 2.71 by medians), panipenem/betamipron (0.30 to 0.00), and clindamycin (3.87 to 2.19) significantly decreased ($P < 0.05$) as did numbers of CDIs (26.5 to 10) ($P = 0.043$). The correlation analysis revealed a significant correlation between AUD for flomoxef and CDIs ($P = 0.004$) and the AUD for piperacillin/tazobactam and CDIs ($P = 0.010$) with a positive Pearson r .

Conclusion: The integrated antimicrobial, diagnostic, and infection control approach used in ipAS may reduce CDIs.

Keywords: broad-spectrum antibiotics, infection control, diagnosis, multidisciplinary, clindamycin

Introduction

Bui et al reported that antimicrobial stewardship focusing only on high-cost antibiotics results in missed opportunities to reduce *Clostridioides difficile* infection (CDI), while the use of low-cost antibiotics, such as clindamycin (CLDM), was out of control.¹ In addition, Patton et al reported constant CDI in surgery wards despite antibiotic stewardship efforts, demonstrating that the real-world impact of stewardship interventions remains limited.²

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To address the complex task of containing CDIs, Yanke et al attempted an interprofessional approach, leading to the detection of barriers to the successful implementation of a CDI prevention bundle, such as a lack of sinks and *C. difficile* polymerase chain reaction testing.³ Likewise, our community hospital in Japan implemented interprofessional antimicrobial, infection control, and diagnostic stewardship (ipAS) in a similar multifaceted approach, but with cycles of Plan-Do-Check-Act (PDCA). We conducted a retrospective observational study to verify its efficacy in reducing CDIs.

Materials And Methods

Ethics

The institutional ethics board for research (Rinri Kenkyu linkai, in Japanese) permitted this study to be published and approved the study protocol (serial number 2018SCHEC-026).

Materials

In a single institute with a total of 10 wards, we collected a consecutive series of *C. difficile* toxin tests (CDTs) from 2011 to 2018. For the CDTs, we initially employed the TOX A/B QUIK CHEK[®] test (Nissui Co. Tokyo, Japan). By 2012, we employed the *C. DIFF* QUIK CHEK COMPLETE[®] (Alere Medical Co., Ltd, Tokyo, Japan), by 2013, the CD Immunochromato-CD A/B GE test (Nissui Co. Tokyo, Japan), by 2014, the *C. DIFF* QUIK CHEK COMPLETE (Alere Medical Co., Ltd, Tokyo, Japan), and by 2016 and thereafter, the GE Test Immunochromato-CD GDH/TOX[®] test (Nissui Co., Tokyo, Japan).

For antimicrobial use density (AUD), we collected data on annual patient-days and the total dose of 23 agents: ampicillin, ampicillin/sulbactam, cefazolin (CEZ), cefmetazole (CMZ), cefoperazone/sulbactam, cefotaxime (CTX), cefotiam, cefozopran, ceftazidime, ceftriaxone (CTRX), ciprofloxacin (CPFX), CLDM, flomoxef (FMOX), fosfomicin, imipenem/cilastatin (IPM/CS), linezolid, meropenem (MEPM), minocycline, panipenem/betamipron (PAPM/BP), penicillin G, piperacillin (PIPC), piperacillin/tazobactam (PIPC/TAZ), and vancomycin.

Methods

Definition

A positive CDT was defined as being positive for toxin A and/or B in feces or culture isolates, regardless of glutamate dehydrogenase (GDH) results, because historically GDH was not available in the initial years of the study. To

increase the test sensitivity for *C. difficile* toxin, as ordered by the attending doctors, we isolated *C. difficile* strains using cycloserine-cefoxitin-mannitol agar plates, including the Nissui Plate CCMA EX (Nissui Pharmaceutical Co., Ltd, Tokyo, Japan) since 2011, and Vital Media CCMA Medium (Kyokuto Pharmaceutical Industrial Co., Ltd, Tokyo, Japan) since 2015. CDI was defined as a positive CDT in the presence of three or more episodes of diarrhea per day. CDTs were performed in all of the patients who showed diarrhea preceded by antibiotic administration.

Intervention

Previously, physicians had administered antimicrobials to patients at their discretion. Since 2013, however, we restricted the use of carbapenem antibiotics and by 2015, we established a protocol to control the use of broad-spectrum antibiotics, such as MEPM, IPM/CS, cefepime, and PIPC/TAZ based on the following concepts. (1) Antibiotic use must meet the indications and preceding culture sampling as stated by the sepsis guideline⁴ or (2) must be performed in the presence of microbes producing an extended spectrum beta-lactamase inhibitor. In addition, perioperative patients received prophylactic antibiotics in accordance with the Japanese guidelines for the prevention of surgical site infection,⁵ a modification of that released by the Centers for Disease Control and Prevention in 1999.⁶ To assist compliance, we used a clinical pathway in perioperative patients, and administered CEZ as a prophylactic antimicrobial.⁷ During consultations on suitable agents for anaerobic microbes, CLDM usage was discouraged for CDIs, and the use of metronidazole was encouraged to reduce the risk posed by anaerobes. For PDCA cycles to reduce broad-spectrum antibiotic use, the interprofessional team shared AUD data on the intranet and in monthly audits.

For infection control, patients with CDIs underwent isolation, contact precaution, and sodium hypochlorite disinfection of their environment in accordance with British guidelines.⁸ Interprofessional team rounds were performed to detect unreported diarrhea cases, which frequently occurred and were amended in a PDCA cycle.

In terms of diagnostic stewardship, blood or other cultures were mandated before the use of broad-spectrum antibiotics. Additionally, we encouraged point-of-care testing such as a urinary antigen test for *Streptococcus pneumoniae* and *Legionella pneumophila* (QuickChaser; Mizuho Medie Co., Saga, Japan) for targeted antibiotics. On receipt of positive culture results, microbiological

technicians issued intranet alert electronic mails to attending doctors for de-escalation or, on isolation of drug-resistant microbes, for a change to more effective drugs.

Analysis

AUD was calculated as

$$\text{AUD} = (\text{total dosage}) / (\text{DDD} \times \text{patient-day}) \times 1000$$

where DDD stands for defined daily dose, as defined by the World Health Organization.⁹

The primary endpoint was the time shift in the AUDs of 23 antibiotics and numbers of CDIs. For statistical analysis, we used the Kruskal–Wallis test to compare the former (2011–14) and latter (2015–18) periods. Another primary endpoint was the risk of AUDs for CDIs. To assess the correlation between the AUDs of 23 antibiotics and CDI numbers, the Pearson correlation coefficient was analyzed between annual AUDs and CDI numbers.

Secondary endpoints included the time shift in the numbers of blood culture sets, and the number of point-of-care tests performed. For statistical analysis, we used the Kruskal–Wallis test to compare the former and latter periods. We used SPSS Version 24 (IBM Inc., Armonk, NY) for these analyses.

Results

Overview

Of a total 50,970 patients, 1,750 patients underwent CDTs, of whom 171 patients (9.8%) were positive for CDIs. Among the 171 patients, with a median age of 81 (range, 45–105 years), 91 (53.2%) were male and 80 (46.8%) were female.

Primary Endpoint

Comparing the former and latter periods, the AUDs of FMOX, PAPM/BP, and CLDM decreased whereas those of CEZ, CMZ, CTX, and CTRX significantly increased ($P < 0.05$) (Table 1). The numbers of CDI patients decreased significantly ($P = 0.043$). Annually, the number of CDI patients peaked at 35 in 2013 and decreased thereafter (Figure 1).

The correlation analysis revealed a significant correlation ($P < 0.05$) between the AUD of FMOX and CDIs as well as between the AUD of PIPC/TAZ and CDIs, with positive Pearson r values for both (Table 2).

Secondary Endpoints

During the former period, numbers of total blood culture sets and positive blood culture results remained consistently low. After the implementation of ipAS, both numbers

Table 1 Comparison Of AUDs For 23 Antibiotics And Numbers Of Blood Culture Sets And Point-Of-Care Tests For *Streptococcus pneumoniae*, And CDI Cases, As Assessed Using Kruskal–Wallis Tests

		2011–14, Median	2015–18, Median	P
AUD of Antibiotics	Ampicillin	0.9139	2.27223	0.248
	Ampicillin/ sulbactam	32.9589	41.6487	0.021 *
	Cefazolin	36.2477	43.5406	0.021 *
	Cefmetazole	5.02636	9.57001	0.043 *
	Cefoperazone/ sulbactam	4.75143	4.03224	0.248
	Cefotaxime	1.12702	1.92385	0.021 *
	Cefotiam	0.72078	1.39071	0.083
	Cefozopran	0.58756	0	0.166
	Ceftazidime	3.76293	0.96694	0.245
	Ceftriaxone	11.275	16.2497	0.021 *
	Ciprofloxacin	0.48493	0.72586	0.083
	Clindamycin	3.86942	2.18664	0.021 *
	Flomoxef	11.9609	2.70867	0.021 *
	Fosfomycin	0.47529	0.20433	0.386
	Imipenem/ cilastatin	1.20446	1.41945	0.564
	Linezolid	1.37473	1.46061	0.773
	Meropenem	3.76568	4.91714	0.149
	Minocycline	0.23812	0.12157	0.043 *
	Panipenem/ betamipron	0.2988	0	0.018 *
	Penicillin G	1.18094	2.22135	1
	Piperacillin	0.27991	0.14207	0.021 *
	Piperacillin/ tazobactam	26.9828	17.3919	0.386
	Vancomycin	1.60517	2.05975	0.386
Blood culture	Total (sets)	1125	2275	
	Positives (sets)	173.5	287.5	0.021 *
<i>S.</i> <i>pneumoniae</i> testing	Total	367.5	534	
	Positives	29.5	73	0.083
CDIs	(patients)	26.5	10	0.043 *

Note: *Statistical significance ($P < 0.05$).

Abbreviations: AUD, antimicrobial use density; CDI, *Clostridioides difficile* infection.

significantly increased (both $P = 0.021$ by Kruskal–Wallis test) (Table 2). Likewise, levels of point-of-care testing for *S. pneumoniae* showed an increased tendency in the latter period ($P = 0.083$).

Discussion

Herein, we report that ipAS decreased CDIs in hospitalized patients, which was associated with increased AUDs

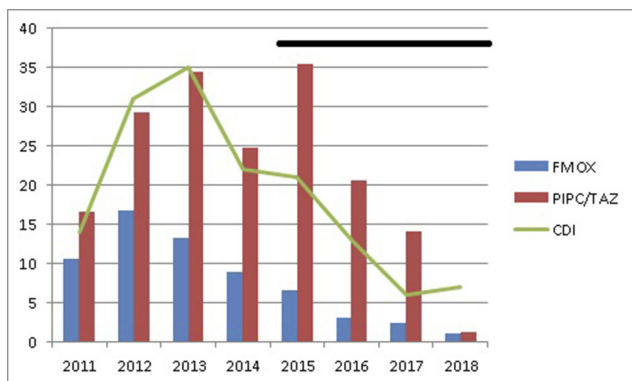


Figure 1 Annual trend of AUDs and number of CDI patients before and after intervention (black bar). FMOX and PIPC/TAZ are significantly correlated with number of CDI patients (Table 2). Time course of AUDs for PIPC/TAZ coincided with that for CDIs. Vertical axis shows AUD and number of CDI patients.

Abbreviations: AUD, antimicrobial use density; CDI, *Clostridioides difficile* infection; FMOX, flomoxef; PIPC/TAZ, piperacillin/tazobactam.

for broad-spectrum antibiotics and CLDM, as previously reported in the literature. Likewise, a correlation analysis showed a significant positive relationship between the AUD of PIPC/TAZ and CDI cases. The numbers of blood culture tests and point-of-care tests for *S. pneumoniae* also increased in the latter period, supporting the role of diagnostic stewardship.

Relevant guidelines, such as those published by the German Society of Infectious Diseases, state that antimicrobial stewardship helps to control CDIs.¹⁰ Huttner et al addressed the “4C” (cephalosporins, CPFX and other fluoroquinolones, co-amoxiclav, and CLDM) approach to reduce CDIs.¹¹ We also observed decreased use of CLDM in the current study.

In terms of clinical pathways and antimicrobial stewardship, the combined medical associations of Germany reported that antimicrobial stewardship for surgical site infection (SSI) reduced CDIs.¹² Our clinical pathways for perioperative care routinely designated CEZ for prophylaxis against SSI and a duration of treatment of 2 days in accordance with the Japanese guidelines. Recently, a “Global Declaration on Appropriate Use of Antimicrobial Agents” was issued to enhance the use of the surgical pathway.¹³

In terms of the quantitative evaluation of antimicrobial stewardship, several authors have used AUDs. Niwa et al used AUDs in 2012 to assess their intervention.¹⁴ In 2014, Yoon and others used AUDs for carbapenems to measure the effect of an intervention with carbapenems on the susceptibility of *Acinetobacter baumannii*.¹⁵ In 2015, Borde et al used AUDs for third-generation cephalosporin and fluoroquinolone as a metric.¹⁶ Hohn and others assessed AUDs before and after their intervention with surgical prophylactic

Table 2 Correlation Between Antimicrobial Use Density (AUD) Of 23 Antibiotics And Number Of CDI Patients, As Assessed Using A Pearson Correlation Analysis. Positive Pearson r Indicates That Increased AUD Is Correlated With Increased Number Of CDI Cases

		Pearson r	P
AUD of Antibiotics	Ampicillin	-0.512	0.195
	Ampicillin/sulbactam	-0.458	0.235
	Cefazolin	-0.447	0.267
	Cefmetazole	-0.674	0.067
	Cefoperazone/sulbactam	0.008	0.948
	Cefotaxime	-0.337	0.414
	Cefotiam	-0.521	0.185
	Cefozopran	0.031	0.947
	Ceftazidime	0.342	0.407
	Ceftriaxone	0.542	0.165
	Ciprofloxacin	-0.641	0.098
	Clindamycin	0.762	0.028
			*
	Flomoxef	0.875	0.004
			*
	Fosfomycin	0.225	0.576
	Imipenem/cilastatin	0.241	0.566
	Linezolid	0.289	0.341
	Meropenem	-0.194	0.646
	Minocycline	0.151	0.722
	Panipenem/betamipron	0.263	0.530
	Penicillin G	-0.045	0.915
	Piperacillin	0.692	0.052
Piperacillin/tazobactam	0.832	0.010	
		*	
Vancomycin	0.027	0.949	

Note: *Statistical significance ($P < 0.05$).

Abbreviations: AUD, antimicrobial use density; CDI, *Clostridioides difficile* infection.

antimicrobials.¹⁷ Likewise, Kawamura and associates used AUDs for CEZ and the rate of surgical site infection with methicillin-resistant *Staphylococcus aureus* to evaluate their intervention.¹⁸ In 2018, Hagiwara et al reported that their intervention decreased AUDs for carbapenems and PIPC/TAZ with a decrease in resistant strains of *Pseudomonas aeruginosa*.¹⁹ Therefore, the use of AUDs as a metric following an intervention has been established, but had not yet been described in the context of CDI cases.

Next arises a question as to why AUDs affect CDIs. In 2016, Freedberg and others reported that receipt of antimicrobials in inpatients was a risk for CDI in subsequent patients in the same bed.²⁰ In addition, Tarrant et al

described the survival of *C. difficile* spores on hospital bed sheets following a laundry process.²¹ Therefore, AUDs may represent antibiotic pressure in the ward environment.

In terms of isolation policies for infection control, García-Lecona et al reported that CDI patients in a common isolation unit showed a decreased mortality rate but an increased rate of recurrence than those managed alone.²² Recently, ultraviolet disinfection has been trialed in this context with promising outcomes.^{23,24} We have not employed this disinfection strategy but a previous study supports its future utilization by our team.

The idea of an interprofessional approach to antimicrobial stewardship was reviewed at the turn of the 21st century.²⁵ In 2015, the Centers for Disease Control and Prevention issued the “Core Elements” of antimicrobial stewardship, stressing the importance of a multidisciplinary approach.²⁶ Subsequently in 2017, Dik et al reported an antimicrobial, infection control, and diagnostic approach to reduce CDIs.²⁷ Our ipAS method has merits in the measurement of AUDs to document a reduction in the use of broad-spectrum antimicrobials.

The limitations of our study include a retrospective comparison of AUDs before and after the establishment of ipAS, a graded initiation time in 2013 because of a multidisciplinary approach and the use of PDCA cycles, historical bias in vendor difference in CDTs, and the repeat counting of recurrent CDIs for the same patient over numerous years. The last issue has been addressed elsewhere.²⁸ Our results, however, await future validation in prospective studies.

Conclusion

The integrated antimicrobial, diagnostic, infection control approach represented by ipAS may reduce CDIs.

Disclosure

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