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Third-generation cephalosporin for antimicrobial prophylaxis in pancreatoduodenectomy in patients with internal preoperative biliary drainage

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ABSTRACT

Background: The aim of the present study was to investigate whether the incidence of surgical site infection after pancreatoduodenectomy decreased after changing the prophylactic antibiotic to a third-generation cephalosporin in patients with unknown preoperative bile culture results after biliary drainage.

Methods: In a retrospective study of 138 pancreatoduodenectomy patients who underwent endoscopic biliary stenting and for whom recent preoperative bile culture results were unavailable, cefazolin sodium hydrate was administered as perioperative prophylactic antibiotic therapy from 2010 to 2014 ($n = 69$); whereas ceftriaxone was administered from 2014 to 2017 ($n = 69$) based on the results of institutional culture surveillance. The incidence of surgical site infection was compared between the two groups and the risk factor of surgical site infection was also evaluated.

Results: The incidence of overall surgical site infection in the ceftriaxone group was significantly lower than that in the cefazolin sodium hydrate group for both Clavien-Dindo grade ≥II (28% versus 52%, $P = .005$) and Clavien-Dindo grade ≥IIIa (20% vs 41%, $P = .016$). A multivariate analysis revealed that the prophylactic administration of cefazolin sodium hydrate was associated with a higher incidence of overall surgical site infection in both Clavien-Dindo grade ≥II and Clavien-Dindo grade ≥IIIa (odds ratio 2.56, $P = .019$; odds ratio 3.03, $P = .020$, respectively). In the cefazolin sodium hydrate group, most of the patients with positive perioperative cultures had Enterobacteriaceae, which were intrinsically resistant to cefazolin sodium hydrate, and most were susceptible to ceftriaxone.

Conclusion: The prophylactic administration of third-generation cephalosporin reduced the incidence of surgical site infection after pancreatoduodenectomy in patients who underwent preoperative endoscopic biliary stenting.

Introduction

In hepatobiliary pancreatic surgery for periampullary tumors, pancreatoduodenectomy (PD) is one of the most common operations. Despite cumulative efforts in surgery and perioperative management, the morbidity rate of PD remains high—even in high-volume centers. The rate of surgical site infection (SSI), as a representative complication after PD, ranges 13%–47%.[1–7]

The Infectious Diseases Society of America Practice Guideline, the world's most quoted consensus guideline for antimicrobial prophylaxis in surgery, recommends a first-generation cephalosporin (cefazolin sodium hydrate [CEZ]) uniformly as an antimicrobial prophylaxis for any PD.[8] However, because preoperative biliary drainage (PBD) is associated with the development of bile contamination and a higher rate of infectious complications after PD, the appropriate perioperative prophylactic antibiotic may differ, depending on the presence of PBD.[1,3,7,9–11] When a patient undergoes external PBD (endoscopic nasobiliary drainage or percutaneous biliary drainage), a prophylactic antibiotic can be selected based on the susceptibility of biliary microorganisms sampled

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through the external conduit before surgery, which reduces the incidence of postoperative infectious complications after PD.[6–8,12] However, it is impractical to obtain bile cultures before surgery in patients who have undergone internal PBD (endoscopic biliary stenting). In accordance with the Infectious Diseases Society of America Practice Guideline, we have in the past selected CEZ for the prophylactic treatment of patients with internal PBD, undergoing PD, and for those without PBD. However, in the surveillance of perioperative bacterial cultures in such patients, *Enterobacter* and *Enterococcus* species, which tended to be resistant to CEZ, were frequently detected in the intraoperative bile and intraoperative lavage fluid.[10,13,14] *Enterococcus* species are low-virulence bacteria, and whether they become pathogenic to cause infection remains controversial.[7,12,15] Thus, to guard against *Enterobacter* species, the prophylactic antibiotic for the patients with internal PBD, undergoing PD was changed from CEZ to a third-generation cephalosporin (ceftriaxone [CTRX]) after May 2014. The aim of this study was therefore to investigate the incidence of SSI before and after the change of the prophylactic antibiotic in patients with internal PBD, undergoing PD.

Methods

Between January 2010 and June 2017, a total of 557 PDs were performed at Shizuoka Cancer Center, Shizuoka, Japan. Of these, 295 patients (53%) underwent PBD placement, and 262 patients (47%) did not. Among the 295 patients who underwent PBD placement, 132 had external PBD, and the remaining 163 had internal PBD throughout the preoperative management period. Among the 163 patients who had an internal PBD, those who underwent PD with concomitant other organ resection ($n = 10$) and those who were administered other prophylactic antibiotics ($n = 15$) were excluded, as were those with a history of isolated multidrug-resistant bacteria ($n = 9$), preparation for colectomy ($n = 2$), and uncertain reason ($n = 4$) (numbers were duplicated). The remaining 138 patients were ultimately included in the subsequent analysis.

During study periods, CEZ was used as a prophylactic antibiotic for PD in patients whose last PBD type was internal PBD (CEZ group, $n = 69$) between January 2010 and April 2014, and from May 2015 to June 2017, the prophylactic antibiotic was changed to CTRX (CTRX group, $n = 69$).

The incidence of SSI was compared between two groups and the risk factor of SSI was also evaluated. The Institutional Review Board approved the retrospective collection and the analysis of the data in the present study.

The details of perioperative management

PBD was performed for patients with obstructive jaundice, and the type of PBD was determined at the discretion of the surgeons and endoscopists. In principle, plastic drains were used for internal PBD. When cholangitis occurred, or the effect of the biliary drainage was insufficient, the drainage tube was exchanged or converted to other types of biliary drainage. The details of our standard surgical procedure for PD have been mentioned elsewhere.[10,16,17] We used povidone iodine for skin preparation but did not use a skin drape. During surgery, bile juice was sampled for bacterial culture when the bile duct was transected. At the end of the operation, peritoneal lavage was performed using a total of 7,000 ml normal saline (7 washings of 1,000 mL). A clean suction apparatus was used, surgeons donned fresh gloves before abdominal lavage, and the fluid from the final lavage was collected for bacterial culture. The linea alba was sutured with monofilament absorbable sutures, and the skin was sutured with monofilament polydioxanone sutures after using 500 mL of warm saline to lavage the subcutaneous fat layer. Drainage tubes were removed on postoperative day (POD) 4 unless the amylase level was within 3 times the upper limit of the normal range, as determined by our institution. Otherwise, the drainage tubes were routinely exchanged 1 week after the operation. Bacterial cultures of drainage fluid were obtained routinely on PODs 1 and 3. When an SSI was suspected, additional cultures from the wounds or drainage fluid were examined. This perioperative management remained the same throughout the study period.

In the CEZ group, CEZ (1.0 g, intravenous) was administered as prophylactic antibiotic therapy just before the skin incision, repeated at approximately 3-hour intervals on the day of surgery, and then twice daily for 2 days after the operation. In the CTRX group, the patients received a single dose of CTRX (2.0 g, intravenous) just before the skin incision, with no additional intraoperative administration, and then once daily for 2 days after the operation. The dose and duration of the antibiotic treatment were in accordance with the Japanese Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery.[18]

The definitions of complications

Postoperative complications were described according to the Clavien-Dindo (C-D) classifications.[19] The presence of SSI was determined according to the Centers for Disease Control and Prevention's national nosocomial infections surveillance system.[20] Organ/space SSIs included postoperative pancreatic fistula (POPF) and bile leakage, with positive culture results. Overall SSI was defined as incisional SSI, organ/space SSI, or both. POPF was classified according to the International Study Group on Pancreatic Surgery classification.[21]

Statistical analyses

Differences in the numerical data of the two groups were examined by the $\chi 2$ test or the Fisher exact test, as appropriate. Quantitative variables were expressed as the median and interquartile range and were evaluated by the Mann-Whitney *U* test. A multivariate logistic regression analysis was performed to identify risk factors for SSI. Variables with a *P* value of $< .10$ in a univariate analysis were entered into the multivariate model. *P* values of $< .05$ were considered to indicate statistical significance. All statistical analyses were performed using SPSS v 19.0 (IBM, Armonk, NY, USA).

Results

The characteristics of the patients who received CTRX and CEZ as prophylactic antibiotic therapy are presented in Table 1. A longer interval between last PBD and the operation ($P < .001$), lower preoperative serum total bilirubin ($P = .004$), and higher frequency of preoperative cholangitis ($P = .009$) were seen in the CTRX group.

The incidence of overall SSI in the CTRX group was significantly lower than that in the CEZ group for both C-D grade ≥II (26% versus 51%, $P = .005$) and C-D grade ≥IIIa (16% versus 38%, $P = .007$) (Table 2). With the exception of all grade SSIs and C-D grade ≥IIIa incisional SSI, lower incidences of each type of C-D grade ≥II (incisional SSI: $P = .004$, organ/space SSI: $P = .023$, respectively), and C-D grade ≥IIIa SSI (organ/space SSI, $P = .029$) were seen in the CTRX group. There was no significant difference between the 2 groups with regard to the incidence of other postoperative complications.

Table 3 presents the results of the univariate and multivariate analyses of the risk factors for overall SSI. The multivariate analysis revealed that the prophylactic administration of CEZ was associated with a higher incidence of overall SSI in both C-D grade

Table 1
The characteristics of the patients who received CTRX and CEZ as prophylactic antibiotic therapy.

		CTRX ($n=69$)	CEZ ($n=69$)	P
Sex	Male/female	33/36	43/26	.123
Age (years)	Median (IQR)	68 (63–76)	68 (61–76)	.900
Body weight (kg)	Median (IQR)	52.6 (47.6–61.1)	53.5 (45.3–61.1)	.939
BMI (kg/m^2)	Median (IQR)	21.9 (19.6–23.3)	21.3 (19.0–22.5)	.496
ASA-PS	1/2/3	3/61/5	9/57/3	.177
Diabetes	Present (%)	17 (25)	15 (22)	.840
Disease				.740
Pancreatic cancer	Present (%)	48 (70)	49 (71)	
Cancer of the papilla of Vater	Present (%)	12 (17)	10 (15)	
Bile duct cancer	Present (%)	7 (10)	8 (12)	
Other pancreatic tumors	Present (%)	3 (4)	1 (1)	
Interval between last PBD and operation	Days (IQR)	35 (21–84)	22 (16–30)	< .001
Preoperative cholangitis	Present (%)	17 (25)	5 (7)	.009
Preoperative antibiotics within 7 days before operation	Present (%)	5 (7)	2 (3)	.441
Albumin	g/dl (IQR)	3.7 (3.3–4.1)	3.9 (3.6–4.2)	.050
Total bilirubin after PBD	mg/dl (IQR)	0.8 (0.5–1.8)	1.5 (0.9–2.4)	.004
C-reactive protein	mg/dl (IQR)	0.3 (0.1–0.5)	0.2 (0.1–0.6)	.805
Portal vein resection	Present (%)	27 (39)	32 (46)	.491
Pancreatic texture	Soft (%)	30 (44)	29 (42)	1.000
MPD diameter	mm (IQR)	4.0 (3.0–5.0)	3.6 (2.5–5.9)	.504
Operation time	Minutes (IQR)	441 (374–510)	435 (377–502)	.472
Intraoperative blood loss	ml (IQR)	664 (450–1056)	895 (512–1342)	.082
Blood transfusion	Present (%)	5 (7)	10 (15)	.274

BMI, body mass index; *ASA-PS*, American Society of Anesthesiologists Physical Status; *MPD*, main pancreatic duct; *IQR*, interquartile range.

Table 2
The incidence of postoperative complications in the CTRX and CEZ groups.

		CTRX ($n=69$)	CEZ ($n=69$)	P
Abdominal abscess	Present (%)	5 (7)	13 (19)	.075
Bile leakage	Present (%)	1 (1)	1 (1)	1.000
Abdominal bleeding	Present (%)	0 (0)	4 (6)	.120
Clinically relevant POPF	Present (%)	20 (29)	21 (30)	1.000
Drain removed on POD > 21	Present (%)	12 (17)	20 (29)	.157
Sepsis	Present (%)	0 (0)	5 (7)	.058
Clostridium infections	Present (%)	4 (6)	1 (1)	.366
Cholangitis	Present (%)	2 (3)	3 (4)	1.000
Length of postoperative hospital stay	Days (IQR)	20 (16–28)	21 (16–35)	.146
Readmission	Present (%)	1 (1)	1 (1)	1.000
Overall morbidity	Present (%)	37 (53)	45 (65)	.225
Mortality	Present (%)	0 (0)	0 (0)	1.000
Infectious complications ≥C-D grade II	Present (%)	21 (30)	38 (55)	.006
Overall SSI (total)	Present (%)	30 (44)	38 (55)	.223
≥C-D grade II	Present (%)	18 (26)	35 (51)	.005
≥C-D grade IIIa	Present (%)	11 (16)	26 (38)	.007
Incisional SSI (total)	Present (%)	18 (26)	28 (41)	.104
≥C-D grade II	Present (%)	6 (9)	20 (29)	.004
≥C-D grade IIIa	Present (%)	0 (0)	4 (6)	.120
Organ/space SSI (total)	Present (%)	17 (25)	26 (38)	.141
≥C-D grade II	Present (%)	13 (19)	26 (38)	.023
≥C-D grade IIIa	Present (%)	11 (16)	23 (33)	.029

≥II and C-D grade ≥IIIa (odds ratio [OR] 2.56, $P=.019$; OR 3.03, $P=.020$, respectively).

Table 4 presents the distribution of the microorganisms isolated from perioperative cultures and the association between the isolated microorganisms from SSI fluid and that from each perioperative culture. With the exception of the strains isolated in intraoperative bile cultures, the majority of Gram-negative rod (GNR) bacteria isolated in the CEZ group were *Enterobacter* species followed by *Serratia* and *Citrobacter* species; these are enterobacteria intrinsically resistant to CEZ but susceptible to CTRX. In contrast, GNR bacteria were rarely detected in the CTRX group. In both groups, the bacteria isolated from the drainage fluid in organ/space SSI and incisional SSI were almost identical to those isolated from perioperative cultures.

The Figure presents the prevalence of each bacterium isolated in the perioperative cultures among all microorganisms (Fig, *A*) and *Enterobacter, Citrobacter*, and *Serratia* species (Enterobacteriaceae intrinsically resistant to CEZ) (Fig, *B*). The overall prevalence of microorganisms in the CTRX group was lower in the intraoperative lavage fluid (5/69; 7% vs 27/59; 46%, $P < .001$), the drainage fluid on POD 1 (7/69; 10% vs 17/69; 25%, $P=.042$), and the drainage fluid on POD 3 (15/69; 22% vs 28/69; 41%, $P=.027$) than in the CEZ group (Fig, *A*). With regard to *Enterobacter, Citrobacter*, and *Serratia* species, the prevalence of species was significantly lower in the perioperative cultures of the CTRX group than in that of the CEZ group (Fig, *B*).

Table 5 presents the postoperative outcomes in patients in whom *Enterococcus* species were detected from SSI fluid. There were no significant differences in the postoperative outcomes of with or without the detection of *Enterococcus* species. However, the patients with *Enterococcus* species detected from organ/space SSI fluid had a relatively high incidence of clinically relevant

Table 3
The univariate and multivariate analyses of risk factors for SSI.

Variables	SSI ≥ C-D grade II					SSI ≥ C-D grade IIIa				
	(+)	(−)	Univariate	Multivariate		(+)	(−)	Univariate	Multivariate	
	$n=53$	$n=85$	P	Odds ratio (95% CI)	P	$n=37$	$n=101$		Odds ratio (95% CI)	P
Sex (male, %)	30 (57)	46 (54)	.861			20 (54)	56 (55)	1.000		
Age (≥70 years, %)	24 (45)	36 (42)	.860			18 (49)	42 (42)	0.561		
BMI (≥ 25 kg/m^2, %)	6 (11)	5 (6)	.335			4 (11)	7 (7)	0.485		
Diabetes (present, %)	12 (23)	20 (24)	1.000			9 (24)	23 (23)	0.824		
Tumor (pancreatic cancer, %)	31 (59)	66 (78)	.022	0.62 (0.23–1.66)	.340	21 (57)	76 (75)	0.047	1.31 (0.44–3.92)	.620
Length of the PBD placement (≥30 days, %)	27 (51)	49 (58)	.484			19 (51)	57 (56)	0.700		
Preoperative cholangitis (present, %)	5 (9)	17 (20)	.150			4 (11)	18 (18)	0.434		
Pancreatic texture (soft pancreas, %)	29 (55)	30 (35)	.034	1.15 (0.43–3.05)	.780	25 (68)	34 (34)	<0.001	2.91 (0.97–8.74)	.057
MPD diameter (≤3 mm, %)	28 (53)	28 (33)	.032	2.34 (0.99–5.53)	.052	24 (65)	32 (32)	0.001	3.48 (1.35–9.01)	.010
Portal vein resection (performed, %)	22 (42)	37 (44)	.861			14 (38)	45 (45)	0.562		
Prophylactic antibiotic (CEZ, %)	35 (66)	34 (40)	.005	2.56 (1.16–5.56)	.019	26 (70)	43 (43)	0.007	3.03 (1.19–7.69)	.020
Operation time (≥7 hours, %)	29 (55)	51 (60)	.597			19 (51)	61 (60)	0.436		
Intraoperative blood loss (≥1,000 ml, %)	23 (43)	25 (29)	.102			15 (41)	33 (33)	0.424		

CI, confidence interval.

Table 4
The distribution of microorganisms isolated form intraoperative bile and lavage cultures, drainage fluid, and SSI fluid.

	Intraoperative bile		Intraoperative lavage		POD 1		POD 3		Drainage fluid in organ/space SSI		Drainage fluid in incisional SSI	
	CTRX ($n=69$)	CEZ ($n=63$)	CTRX ($n=69$)	CEZ ($n=59$)	CTRX ($n=69$)	CEZ ($n=69$)	CTRX ($n=69$)	CEZ ($n=69$)	CTRX ($n=24$)	CEZ ($n=21$)	CTRX ($n=18$)	CEZ ($n=26$)
Positive culture (%)	91	95	7	46	10	25	22	41	63	86	89	100
E. coli (%)	19	16	0	0	0	0	0	0	0	0	5	0
Klebsiella species (%)	26	48	0	3	0	0	0	0	4	5	0	0
Proteus species (%)	3	6	0	0	0	0	0	0	0	5	0	0
Enterobacter species (%)	21	38	1	17	1	17	0	28	4	57	10	65
Citrobacter species (%)	10	29	0	3	0	0	0	3	0	19	0	19
Serratia species (%)	0	2	0	2	0	4	0	6	0	5	0	8
Pseudomonas species (%)	1	5	0	3	0	1	0	1	13	14	5	4
Acinetobacter species (%)	0	0	0	0	0	0	0	0	0	0	0	0
Stenotrophomonas maltophilia (%)	1	0	0	0	0	0	0	0	4	0	0	0
MSSA (%)	4	16	1	0	0	0	0	0	4	5	0	4
MRSA (%)	0	3	0	0	0	0	0	1	0	5	0	0
CNS (%)	1	5	0	8	0	0	1	0	4	0	15	12
Enterococcus species (%)	65	56	13	5	9	4	12	12	33	38	45	35
Candida (%)	14	3	0	0	0	0	4	0	8	14	10	0
Others (%)	57	65	1	10	0	0	4	6	13	24	10	46
Same microorganism isolated from organ/space SSI (%)	14/14 (100)	12/16 (75)	2/2 (100)	6/7 (86)	5/5 (100)	9/9 (100)	6/7 (86)	11/13 (85)				
Same microorganism isolated from incisional SSI (%)	11/15 (73)	20/23 (87)	1/1 (100)	14/17 (82)	0/1 (0)	13/13 (100)	2/3 (67)	17/18 (94)				

MRSA, Methicillin-resistant Staphylococcus aureus; *MSSA*, Methicillin-susceptible Staphylococcus aureus; *CNS*, coagulase-negative staphylococci.

POPF (86% vs 36%, $P=.066$) and late drain removal (43% vs 9%, $P=.245$).

Discussion

The results of the present study revealed two points. First, a relatively large number of the Enterobacteriaceae isolates from perioperative cultures during PD for patients with internal PBD were resistant to CEZ in the CEZ group, and the isolated frequency was significantly decreased in the CTRX group without the emergence of additional drug-resistant bacteria. Second, the incidence of SSI after PD was decreased after CEZ was changed to CTRX, and the administration of CEZ as an antimicrobial prophylaxis was associated with a higher incidence of SSI in the patients with internal PBD.

Retrospective studies have reported the benefits of broad-spectrum prophylactic antibiotic therapy for the patients undergoing PD. Sudo et al.[7] showed that the administration of third- or fourth-generation cephalosporins as treatment for bile contamination reduced the incidence of SSI after PD. Donald et al.[4] and Kondo et al.[6] showed that prophylactic broad-spectrum penicillins (piperacillin, piperacillin/tazobactam), selected based on the bacteria detected in SSI in their series, reduced the incidence of SSI. However, these studies included patients who underwent various types of PBD procedures or patients without PBD. In our experience, the incidence of SSI in the external or patients without PBD was relatively low compared with that of the patients with internal PBD (Supplemental Table). These results may be attributed to the appropriate selection of prophylactic antibiotics by referencing the preoperative bile culture in patients with external PBD or the low incidence of bile contamination in patients without PBD. To

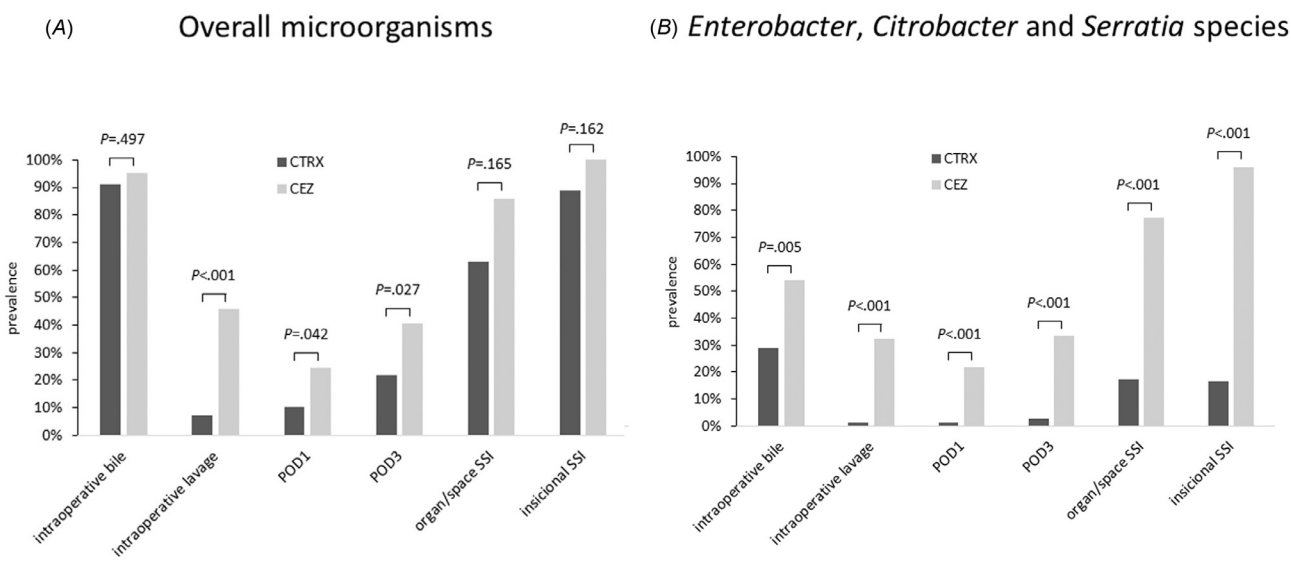

Fig. The prevalence of each bacterium isolated in the perioperative cultures among (*A*) all microorganisms and (*B*) *Enterobacter, Citrobacter*, and *Serratia* species (Enterobacteriaceae intrinsically resistant to CEZ). The prevalence of overall microorganisms in the CTRX group was lower in intraoperative lavage fluid ($P < .001$), drainage fluid on POD 1 ($P = .042$), and drainage fluid on POD 3 ($P = .027$) than in the CEZ group. With regard to *Enterobacter, Citrobacter*, and *Serratia* species, the prevalence of perioperative bacterial culture was lower in the CTRX group than in the CEZ group.

Table 5
The postoperative outcomes in the patients with the detection of *Enterococcus* species from the SSI fluid.

		Organ/space SSI			Incisional SSI		
		Enterococcus alone $n = 7$	None $n = 11$	*P*	Enterococcus alone $n = 7$	None $n = 2$	*P*
Overall postoperative complication		6 (86)	11 (100)	0.389	4 (57)	0 (0)	.444
Infectious complication ≥C-D grade II		4 (57)	7 (64)	0.630	2 (29)	0 (0)	1.000
Clinically relevant POPF		6 (86)	4 (36)	0.066	1 (14)	0 (0)	1.000
Drain removed on POD > 21	Present (%)	3 (43)	1 (9)	0.245	0 (0)	0 (0)	1.000
Lengths of postoperative hospital stay	Days (IQR)	23 (21–33)	21 (20–24)	0.236	17 (16–19)	12 (10–14)	.135

allow for a more precise analysis, the present study limited the subjects to the patients who had internal PBD throughout the preoperative period. Internal PBD was reported to be associated with a higher incidence of postoperative complications after PD in comparison with patient who have external PBD or patients without PBD; the reported rate (41%–46%) was almost comparable with our results in the CEZ group.[3,6,22] The present study showed that the prophylactic administration of CTRX was useful for reducing the incidence of SSI in these high-risk patients.

In the CTRX group, the prevalence of Enterobacteriaceae, which are intrinsically resistant to CEZ, especially *Enterobacter* species, was significantly lower than that in the CEZ group in every type of perioperative culture, with the exception of intraoperative bile cultures. We have mentioned elsewhere the relationship between the presence of bacteria in the peritoneal fluid or postoperative drain fluid and the presence of infection.[14] Thus, the high rate of intraoperative bacterial contamination in the CEZ group had an adverse impact on the development of SSI. The prophylactic administration of CTRX may work gradually, which would lead to a lower prevalence of CTRX-susceptible Enterobacteriaceae in the intraoperative lavage and drainage fluid. Considering the fact that *Enterobacter, Citrobacter*, and *Serratia* species were generally pathogenic and accounted for a large portion of the perioperative bacterial isolates in the CEZ group, perioperative antibiotic in the patients with internal PBD should cover these Enterobacteriaceae to reduce the incidence of SSI after PD for patients with internal PBD.

Although the incidence of preoperative cholangitis was significantly higher in the CTRX group, the rate at which preoperative antibiotics were administered within 7 days before surgery did not differ between the 2 groups. Seven days without antibiotics would be enough to contaminate the bile in patients with internal PBD. Moreover, preoperative cholangitis was not a risk factor for SSI (Table 3). Thus, preoperative antibiotics would not have influenced the perioperative culture results in the present study.

The administration of broad-spectrum antibiotics has the potential to increase the emergence of more resistant types of bacteria. In this study, however, Enterobacteriaceae are intrinsically resistant to CTRX, including *Pseudomonas* and *Acinetobacter* species, and *Stenotrophomonas maltophilia* were rarely identified in the perioperative bacterial cultures. This finding is in concordance with another report.[23] Broad-spectrum antibiotics will be acceptable for short-time prophylactic use.

The selection of CTRX for antimicrobial prophylaxis is not always ideal for all patients with internal PBD undergoing PD. It is well known that the antimicrobial susceptibility of GNR bacteria varies widely depending on the institution, region, and country.[24,25] In our institution, the majority of the Enterobacteriaceae isolated from intraoperative cultures in the CEZ group were susceptible to CTRX; whereas more than half of the bacteria were resistant to CEZ. Based on perioperative culture surveillance of each institution, minimally narrowed antibiotics covering pathogenic Enterobacteriaceae should be selected, even for patients whose preoperative biliary culture results are unknown. Given the relatively high incidence of clinically relevant POPF and subsequent late drain removal in patients in whom *Enterococcus* species were detected from SSI fluid, it seems to be worthwhile to consider the selection of prophylactic antibiotics that cover *Enterococcus* species. Although the association is unclear because of the relatively small

sample size and the lack of statistical significance in the present study, this warrants further examination.

The present study was associated with some limitations. First, because the present study was a historical control study, we could not discount the possibility that the reduced incidence of SSIs in the later period was attributable to improved surgical proficiency in comparison with the early study period. However, during the 7-year study period, there were few changes in perioperative practice other than the prophylactic antibiotics that were administered, and this relatively short period would have reduced some of the potential bias. Second, patient background factors, including preoperative cholangitis and the interval between last PBD and operation, differed between the groups. Thus, multicenter prospective observational studies in cohorts in which the patient characteristics and perioperative managements are matched will be necessary to confirm our results.

In conclusion, a third-generation cephalosporin for antimicrobial prophylaxis based on institutional culture surveillance reduced the incidence of SSI after PD in patients who underwent internal PBD without an increase in the frequency of multidrug-resistant bacteria.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.09.011.

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