Prolonged antibiotics after pancreatoduodenectomy reduce abdominal infections in patients with positive bile cultures: a dual-center cohort study

Droogh, D.H.M.; Dam, J.L. van; Groen, J.V.; Boer, M.G.J. de; Prehn, J. van; Eijck, C.H.J. van; ... ; Mieog, J.S.D.

ORIGINAL ARTICLE

Prolonged antibiotics after pancreatoduodenectomy reduce abdominal infections in patients with positive bile cultures: a dual-center cohort study

Daphne H.M. Droogh[1], Jacob L. van Dam[2], Jesse V. Groen[1], Mark G.J. de Boer[3], Joffrey van Prehn[4], Casper H.J. van Eijck[2], Bert A. Bonsing[1], Alexander L. Vahrmeijer[1], Bas Groot Koerkamp[2] & J. Sven D. Mieog[1]

[1]Department of Surgical Oncology, Leiden University Medical Center, Leiden, the Netherlands, [2]Department of Surgery, Erasmus MC Cancer Institute, Rotterdam, the Netherlands, [3]Department of Infectious Diseases, Leiden University Medical Center, Leiden, the Netherlands, and [4]Department of Medical Microbiology, Leiden University Medical Center, Leiden, the Netherlands

Abstract

Background: Abdominal infections account for substantial morbidity after pancreatoduodenectomy. Contaminated bile is the presumed main risk factor, and prolonged antibiotic prophylaxis might prevent these complications. This study compared organ/space infection (OSIs) rates in patients receiving perioperative versus prolonged antibiotic prophylaxis after pancreatoduodenectomy.

Methods: Patients undergoing pancreatoduodenectomy in two Dutch centers between 2016 and 2019 were included. Perioperative prophylaxis was compared prolonged prophylaxis (cefuroxime and metronidazole for five days). The primary outcome was an isolated OSI: an abdominal infection without concurrent anastomotic leakage. Odds ratios (OR) were adjusted for surgical approach and pancreatic duct diameter.

Results: OSIs occurred in 137 out of 362 patients (37.8%): 93 patients with perioperative and 44 patients with prolonged prophylaxis (42.5% versus 30.8%, $P = 0.025$). Isolated OSIs occurred in 38 patients (10.5%): 28 patients with perioperative and 10 patients with prolonged prophylaxis (12.8% versus 7.0%, $P = 0.079$). Bile cultures were obtained in 198 patients (54.7%). Patients with positive bile cultures showed higher isolated OSI rates with perioperative compared to prolonged prophylaxis (18.2% versus 6.6%, OR 5.7, 95% CI: 1.3–23.9).

Conclusion: Prolonged antibiotics after pancreatoduodenectomy are associated with fewer isolated OSIs in patients with contaminated bile and warrant confirmation in a randomised controlled trial (Clinicaltrials.gov NCT0578431).

Correspondence

Daphne H.M. Droogh, Department of Surgery, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: D.H.M.Droogh@lumc.nl

Introduction

Pancreatoduodenectomy is accompanied with high morbidity rates (35–54%), which are substantially associated with infectious complications as organ space infections (OSIs) and superficial surgical site infections (incisional SSIs).[1–3] Contaminated bile

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could be an important source for infection as previous studies showed an association between positive intraoperative obtained bile cultures (IOBCs) and particularly wound infections.[2–7] The majority of patients who have ampullary carcinomas or undergo preoperative invasive procedures such as endoscopic retrograde cholangiopancreatography (ERCP) have contaminated bile.[7–9] The impact of contaminated bile spillage on the development of abdominal infectious complications remains disputable since other abdominal complications such as pancreatic fistula and enteric leakage are related to OSI development.[6] Studies separately

evaluating abdominal infectious without these confounding complications are limited. Therefore, we previously introduced the term *isolated* OSI, which is defined as an OSI without concurrent anastomotic complications leading to contamination of the intraabdominal space. Previously, a study reported no correlation between isolated OSI rates and bile culture status in patients receiving five days of antibiotic prophylaxis after pancreatoduodenectomy.[8]

Protocols regarding antibiotic prophylaxis vary substantially between institutes.[10] Whereas perioperative antibiotic prophylaxis is widely used to prevent SSIs, the value of postoperative antibiotic prophylaxis remains unclear.[11] The updated Enhanced Recovery After Surgery protocol does not recommend standard use of postoperative antibiotic prophylaxis after pancreatoduodenectomy, but considered postoperative antibiotics to be potentially beneficial in patients with contaminated IOBCs.[12] Some studies investigated the value of prolonged prophylaxis in high risk patients (particularly patients who underwent preoperative biliary drainage) and demonstrated comparable rates of OSIs.[13–15] It was hypothesised that prolonged prophylaxis interferes with the development of isolated OSIs, particularly in patients with contaminated bile. As only a few, predominantly retrospective studies evaluated the use of prolonged prophylaxis, recommendations regarding the use of prolonged antibiotic prophylaxis are limited.

The primary aim of this study is to evaluate the value of prolonged antibiotic prophylaxis after pancreatoduodenectomy on the occurrence of abdominal infectious complications stratified by bile culture status.

Methods

Study design and patient selection
This dual-center cohort study included patients undergoing pancreatoduodenectomy between June 2016 and December 2019 in the Erasmus Medical Center (EMC) and the Leiden University Medical Center (LUMC). The intention-to-treat principle was used to assign patients to the standard or prolonged antibiotic prophylaxis group. Patients with preoperative use of therapeutic antibiotics were excluded. This study reported in accordance with the STROBE-criteria for cohort studies.[16]

Procedures and antibiotic prophylaxis
The centers were similar in volume and perioperative care, except for protocols regarding postoperative antibiotic prophylaxis. The surgical procedure was comparable in both centres. One or two silicon, non-suction drains were placed in neo-Winslow and under the left liver lobe at the end of the surgical procedure. Early drain removal was intended, typically at postoperative day three in case of low drain amylase levels. All patients received perioperative prophylaxis, which consisted of cefazolin (based on patients' weight 1, 2 or 3 g IV) and 500 mg IV metronidazole every 4 h during surgery, in agreement with the Dutch antibiotic guidelines for abdominal surgery. EMC patients did not receive antibiotic prophylaxis after surgery, although antibiotic therapy was initiated in case of clinical signs of infection. LUMC patients received prolonged antibiotics during five postoperative days, consisting of 750 mg IV cefuroxime and 500 mg IV metronidazole three times daily. Pancreatoduodenectomy was performed open or robot-assisted in both centers. Surgical procedures were comparable between the centers. Postoperative care conformed to the ERAS principles and postoperative management adhered to the algorithm described within the PORSCH trial.[12,17] Bile cultures were intraoperatively performed and were obtained with a cotton swab or a syringe after transection of the common bile duct (CBD). Bile cultures were assessed at the Medical Microbiology department according to laboratory's standard operating procedures.[8]

Data collection
Data were collected from medical records and the Dutch Pancreatic Cancer Audit.[18] Variables of interest included patient characteristics, disease- and surgical-related information, bile culture characteristics, postoperative complications (OSIs, incisional SSIs, pancreatic fistula and bile or enteric leakage) and type and duration of peri- and postoperative antibiotic prophylaxis and treatment. Data collection was performed by three authors (DHMD, JLvD and JVG) and a fourth investigator (JSDM) was consulted in case of disagreement.

Definitions
OSIs and incisional SSIs were classified according to the Center of Disease Control definition (Supplemental Table 1).[19] The concept of *isolated OSI* was used to separately classify abdominal infectious complications without concurrent anastomotic leakage. An isolated OSI was defined as a postoperative OSI without simultaneous occurrence of other surgical complications leading to contamination of the intraabdominal space, such as pancreatic fistula, biliary leakage, intestinal anastomotic leakage or gastrointestinal perforation (defined as gastric or intestinal wall discontinuity confirmed by surgery).[8] Pancreatic fistula and bile leakage were defined and classified according to the International Study Group of Pancreatic Surgery definitions.[20,21] A positive bile culture was defined as the presence of any bacterial species, irrespective of virulence, cultured from intraoperative obtained bile spill.

Outcomes and comparison
The primary outcome of this study was the adjusted odds to develop an isolated OSI stratified for bile culture status. Secondary outcomes were OSI and incisional SSI rates, other complications related to pancreatic surgery and timing of OSI occurrence. We hypothesised that the use of prolonged antibiotic prophylaxis would not lead to delayed development of OSIs. Patients receiving standard antibiotic prophylaxis were compared to patients receiving prolonged antibiotic prophylaxis, stratified for bile culture status in subgroup analyses.

Statistical analysis

Continuous variables were presented as mean (standard deviation) or median (interquartile range). For comparison of continuous variables, respectively the Student's T-test or a non-parametric test (Mann–Whitney U test) were performed for normal and non-normal distributed data. Categorical variables were presented as absolute numbers and percentages and were analysed using the Chi-square test or Fisher's exact test in case of small groups. Odds ratios (OR) were calculated and adjusted for surgical approach (open or robotic) and pancreatic duct (PD) diameter (1−3 mm versus >3 mm) using logistic regression analyses. Timing of OSI occurrence was analysed using Kaplan Meier curves and the logranktest. A P-value of <0.05 was considered statistically significant. For the statistical analysis, SPSS for Windows (version 25.0) was used.

Results

Patient characteristics

Of the 383 consecutive patients who underwent pancreatoduodenectomy, 21 patients were excluded after preoperative deviation from antibiotic protocol due to cholangitis (n = 13), cholecystitis (n = 3), pancreatitis (n = 2), patient's immunocompromised status (n = 2) or antibiotic allergy (n = 1). This study included 362 patients, of whom all EMC patients (n = 219) received standard antibiotic prophylaxis and all LUMC patients (n = 143) prolonged antibiotic prophylaxis (Fig. 1). In the group with standard antibiotic prophylaxis, 28 patients (12.8%) were treated with antibiotics because of clinical deterioration or other signs of infection between the first and fifth postoperative day. Baseline characteristics between patients with standard and prolonged antibiotic prophylaxis differed in perioperative blood loss, duration of surgery and pancreatic texture (Table 1). Preoperative biliary drainage was performed in 123 patients (56.2%) receiving standard and in 66 patients (46.2%) receiving prolonged prophylaxis (P = 0.062).

Bile cultures

Bile cultures were obtained in 198 patients (54.7%): 78 patients (35.6%) who received standard and 120 patients (83.9%) who received prolonged antibiotic prophylaxis (Table 1). IOBCs were positive in 131 patients (66.2%): 55 patients (70.5%) with standard prophylaxis and 76 patients (63.3%) with prolonged prophylaxis (P = 0.297). Baseline characteristics between patients with positive and negative bile cultures were different regarding sex, duration of surgery and neoadjuvant therapy (Supplemental Table 2). Bile cultures were positive in 103 patients (95.4%) who underwent preoperative biliary drainage against 28 patients
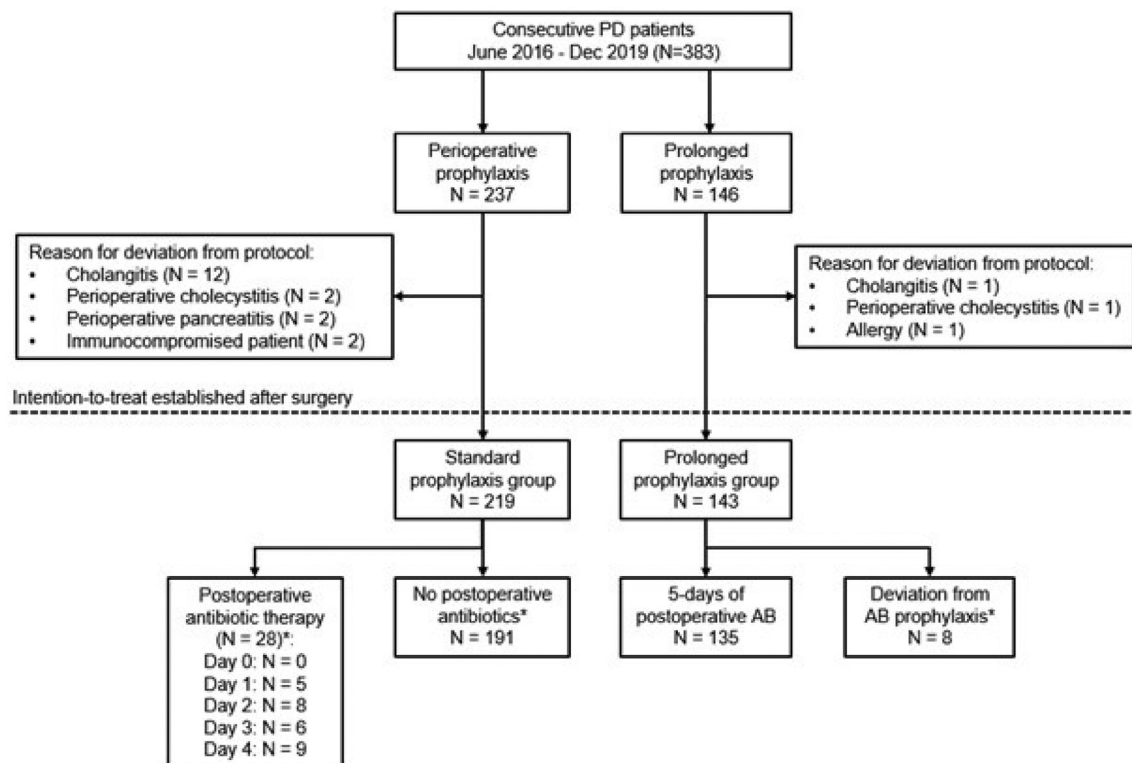
PD: pancreatoduodenectomy. *Within five postoperative days.

Figure 1 Patient selection and allocation

Table 1 Baseline characteristics

		Total		Antibiotic prophylaxis				
				Standard		Prolonged		
		n	%	n	%	n	%	P
Total		362	100	219	60.5	143	39.5	
Sex	Male	195	53.9	113	51.6	82	57.3	0.284
	Female	167	46.1	106	48.4	61	42.7	
Age (years), median (IQR)		67 (59–73)		67 (59–73)		67 (58–73)		0.828
BMI (kg/m2), mean (SD)		25.5 (4.6)		25.2 (4.4)		25.9 (4.9)		0.757
ASA score	I-II	257	71.0	149	68.0	108	75.5	0.125
	III-IV	105	29.0	70	32.0	35	24.5	
Robotic surgery		103	28.5	89	40.6	14	9.8	<0.001
Blood loss (mL), median (IQR)		700 (300–1200)		500 (200–1000)		900 (500–1300)		<0.001
	Missing	1				1		
Duration of surgery (min), median (IQR)		326 (258–412)		375 (302–432)		265 (241–324)		<0.001
Pathological diagnosis								
	PDAC	163	45.0	92	43.8	71	49.7	0.280
	Distal CCA	29	8.0	16	7.6	13	9.1	0.621
	Ampullary carcinoma	42	11.6	26	12.4	16	11.2	0.734
	NET	11	3.0	6	2.9	5	3.5	0.734
	Cystic disease	34	9.4	20	9.5	14	9.8	0.934
	Benign disease	31	8.6	22	10.5	9	6.3	0.173
	Other	43	11.9	28	13.3	15	10.5	0.423
Missing		9		9				
Aspect of pancreas								
	Soft	168	46.4	91	41.6	77	53.8	0.021
	Hard	180	49.7	116	53.0	64	44.8	
	Missing	14		12		2		
PD diameter (mm), median (IQR)		3^{2-5}		3^{2-5}		3^{2-6}		0.670
	Missing	28		28		0		
Neoadjuvant therapy		43	11.9	28	12.8	15	10.5	0.509
Preoperative biliary drainage		189	52.2	123	56.2	66	46.2	0.062
IOBC obtained		198	54.7	78	35.6	120	83.9	<0.001
	Positive	131	66.2	55	70.5	76	63.3	0.297
	Negative	67	33.8	23	29.5	44	36.7	

IQR: Interquartile range. BMI: Body Mass Index. SD: standard deviation. ASA: American Society of Anesthesiologists. PDAC: pancreatic ductal adenocarcinoma. CCA: cholangiocarcinoma. NET: neuroendocrine tumor. PD: pancreatic duct. IOBC: intraoperative bile culture.

(31.1%) without preoperative biliary drainage ($P < 0.001$). In patients with prolonged antibiotics, multi-drug resistant bacteria were observed in three bile cultures which reported two resistant *Klebsiella* spp. and two resistant *Escherichia coli* spp. In patients with prolonged antibiotics, 36 bile cultures reported microorganisms with an intrinsic resistance for cefuroxime and metronidazole.

Primary outcome

Isolated OSIs occurred in 38 patients (10.5%): 28 patients (12.8%) with standard prophylaxis and 10 patients (7.0%) with prolonged prophylaxis ($P = 0.079$. Table 2). After adjustment for surgical approach and PD diameter, the OR to develop an isolated OSI with standard compared to prolonged antibiotic prophylaxis was 1.4 (95% CI: 0.8–2.3, $P = 0.196$). Thirty-one of the 38 isolated OSIs (81.6%) were diagnosed within 14 days after surgery. Timing of isolated OSI development was comparable in patient with standard and prolonged prophylaxis ($P = 0.081$. Fig. 2A).

In patients with a positive bile culture, isolated OSIs occurred in ten patients (18.2%) with standard prophylaxis and in five patients (6.6%) with prolonged prophylaxis ($P = 0.040$. Table 3,

Table 2 Infectious complications

		Total (n = 362)		Antibiotic prophylaxis				
				Standard (n = 219)		Prolonged (n = 143)		
		N	%	N	%	N	%	P
OSIs		137	37.8	93	42.5	44	30.8	0.025
Isolated OSI[a]		38	10.5	28	12.8	10	7.0	0.079
Timing	<14 Days	31	81.6	24	85.7	7	70.0	0.271
	>14 Days	7	18.4	4	14.3	3	30.0	
Non-isolated OSIs[b]		99	27.3	65	29.7	34	23.8	0.367
Pancreatic fistula		87 rowhead	87.9	59	90.8	28	82.4	0.223
Biliary leakage		9 rowhead	9.1	6	9.2	3	8.8	0.947
Enteric leakage of perforation		3 rowhead	3.0	0	0.0	3	8.8	0.015
Incisional SSIs		77 rowhead	21.3	48	21.9	29	20.3	0.710
Superficial		70 rowhead	90.9	44	91.7	26	89.7	0.893
Deep		7 rowhead	9.1	4	8.3	3	10.3	

OSI: Organ space infection. Incisional SSI: incisional surgical site infection (wound infection).
[a] OSI without simultaneous occurrence of confounding complications.
[b] OSI with simultaneous occurrence of intraabdominal complications.

Fig. 2B−C). After adjustment for surgical approach and PD diameter, the OR to develop an isolated OSI in case of a positive bile culture when receiving standard compared to prolonged antibiotic prophylaxis was 5.7 (95% CI: 1.3−23.9, P = 0.018). The number needed to treat (NNT) to prevent one isolated OSI with prolonged antibiotic prophylaxis in patients with a positive bile culture was 8.6. One patient (10.0%) with standard and in two patients (40.0%) with prolonged prophylaxis and a positive bile culture developed an isolated OSI more than 14 days after surgery (P = 0.171). In patients with a negative bile culture, isolated OSIs occurred in two patients (8.7%) with standard and in four patients (9.1%) with prolonged prophylaxis (P = 0.957. Adjusted OR: 2.3; 95% CI: 0.4−14.6).

Among patients with standard antibiotic prophylaxis, ten patients (18.2%) with a positive bile culture and two patients (8.7%) with a negative bile culture developed an isolated OSI (P = 0.290. Table 3). Among patients with prolonged antibiotic prophylaxis, five patients (6.6%) with a positive bile culture and four patients (9.1%) with a negative bile culture developed an isolated OSI (P = 0.615).

Secondary outcomes

OSIs occurred in 137 patients (37.8%): 93 patients (42.5%) with standard prophylaxis and 44 patients (30.8%) with prolonged prophylaxis (P = 0.025. Table 2). After adjustment for surgical approach and PD diameter, the odds ratio to develop an OSI with standard compared to prolonged antibiotic prophylaxis was 1.4 (95% CI: 0.8−2.3. P = 0.196). OSIs were considered non-isolated in 99 patients (27.3%), because of pancreatic fistula in 87 patients (87.9%).

In the group with a positive bile culture, OSIs occurred in 24 patients (43.6%) with standard prophylaxis and in 20 patients (26.3%) with prolonged prophylaxis (P = 0.038. Table 3). After adjustment for surgical approach and PD diameter, the OR to develop an OSI with standard compared to prolonged prophylaxis was 1.7 (95% CI: 0.6−4.7, P = 0.327). In patients with a negative bile culture, OSIs occurred in six patients (26.1%) with standard and in 17 patients (38.6%) with prolonged prophylaxis (P = 0.304).

Incisional SSIs developed in 77 patients (21.3%), of whom 70 infections (90.9%) were superficial. Incisional SSIs occurred in 48 patients (21.9%) with standard prophylaxis and in 29 patients (20.3%) with prolonged prophylaxis (P = 0.710. Table 2). Incisional SSI rates were comparable after stratification by bile cultures status (Table 3).

With regard to the microbiology of OSI cultures, acquired antibiotic resistance was found in only four patients with prolonged prophylaxis. Besides, no *clostridium difficile* infections were observed in patients receiving prolonged antibiotic prophylaxis.

Discussion

This dual-center cohort study demonstrated that prolonged antibiotic prophylaxis was associated with a promising reduction of isolated abdominal infectious complications in patients with contaminated bile (6.6% versus 18.2%. Adjusted OR: 5.7; 95% CI: 1.3−23.9), whereas no difference was found in patients with negative bile cultures (9.1% versus 8.7%. OR: 2.3; 95% CI: 0.4−14.6). OSI rates were higher in patients with standard compared to prolonged prophylaxis (42.5% versus 30.8%), although not significant after adjustment for surgical approach and PD diameter. Incisional SSI rates were comparable between patients with standard en prolonged prophylaxis (21.9% versus
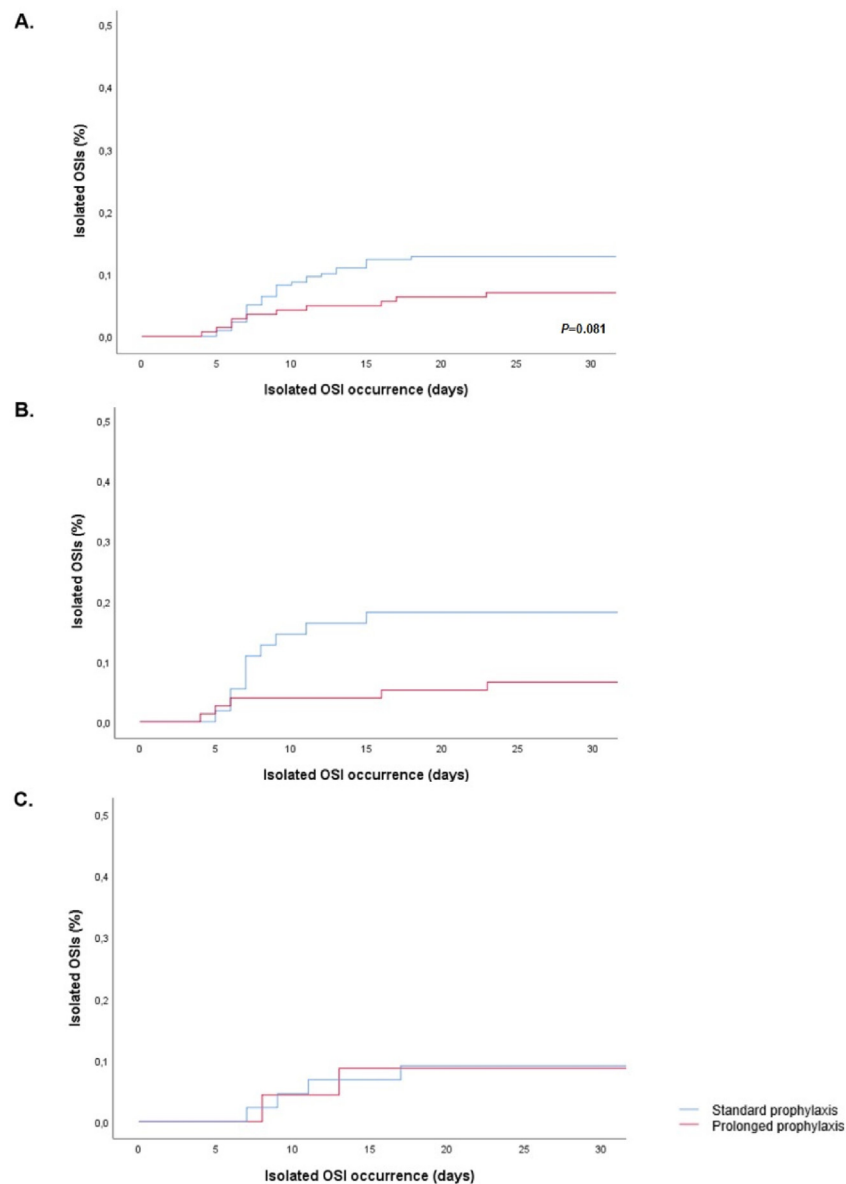
Figure 2 Timing of isolated OSI occurrence in patients with standard and prolonged prophylaxis (A), stratified for positive (B) and negative bile cultures (C)

20.3%, $P = 0.710$). Preoperative biliary drainage was highly associated with contaminated bile as 95% of these patients had positive intraoperative bile cultures ($P < 0.001$).

Abdominal complications after pancreatoduodenectomy are known for their complex and multifactorial origin and account for a substantial part of the postoperative morbidity.[22] Previous studies demonstrated an overall OSI incidence of 12–43% after pancreatoduodenectomy, corresponding to the OSI rate of 38% in this study.[6,23] Generally, studies distinguish incisional SSIs such as wound infections from abdominal SSIs such as abdominal abscesses, pancreatic fistula and bile or enteric leakages.[24] These abdominal complications contain both complications

with an infectious origin as anastomotic-related complications.[6] This study distinguished isolated abdominal infections from abdominal infections with simultaneous occurrence of pancreatic fistula, bile or enteric leakage to investigate the effect of prolonged antibiotic prophylaxis more critically.

Previous studies suggested that contaminated bile is associated with abdominal infectious complications and that intraoperative bile spillage may account for this.[2-5] Bile duct clamping was evaluated in a randomised controlled trial and showed similar rates of intraabdominal collections in the groups with and without bile duct clamping.[25] However, all patients in this study received prolonged antibiotic prophylaxis,

Table 3 Infectious complications stratified for bile culture status

	Total IOBC		Positive IOBC (n = 131)					Negative IOBC (n = 67)				
			Standard AB		Prolonged AB			Standard AB		Prolonged AB		
	n = 198	%	n = 55	%	n = 76	%	P	n = 23	%	n = 44	%	P
OSIs	67	33.8	24	43.6	20	26.3	0.038	6	26.1	17	38.6	0.304
Isolated OSIs[a]	21	10.6	10	18.2	5	6.6	0.040	2	8.7	4	9.1	0.957
Timing <14 Days	17	81.0	9	90.0	3	60.0	0.171	2	100	3	75.0	0.439
>14 Days	4	19.0	1	10.0	2	40.0		0	0.0	1	25.0	
Non-isolated OSIs[b]	46	23.2	14	25.5	15	19.7	0.246	4	17.4	13	29.5	0.638
Pancreatic fistula	41	89.1	14	100	12	80.0	0.077	4	100	11	84.6	0.404
Biliary leakage	3	6.5	0	0.0	1	6.7	0.326	0	0.0	2	15.4	0.404
Enteric leakage of perforation	2	4.3	0	0.0	2	13.3	0.157	0	0.0	0	0.0	-
Incisional SSIs	36	18.2	11	20.0	15	19.7	0.970	2	8.7	8	18.2	0.301
Superficial	32	88.9	10	90.1	13	86.7	0.945	2	100	7	87.5	0.531
Deep	4	11.1	1	9.1	2	13.3		0	0.0	1	12.5	

IOBC: intraoperative bile culture. AB: antibiotic prophylaxis. OSI: Organ space infection. SSI: incisional surgical site infection (wound infection).
[a] OSI without simultaneous occurrence of confounding complications.
[b] OSI with simultaneous occurrence of intraabdominal complications.

which may have mitigated the effect of clamping. Other studies in centers using prolonged prophylaxis reported comparable rates of abdominal and superficial surgical site infections in patients with positive and negative bile cultures.[8,15] This study showed isolated OSI rates of 18.2% versus 8.7% ($P = 0.290$) in patients receiving standard prophylaxis with positive and negative bile cultures, respectively, whereas isolated OSI rates between patients with positive and negative bile cultures receiving prolonged prophylaxis were similar (respectively 6.6% versus 9.1%, $P = 0.615$). Moreover, isolated OSIs predominantly occurred within 14 days after surgery both in patients with and without prolonged prophylaxis. Altogether, use of prolonged antibiotic prophylaxis seems to lower the rate of abdominal infections in patients with contaminated bile undergoing pancreatoduodenectomy.

The value of prolonged antibiotic prophylaxis after pancreatoduodenectomy has not been widely investigated. To our knowledge, only a few studies investigated the effect of prolonged antibiotic prophylaxis in patients with a high risk for positive bile cultures and found comparable rates of abdominal infectious complications after pancreatoduodenectomy, although these studies did not distinguish isolated OSIs.[13–15,26] The effect of targeted antibiotic prophylaxis, predominantly based on previously obtained bile cultures, was evaluated in a recent meta-analysis including seven studies and 849 patients and showed a positive effect of targeted antibiotic prophylaxis on the occurrence of SSIs.[24] This effect was particularly observed in patients with a positive bile culture. However, personalised prophylaxis has several practical issues as bile culture results are generally available after three-to-five postoperative days, until new developments such as nanopore sequencing will provide bile

culture results within several hours after surgery.[27] Since the duration of antibiotic prophylaxis was 48 h in five out of seven included studies, prolonged antibiotic prophylaxis could be a practical alternative for targeted prophylaxis based on preoperative obtained bile cultures. Nevertheless, unnecessary use of antibiotics should be avoided considering the increasing microbial resistance rate. Tailored antibiotic prophylaxis could be provided based on an intermediate bile culture result, which could be obtained within 48 h after surgery. In this situation, all patients would receive antibiotic prophylaxis for at least 48 h (NNT of 13.6 patients). If only patients with contaminated bile receive prolonged antibiotic prophylaxis, the NNT would decrease to 8.6 patients to prevent one isolated OSI. Hence, optimising the preoperative identification of patients with contaminated bile is preferred to provide tailored antibiotic prophylaxis.

Preoperative biliary drainage could be an indication for prolonged antibiotic prophylaxis as preoperative biliary drainage is predominantly associated with contaminated bile.[7–9,28] However, OSI and isolated OSI rates are not identical between patients with a positive bile culture and patients with preoperative biliary drainage (Table 3 and Supplemental Table 3). Other preoperative interventions or conditions such as ERCP or ampullary carcinomas are also associated to contaminate bile juice (Supplemental Table 2).[8,29] Due to the development of neoadjuvant therapy, use of preoperative biliary instrumentation is likely to increase. Standard use of prolonged antibiotic prophylaxis should be considered for these patients. Future randomised trials should identify groups of patients with a high risk for positive bile cultures and confirm the value of prolonged prophylaxis in these patients.

Limitations of this study are its observational design and the participation of only two centers. Although treatment was generally equal between the two participating centers, differences in technical procedures and protocols could have interfered with the results. Both centres participated in the PORSCH trial: a national, stepped-wegde, cluster-randomised controlled trial to improve early recognition and management of postoperative complications, and adhered to the algorithm for clinical decision-making after pancreatoduodenectomy.[17] A consequence of the PORSCH trial was a higher rate of performed CT-scans, and a subsequent higher POPF and OSI rate. However, the rate of OSIs was lower in the LUMC, despite the earlier start of the PORSCH trial. Furthermore, bile cultures were not obtained in all included patients, which could indicate a potential selection bias although baseline characteristics and the percentage of positive bile cultures were comparable between the standard and prolonged prophylaxis group. Furthermore, bile cultures were not obtained in all included patients, which could indicate a potential selection bias although baseline characteristics and the percentage of positive bile cultures were comparable between the standard and prolonged prophylaxis group. Therefore, relevant variables (surgical approach and PD diameter) were incorporated in the multivariate analysis. Other potential relevant variables were assessed as an interaction term and found not relevant to adjust for in a multivariate analysis. Another potential limitation was the indication for postoperative antibiotic treatment, which was based on clinical parameters. Conforming to the intention-to-treat principle, some patients were allocated to the standard antibiotic prophylaxis group and were treated with antibiotic within five days after surgery, which may have influenced the development of abdominal infections. However, clinical signs of infection imply the presence of an infectious complication and treatment with antibiotics potentially lead to an underestimated number of estimated infections in this group. Notwithstanding these limitations, this study evaluated the use of prolonged antibiotic prophylaxis in a realistic clinical setting, which makes the results directly applicable to daily practice. To diminish differences in the grading of abdominal infections, data collection was performed by three authors and the main outcomes were double-checked by at least two authors. Furthermore, this study used the definition of an isolated OSI to diminish the effect of confounding surgical complications.

In conclusion, prolonged antibiotic prophylaxis was associated with a promising reduction of isolated abdominal infectious complications in patients with contaminated bile, whereas no difference was found in patients with negative bile cultures. It should be considered that unnecessary use of antibiotics contributes to the development of antimicrobial resistance, although not observed within the short-term follow-up of this study. Therefore, we propose that prolonged antibiotic prophylaxis is not recommended for all patients undergoing pancreatoduodenectomy, but should be considered for patients with a high risk for contaminated bile, in particular patients with preoperative biliary drainage. The effect of prolonged antibiotic prophylaxis in patients undergoing pancreatoduodenectomy with a high risk for contaminated bile warrants confirmation in an adequately powered randomised controlled trial (Clinicaltrials.gov NCT0578431).

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.05.008.