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ORIGINAL ARTICLE

Cefotaxime resistance in bile samples is an independent predictor of deep infectious complications after pancreaticoduodenectomy in patients with endoprosthesis

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Abstract

Background: Bacteriobilia may increase the rate of deep infectious complications (DIC) after pancreaticoduodenectomy. To better adjust prophylactic and empirical antibacterial treatment, we aimed to characterize bacteriobilia in patients with preoperative endoprosthesis, and its association with postoperative DIC.

Methods: All patients who underwent pancreaticoduodenectomy in our center between 2010 and 2019 were included. The association between microbiological findings from bile samples, and postoperative DIC was analyzed, and we compared microbiology data between 2010-2014 and 2015-2019 periods.

Results: We enrolled 578 patients (median age 67years [59-72], 58.7% males), of whom 220 (38.1%) had preoperative biliary endoprosthesis, with 197 (89.5%) positive preoperative bile samples pathogens were Enterobacterales, enterococci, and *Candida albicans*. The incidence of DIC was similar in patients with or without endoprosthesis (20.4% vs 17.8%, $P = .352$). Bacterial isolates collected during 2015-2019 were more resistant to cefotaxime than those recovered from 2010-2014 (45.5% vs 25.5%, $P = .009$). The only independent risk factor for DIC in patients with endoprosthesis was cefotaxime resistance in bile (hazard ratio 3.027 [1.115-8.216], $P = .03$).

Conclusions: The incidence of DIC is high after pancreaticoduodenectomy, with or without endoprosthesis, despite routine postoperative treatment. Cefotaxime resistance, the only independent predictor of DIC in patients with endoprosthesis, has increased over time. Hence, cefotaxime may no longer be an appropriate empirical treatment.

KEYWORDS

bacteriobilia, complications, endoprosthesis, infection, pancreatoduodenectomy

The authors Pierre Tattevin and Laurent Sulpice contributed equally.

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1 | INTRODUCTION

Pancreaticoduodenectomy is the primary treatment of most periampullary cancers, including pancreatic adenocarcinoma. Despite major progress in patient selection and surgical techniques over the last decades, this procedure is still associated with a significant risk of life-threatening complications. Among them, postoperative deep infectious complications (DIC) remain a major risk of poor outcome.¹

Since hyperbilirubinemia is associated with increased risk of postoperative complications, preoperative biliary drainage by endoprosthesis is routinely performed.² However, endoprosthesis insertion carries its own burden of complications including: (a) hepatic impairment (i.e. coagulopathy, immune dysfunction), (b) complications associated with stent insertion (i.e. pancreatitis, bleeding), and (c) infectious complications. Indeed, the stent creates a communication between the biliary and the alimentary tracts, thus favoring the retrograde migration of pathogens from the intestinal microbiota. Several studies have highlighted the link between contaminated bile and DIC risk.³⁻⁵

The consequences of bacteriobilia may be prevented by per- and postoperative antibiotics active on common pathogens originating from the digestive tract, e.g. enterobacteriales and strict anaerobes.^{6,7} However, there is no consensus on the indications, and the optimal regimen, for the prevention of post-pancreaticoduodenectomy DIC, so that practices remain heterogeneous. In addition, the worldwide emergence of antimicrobial resistance further complicates this issue, as it increases the risk that even broad-spectrum empirical antibiotics will not cover all pathogens of concern. Indeed, antimicrobial resistance has been associated with increased risk of complications after pancreaticoduodenectomy, including non-infectious complications.⁸ To date, few studies have focused on the microbiology of bile in patients who require pancreaticoduodenectomy, although these data are of paramount importance to guide the indications and to identify the targets of empirical antibacterial treatment. We aimed to analyze the microbiology of bile in patients who require pancreaticoduodenectomy and to evaluate the potential associations with outcomes, in a referral centre with systematic use of empirical antibacterial therapy after pancreaticoduodenectomy.

2 | MATERIALS AND METHODS

2.1 | Patients

A retrospective analysis was conducted using a prospective cohort study of patients who underwent pancreaticoduodenectomy, with or without biliary drainage,

between January 2010 and December 2019 at the Rennes University Hospital, a 1500-bed tertiary care hospital that serves as a referral center for Western France (population catchment area, 1.5 million inhabitants). Demographic and perioperative characteristics, data on postoperative complications, and indication for surgery were collected. General status was assessed using age-adjusted Charlson comorbidity index⁹ and the American Society of Anesthesiologists (ASA) scores. This study was retrospective and noninterventional, and since the collected data were anonymous, the Research Ethics Committee of the University of Rennes-1 approved the study and waived the requirement for patient consent (Approval number: 21.158).

2.2 | Surgical technique and postoperative antimicrobial treatment

All pancreaticoduodenectomies were performed according to the Whipple and Child procedures, without pyloric conservation. A pancreaticojejunostomy was routinely performed with a stent in case of thin pancreatic duct or soft pancreatic parenchyma. Systematic abdominal drainage system was placed around the pancreatic anastomosis. When endoprosthesis had been previously inserted, a bile sample from the common bile duct and another from the gallbladder were collected at the beginning of the surgery. According to the institutional protocol, the combination of intravenous cefotaxime and metronidazole was started during the surgery, after bile sampling and reapplied every 8 h. Antibacterial treatment was adapted according to microbiological results, when appropriate, at the discretion of the infectious diseases consultant, for a total duration of 5 days postoperative. For patients without endoprosthesis, antibioprophyllaxis was limited to one dose of cefazolin, to be administered not earlier than 1 h before surgery, and to be repeated once if surgery lasts more than 4 h.

2.3 | Postoperative management

Pancreatic fistula, delayed gastric emptying, and post-pancreatectomy hemorrhage were defined according to the International Study Group of Pancreatic Surgery.¹⁰⁻¹² The primary outcome, DIC was defined as a composite criteria, including at least one of the following: infected postoperative pancreatic fistula, cholangitis, intra-abdominal abscess, or any surgical site infection with the exception of wound infection. Postoperative cholangitis was defined by the association of clinical signs of infection, an increase in inflammation markers and a disorder of biological liver

parameters improving with time under antibiotic treatment.¹³ Biliary fistula was defined according to ISGPS definition as any bilious fluid from abdominal drains, or bile collection requiring drainage radiologic or operative intervention.¹⁴ Postoperative complications were defined according to the Clavien-Dindo classification, and classified as “major” when the score was >3.¹⁵ Postoperative mortality was defined as death occurring within 90 postoperative days, whatever the cause.

2.4 | Bile microbiology

For all patients with endoprosthesis, bile samples were collected from both the common bile duct and the gallbladder, and immediately sent to the microbiology lab. Direct examination after Gram staining and cultures on aerobic and anaerobic media were performed and analyzed until day 5. Identification of bacteria and fungi was usually performed using the MALDI-TOF mass spectrometry, and drug susceptibility testing was performed according to the CA-SFM/EUCAST guidelines. Microbiological data were exhaustively collected through the database of the microbiology lab. In order to assess the evolution of resistance patterns, we compared data from the two consecutive 5-year periods, 2010-2014 and 2015-2019.

2.5 | Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQR), and were compared using the Mann-Whitney *U* test. Comparisons between the categorical variables were analyzed by chi-squared test or Fisher-exact test, when appropriate. All variables associated with DIC with a *P*-value of <.05 on univariate analysis were entered into a multivariate logistic regression analysis to identify independent risk factors. Analyses were performed using SPSS 25.0 (IBM Corp.) and graphics using GraphPad Prism 8.0.

3 | RESULTS

3.1 | Baseline characteristics

During the study period, 578 patients (median age 67 years [59-72], 58.7% males) underwent pancreaticoduodenectomy in our institution (Table 1). Among these procedures, 220 (38%) were performed after a biliary endoprosthesis was inserted. Baseline characteristics were similar in patients with or without endoprosthesis,

except for sex-ratio (64.1% males in patients with endoprosthesis, vs 55.3% in patients without, *P* = .037) and tumor type (*P* < .001), with higher proportion of pancreatic duct adenocarcinoma and cholangiocarcinoma in patients with endoprosthesis.

3.2 | Per- and postoperative events

Patients with endoprosthesis were more likely to require vascular resection (31.8% vs 21.4%, *P* = .005), and less likely to present the following postoperative complications: biliary leak (2.7% vs 8.9%, *P* = .004) and delayed gastric emptying (46.8% vs 61.9%, *P* < .001) (Table 2). Their hospital stay was also shorter (median 12 vs 14 days, *P* = .016) while they were less likely to require surgical revision (8.2% vs 15.6%, *P* = .009). In the overall population, the rate of DIC increased between the 2010-2014 period and the 2015-2019 period from 33 (15.1%) to 78 (21.8%) respectively (*P* = .024). Concerning the population of patients with previous biliary drainage, the rate of DIC increased from eight (13.3%) to 31 (19.5%), without reaching significance (*P* = .28).

3.3 | Bile microbiology in patients with preoperative endoprosthesis

Among the 220 patients who underwent preoperative bile samples, at least one potential pathogen was identified in 197 (89.5%) cases (Table 3; Figure 1). The main pathogens were Gram-negative bacilli (245/507, 48.3%), Gram-positive cocci (222/507, 43.8%) and yeasts (40/507, 7.9%). We found no association between pathogens and postoperative complications, including mortality (data not shown). The repartition of pathogens remained unchanged throughout the period (Tables S1 and S2), but cefotaxime resistance was higher in the second study period (45.5% in 2015-2019 vs 25.5% in 2010-2014, *P* = .009).

3.4 | Risk factors for deep infectious complications in patients with preoperative biliary endoprosthesis

On univariate analysis, preoperative pain, previous upper gastrointestinal surgery, and bacteriobilia resistance to either piperacillin-tazobactam, gentamicin, or cefotaxime were associated with increased risk of DIC (Table 4). On multivariate analysis, only bacteriobilia with cefotaxime-resistant germs remained predictive of DIC, with a hazard ratio of 3.027 (1.115-8.216), *P* = .03.

TABLE 1 Baseline characteristics

Clinicopathological features	Total (n = 578)	No endoprosthesis (n = 358)	Endoprosthesis (n = 220)	P-value
Male gender	339 (58.7%)	198 (55.3%)	141 (64.1%)	.037
Age, years [IQR]	67 [59-72]	64 [55-72]	66 [53-74]	.061
ASA Score				.079
1-2	456 (78.9)	272 (76.4)	180 (82.6)	
3-4	122 (21.1)	84 (23.6)	38 (17.4)	
Body mass index, kg/m ² [IQR]	23.6 [21.6-25.2]	23.8 [21.6-26.7]	23.8 [21.9-26.9]	.625
Comorbidities				
Diabetes	102 (17.6)	61 (17)	41 (18.6)	.625
Coronary disease	48 (8.3)	32 (8.9)	26 (7.3)	.481
Chronic kidney failure	16 (2.8)	9 (2.5)	7 (3.2)	.408
ACCI	2 (1-4)	3 (2-4)	3 (2-4)	.63
Preoperative pain	227 (39.3)	149 (41.9)	78 (35.6)	.137
Type of stent				
Metallic	—	—	132 (60)	
Plastic	—	—	88 (40)	
Tumor type				<.001
PDAC	259 (44.8)	135 (38)	124 (56.6)	
Cholangiocarcinoma	84 (14.5)	30 (8.5)	54 (24.7)	
Ampulloma	54 (9.3)	38 (10.7)	16 (7.3)	
Neuroendocrine tumor	28 (4.8)	26 (7.3)	2 (0.9)	
IPMN	39 (6.7)	38 (10.7)	1 (0.5)	
Other cancers	36 (6.2)	30 (8.5)	6 (2.7)	
Other benign lesions	73 (12.7)	16 (16.1)	16 (7.3)	
Neoadjuvant treatment	67 (11.6)	32 (9)	35 (15.9)	.012

Note: Qualitative variables are presented as numbers (%), and quantitative variables as medians [interquartile range].

Abbreviations: ACCI, age-adjusted Charlson comorbidity index; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; PDAC, pancreatic ductal adenocarcinoma.

4 | DISCUSSION

The primary findings of this prospective cohort study of 220 patients treated with pancreaticoduodenectomy and biliary endoprosthesis are the followings: (a) at least one potential pathogen is identified in the bile by the time of surgery in most patients (i.e. 9/10), primarily Enterobacteriales, enterococci, strict anaerobes, and yeasts; (b) DIC is a common event, reported in one-fifth of patients, similar to the incidence in patients without biliary endoprosthesis; (c) in this cohort with routine use of cefotaxime plus metronidazole combination as postoperative empirical treatment, only cefotaxime resistance was an independent predictor of DIC; (d) cefotaxime resistance in Enterobacteriales has dramatically increased throughout the study period (from 25.5% to 45.5% of bile samples), as could be expected given the worldwide spread of antimicrobial resistance, especially among Enterobacteriales during the study period. This led us to adjust postoperative

empirical treatment in our institution: we now routinely use piperacillin-tazobactam instead of cefotaxime plus metronidazole in patients treated with biliary endoprosthesis and pancreaticoduodenectomy.

Since it has been established that the presence of potential pathogens in bile samples is associated with increased risk of DIC in these patients,¹⁶ most experts recommend pre- and postoperative use of antimicrobials active on the main pathogens.^{6,17} Although no definite conclusion can be obtained from our observational study, the fact that the incidence of DIC was similar in patients with or without endoprosthesis suggests that routine use of broad-spectrum antimicrobials in patients with endoprosthesis was able to prevent a substantial proportion of DIC. Indeed, endoprosthesis has been associated with increased risk of DIC in several studies.¹⁸⁻²⁰

Biliary drainage prior pancreaticoduodenectomy remains a topic of extensive debate for resectable cancers, due to its own burden of postoperative complications (in

TABLE 2 Pro- and postoperative events

Clinicopathological features	No endoprosthesis (n = 359)	Endoprosthesis (n = 220)	P-value
Preoperative			
Intraoperative time, minutes [IQR]	282 [240-360]	300 [240-345]	.138
Hard pancreas	121 (52.6)	73 (47.4)	.317
Transfusion	74 (20.8)	41 (18.6)	.531
Vascular resection	77 (21.4)	70 (31.8)	.005
Tumor size, cm	3 (2-4)	2.5 (1.9-3.5)	.059
Wirsung drainage	215 (60.2)	123 (56.4)	.369
Postoperative			
Clavien-Dindo score ≥ 3	84 (23.5)	49 (23.4)	.741
Pancreatic fistula	53 (14.8)	26 (11.9)	.314
Biliary leak	32 (8.9)	6 (2.7)	.004
Hemorrhage	47 (13.1)	21 (9.6)	.201
Deep infectious complication	73 (20.4)	39 (17.8)	.447
Infected pancreatic fistula	45 (12.6)	21 (9.6)	
Deep abscess ^a	15 (4.2)	13 (6)	
Cholangitis	9 (2.5)	4 (1.9)	
Any other SSI	4 (1.1)	1 (0.4)	
Wound abscess	15 (4.2)	10 (4.6)	.835
Lymphatic leak	52 (14.5)	41 (18.7)	.183
Pancreatitis	19 (5.3)	7 (3.2)	.236
Surgical revision	56 (15.6)	18 (8.2)	.009
Length of hospital stay, days ^a	14 [11-20]	12 [10-17]	.016
Mortality rate at 30 days	14 (3.9)	7 (3.2)	.657
Mortality rate at 90 days	20 (5.6)	10 (4.6)	.587

Note: Qualitative variables are presented as numbers (%), and quantitative variables as medians.

Abbreviations: IQR, interquartile range; SSI, surgical site infection.

^aExcept pancreatic fistula.

particular DIC), and contradictory results have been reported from different cohorts.²¹⁻²³ Recently, Sandini et al²⁴ reported that delaying surgery up to 1 month after biliary stenting may reduce major morbidity. However, the increased use of neoadjuvant treatment in the management of pancreatic adenocarcinomas implies an extended delay before diagnosis and treatment of biliary obstruction through drainage. Endoprosthesis has therefore become an essential point in the management of periampullary cancers. The question is not whether endoprosthesis should be performed or not, but how to define the optimal perioperative antibiotic prophylaxis and treatment based on bile microbiology. Mechanical means such as last-generation stents designed to limit digestive reflux in the biliary tract have not yet reached the stage of routine clinical practice.²⁵

The use of appropriate empirical antibacterial therapy per- and postoperatively has been associated with decreased incidence of DIC in patients treated with biliary

endoprosthesis and pancreaticoduodenectomy.²⁶ The 5-day duration was documented as effective by Sourrouille et al.⁶ The choice of the optimal antimicrobial spectrum must take into account (a) the main pathogens involved and their antimicrobial resistance profiles, ideally in similar settings (i.e. local data on bile samples obtained by the time of surgery in similar patients); (b) the impact of extended use of broad-spectrum antibiotics, which contribute to the emergence of multidrug resistance. For these reasons, although carbapenems would probably be the treatment most likely to cover the largest proportion of potential pathogens, they are not an option, as they should be preserved as “salvage regimen” in patients with multidrug-resistant sepsis.²⁷

Our 10-year retrospective cohort study provided insights on the evolution of biliary microbiota in patients treated with biliary endoprosthesis and pancreaticoduodenectomy. While repartition of pathogens remained unchanged throughout the period (data not shown),

TABLE 3 Main bacteria and fungi isolated from preoperative bile samples^a

Microbiology	n	%
Gram-negative bacilli		
<i>Escherichia coli</i>	85	43.1
<i>Enterobacter cloacae</i> complex	36	18.3
<i>Klebsiella pneumoniae</i>	30	15.2
<i>Hafnia alvei</i>	27	13.7
<i>Klebsiella oxytoca</i>	20	10.2
<i>Citrobacter freundii</i>	14	7.1
<i>Pseudomonas aeruginosa</i>	11	5.6
<i>Citrobacter koseri</i>	6	3.0
<i>Enterobacter aerogenes</i>	6	3.0
<i>Raoultella ornithinolytica</i>	5	2.5
<i>Serratia marcescens</i>	5	2.5
Gram positive cocci		
<i>Enterococcus faecalis</i>	129	65.5
<i>Enterococcus faecium</i>	49	24.9
<i>Streptococcus anginosus</i>	25	12.7
<i>Enterococcus durans</i>	7	3.6
<i>Enterococcus avium</i>	6	3.0
<i>Enterococcus</i> spp.	6	3.0
Fungi		
<i>Candida albicans</i>	40	20.3
Others	54	27.4

^aAll bacteria and fungi isolated in at least five patients are reported.

resistance to antibiotic therapy has largely evolved, up to the situation where almost half of patients presented bacteriemia with resistance to the empirical treatment in use during the study period. These findings are in line with the literature review and modeling study by Teillant et al on surgery and cancer, with approximately 50% of pathogens responsible for surgical site infection resistant to the antibiotics used for prophylaxis²⁸ and with the globalization of antimicrobial resistance.^{29,30} In addition, patients treated with biliary endoprosthesis and pancreaticoduodenectomy are likely to have received recent antibacterial treatments, at least as surgical prophylaxis by the time of biliary endoprosthesis insertion, according to our national guidelines, or in case they developed febrile neutropenia following cancer chemotherapy, a common event (25%-45%) with folfirinox-based regimens, commonly prescribed as neoadjuvant therapy for pancreatic cancer.³¹

Following the emergence of antimicrobial resistance in this population, several teams have selected piperacillin-tazobactam as the first-line empirical treatment for perioperative antibiotic prophylaxis.^{6,32,33} Krüger et al found that the prevalence of resistance in bacteriemia was 50% for cefotaxime vs 26% for piperacillin-tazobactam.³⁴ A study from the American College of Surgeons National Surgical Quality Improvement Program database analyzing 15 182 pancreatic surgeries found that patients with biliary endoprosthesis who received perioperative prophylaxis

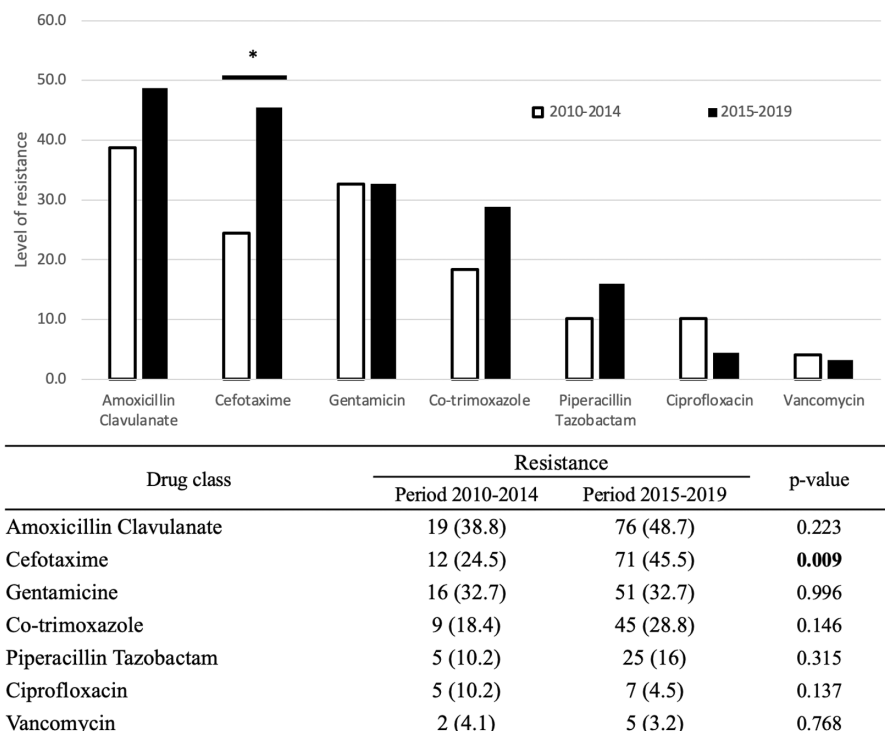
FIGURE 1 Evolution of antibiotic resistance between periods 2010-2014 and 2015-2019.

TABLE 4 Uni- and multivariate analysis of risk factors for deep infectious complications in patient with endoprosthesis

Clinicopathological features	Deep intra-abdominal infection		Univariate analysis	Multivariate analysis		
	No	Yes	P-value	HR	95% CI	P-value
Pre- and per-operative						
BMI >25 kg/m ²	65 (37.1)	16 (41)	.651	—	—	—
Diabetes mellitus	32 (17.8)	8 (20.8)	.689	—	—	—
Smoking	66 (36.7)	16 (41)	.61	—	—	—
Preoperative weight loss	92 (52)	15 (39.5)	.162	—	—	—
Preoperative pain	57 (31.8)	20 (51.3)	.021	1.909	(0.871-4.185)	.106
Previous upper GI surgery	16 (8.9)	8 (21.1)	.029	2.155	(0.748-6.210)	.155
Neoadjuvant treatment	30 (16.7)	5 (12.8)	.552	—	—	—
Soft pancreas	71 (55)	9 (37.5)	.114	—	—	—
Red blood cells transfusion	35 (19.4)	6 (15.4)	.556	—	—	—
Operative time over 7 h	14 (7.8)	5 (12.8)	.31	—	—	—
Microbiology						
Yeast	47 (27.6)	7 (18.4)	.241	—	—	—
Amoxicilline-clavulanate resistance	72 (45)	19 (52.8)	.398	—	—	—
Piperacillin-tazobactam resistance	16 (8.9)	9 (25)	.031	1.41	(0.520-3.825)	.612
Cefotaxime resistance	56 (35)	24 (66.7)	.001	3.027	(1.115-8.216)	.03
Gentamicin resistance	48 (30)	18 (50)	.022	1.255	(0.507-3.107)	.624
Vancomycin resistance	6 (3.8)	1 (2.8)	.776	—	—	—
Cotrimoxazole resistance	40 (25)	12 (33.3)	.306	—	—	—

with broad-spectrum antibiotics had a decreased risk of postoperative complications than patients who received 1st- to 3rd-generation cephalosporins.³⁵ A randomized controlled trial comparing cefoxitin and piperacillin-tazobactam as antibiotic prophylaxis in all patients undergoing pancreaticoduodenectomy is ongoing (NCT03269994). The composition of gut microbiome may be associated with increased risk of surgical complications, including anastomotic fistula or adhesions.³⁰ The presence of *Klebsiella pneumoniae* in bile samples from patients undergoing pancreaticoduodenectomy has been associated with chemoresistance to adjuvant gemcitabine in one study, which suggests that quinolone therapy may be associated with survival.³⁶ These data as well as our study advocate for additional studies on the biliary microbiome, and its impact on outcome in patients with pancreatic cancer.

Our study has several limitations. Firstly, as it was a single-center study our findings may not apply to other settings with different epidemiology and different practices in terms of surgical treatment as well as perioperative antibacterial prophylaxis. Secondly, as it was observational over a 10-year study period and patient management may have been heterogeneous, with potential biases. Thirdly, although data were prospectively collected, the analysis of the association between bile

microbiology and outcome was not initially planned, so that we had to merge data from the microbiology lab and those from the prospective cohort. Fourthly, we focused on bile microbiology, as these were the only microbiological samples standardized during the study period, so that our study was not powered to analyze the impact of other microbiomes, such as gut microbiome. Finally, the prospective cohort study enrolled patients who underwent pancreaticoduodenectomy, and we have no data on patients who presented serious complications following biliary endoprosthesis that precluded pancreaticoduodenectomy. However, our study also has several strengths, including the large sample size, the enrolment of all consecutive patients who underwent pancreaticoduodenectomy in our center, and the systematic evaluation of bile microbiology and outcomes in these patients.

In conclusion, while preoperative insertion of biliary endoprosthesis is increasingly performed in patients with pancreatic cancers, our study suggests that perioperative antimicrobial treatment should be adjusted to local epidemiology of antimicrobial resistance. As we found that the prevalence of bacteriobilia with cefotaxime-resistant germs has increased over time, and is an independent predictor of DIC in patients with endoprosthesis.

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CONFLICT OF INTEREST

Authors declare no conflict of interest for this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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