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ORIGINAL ARTICLE

Five days of postoperative antimicrobial therapy decreases infectious complications following pancreaticoduodenectomy in patients at risk for bile contamination

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Abstract

Objectives: Pancreaticoduodenectomy (PD) is associated with high morbidity, in part as a result of infectious complications increased by preoperative bile contamination. The aim of the present study was to assess the effect on the incidence of infectious complications of short-term antimicrobial therapy (AMT) in high-risk patients.

Methods: Patients with a high risk for positive intraoperative bile culture (i.e. those with ampulloma or pancreatic adenocarcinoma with preoperative endoscopic procedures) (high-risk group, $n = 99$) were compared with low-risk patients (i.e. those with pancreatic adenocarcinoma without preoperative endoscopic procedures) (low-risk group, $n = 76$). The high-risk group received a 5-day course of perioperative AMT secondarily adapted to the bile antibiogram. The low-risk group received only the usual antimicrobial prophylaxis.

Results: Positive bile cultures were significantly more frequent in high-risk patients (81% versus 12%; $P < 0.001$). The overall rate of infectious complications was lower in the high-risk group (29% versus 46%; $P = 0.018$). The statistically significant decrease in the rate of infectious complications reflected reduced rates of urinary tract infections, pulmonary infections and septicaemia. Rates of wound infection (3% versus 5%; $P = 0.639$) and intra-abdominal abscess (7% versus 7%; $P = 0.886$) were similar in the high- and low-risk groups, as was the need for curative AMT.

Conclusions: This exploratory study suggests that a postoperative short course of AMT in patients at high risk for biliary contamination reduces the overall rate of infectious complications after PD. The adaptation of perioperative antimicrobial policy to the patient's risk for bile contamination seems promising and should be further evaluated.

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Introduction

Thanks to improvements in surgical techniques and perioperative management, pancreaticoduodenectomy (PD) is now routinely performed in high-volume centres with mortality rates ranging from <3% to 5%.[1,2] Nevertheless, perioperative morbidity is still substantial and affects up to 60% of patients.[1–4] Pancreatic fistula[5] and delayed gastric emptying (DGE)[6] account for most perioperative morbidity and their prevention after PD has been widely studied, including in numerous prospective randomized trials.[7–10] In addition, infectious complications are also frequent, affecting around 35% of patients[4,11,12] with deleterious consequences, but to date these events have been poorly investigated. Preoperative bile

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contamination is a well known and important risk factor for infectious complications.[13–17] This condition is frequent in malignant ampulloma[18–20] and following endoscopic procedures,[21] which are still widely performed[16] despite evidence-based limitations in indications.[22] Overall, it would make sense to actively reduce the occurrence of infectious complications in this high-risk group of patients because such a reduction would decrease overall postoperative morbidity and hospital length of stay (LoS) following PD.

Previously, the usual antimicrobial prophylaxis (AMP) used for PD has been shown to be frequently inefficient against microorganisms present in contaminated bile. This may explain the higher rate of infectious complications in this setting,[18] confirmed in several high-volume centres.[15–17] In order to prevent infectious complications in high-risk patients, the use of a broader empiric antimicrobial therapy (AMT) administered for a longer period might be promising. Consequently, the aim of the present study was to assess the effects on the postoperative occurrence of infectious complications of a short course of appropriate postoperative AMT in patients at risk for bile contamination.

Materials and methods

Patient selection

From 2004 to 2009, 175 consecutive patients underwent PD for periampullary malignancy involving either malignant ampulloma or pancreatic head adenocarcinoma. Patients with benign tumours were excluded from this study because they are almost never jaundiced and rarely need PD. Patients with percutaneous transhepatic biliary drainage were also excluded in order to ensure that the present analysis included only a homogeneous group of patients with endogenous bile contamination.

Patients were classified according to their preoperative risk for the presentation of a positive intraoperative bile culture (PIBC). Patients were considered at risk for PIBC (high-risk group, $n = 99$) if they had a malignant ampulloma[18–20] or if they underwent at least one preoperative endoscopic procedure including sphincterotomy, brushing, endoprosthesis or nasobiliary drain.[11,18] Patients were considered without risk for PIBC if they had a pancreatic head adenocarcinoma and did not submit to a preoperative endoscopic procedure (low-risk group, $n = 76$). Groups were compared for the occurrence of postoperative complications, with specific attention to infectious complications. Data were obtained from a prospective database and additional retrospective medical records were reviewed when necessary.

Surgical procedure and postoperative management

Pancreaticoduodenectomy without pylorus preservation was performed with regional lymphadenectomy and pancreaticogastrostomy, as previously described.[23] The abdominal cavity was routinely drained using an open multichannel silicone drain. Octreotide (Sandostatin®; Novartis France SA, Rueil Malmaison, France) was given to patients with a soft pancreas and started intraoperatively (100 μg subcutaneously three times per day). Oral diet was initiated on postoperative day (PoD) 5 in patients without pancreatic leak or other intra-abdominal complication.

Antimicrobial prophylaxis and therapy

According to the institutional protocol for AMT, patients without risk for PIBC (low-risk group, $n = 76$) received intraoperative injections of cefoxitin (2 g i.v. prior to skin incision, then 1 g every 2 h), based on French guidelines for the administration of AMP.[24] All patients considered to be at risk for PIBC (high-risk group, $n = 99$) received intraoperative AMP, commenced prior to skin incision, consisting of a combination of gentamicin (5 mg/kg up to 500 mg in a single shot, $n = 99$) with piperacillin + tazobactam (4 g, three times per day, $n = 28$). The piperacillin + tazobactam protocol was subsequently switched to ticarcillin + clavulanic acid (5 g, three times per day, $n = 71$). This modification was a recommendation of the Institutional Antimicrobials Committee intended to limit the use of piperacillin + tazobactam in the setting of AMP because this treatment was already widely used in AMT. Immediately after abdominal exploration, all patients underwent bile sampling from the gallbladder and/or the common bile duct for microbiological culture. No intraoperative Gram staining was performed. Pathogens were identified with standard microbiological methods. Antibiotic sensitivity was tested with Mueller–Hinton agar diffusion.

In patients at risk for bile contamination, empirical AMT was given until PoD 2, when the results of microbiological culture became available. If bile culture was negative, AMT was stopped. If bile culture was positive, AMT was adapted to strain sensitivity and continued until PoD 5. Empirical AMT was considered appropriate if all pathogens found in the bile culture were sensitive to either piperacillin + tazobactam or ticarcillin + clavulanic acid, according to the period of inclusion. Conversely, AMT was considered inappropriate if microorganisms resistant to the empirical antibiotics were present, and subsequent treatment adaptation was required.

Postoperative complications

Postoperative mortality included all deaths occurring before hospital discharge or PoD 90. Morbidity included all complications following surgery until discharge and/or readmission and were graded according to the Clavien–Dindo system of classification.[25] Major postoperative complications were defined as Clavien–Dindo Grade III or above. Postoperative pancreatic fistula, haemorrhage and DGE were defined according to the International Study Group of Pancreatic Surgery (ISGPS).[26–28] Only clinically relevant pancreatic fistulae (Grades B or C) were considered. Infectious complications were defined as bacteriologically positive culture associated with suggestive clinical symptoms. Wound infection was defined as the presence of pus requiring wound opening.[29] Intra-abdominal abscess was defined as a postoperative collection treated by puncture or drainage with bacteriologically positive culture.[29] Pulmonary infection was defined as fever with a suggestive thoracic X-ray image improving under

Table 1 Preoperative characteristics of the patients

	Total cohort (*n* = 175)	High-risk group (*n* = 99)	Low-risk group (*n* = 76)	*P*-value[a]
Male, *n* (%)	92 (52.6%)	58 (58.6%)	34 (44.7%)	0.096
Age, years, median (range)	62 (55–70)	61 (55–69)	64 (55–71)	0.570
Comorbidities and preoperative blood tests				
Diabetes mellitus, *n* (%)	27 (15.4%)	15 (15.2%)	12 (15.8%)	0.955
Body mass index, kg/m^2, median (range)	23.5 (21–26)	24 (21–26)	23 (21–26)	0.806
ASA score 1 or 2, *n* (%)	156 (89.1%)	87 (87.8%)	69 (90.8%)	0.300
Serum bilirubin, μM/l, median (range)	18 (8.3–90.3)	18 (10.5–56.5)	15 (7.0–316.0)	0.859
Indication for PD, *n* (%)				
Pancreatic adenocarcinoma	129 (73.7%)	53 (53.5%)	76 (100%)	**<0.001**
Ampullary carcinoma	46 (26.3%)	46 (46.5%)	0	**<0.001**
Tumour diameter, mm, median (range)	30 (20–35)	30 (20–35)	30 (20–35)	0.484
Hard pancreatic remnant, *n* (%)	96 (54.9%)	46 (46.5%)	50 (65.8%)	**0.002**
Preoperative endoscopic procedures, *n* (%)	76 (43.4%)	76 (76.8%)	0	**<0.001**

[a]Values in bold are significant at $P < 0.05$.
ASA, American Society of Anesthesiologists; PD, pancreaticoduodenectomy.

antibiotics.[30] Bacteraemia was defined as a positive blood culture bottle with a pathogenic organism.[31] For organisms that could potentially be skin contaminants (i.e. coagulase-negative staphylococci, corynebacteria and *Bacillus* species), the isolation of the same bacteria with a similar sensitivity profile from at least two different sets of blood cultures was required to define a bloodstream infection.[32] Catheter-related bacteraemia was documented when the blood isolate was cultured from the catheter tip [10^3 colony-forming units (CFU)/ml] or when blood cultures obtained via the catheter were found to be positive at least 2 h earlier than the corresponding peripheral blood culture.[33] Urinary tract infection was defined as suggestive symptoms associated with a positive urine culture.[34,35] Microorganisms isolated from postoperative samples were compared with those from intraoperative bile samples.

Statistical analysis

Quantitative variables were expressed as medians [interquartile range (IQR)] and compared using the Mann–Whitney *U*-test. Qualitative variables were expressed as rates (%) and compared using the chi-squared test or Fisher's exact test as appropriate. All tests were two-sided. Differences were considered statistically significant at $P < 0.05$. Statistical analysis was performed using R Version 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Pre- and intraoperative patient characteristics

Characteristics of the patients are detailed in Table 1. There were no significant differences in demographic characteristics between the high- and low-risk groups. In the high-risk group, roughly half of the PDs were performed for pancreatic adenocarcinoma (*n* = 53, 54%) and half were performed for malignant ampulloma (*n* = 46, 46%). Patients considered at risk for PIBC were more likely to have a soft pancreatic remnant (54% versus 34%; $P = 0.002$). Endoscopic procedures are detailed in Table 2. Intraoperative data (Table 3) were comparable across the two groups, except that perioperative red cell transfusions trended to be higher in the low-risk group ($P = 0.015$).

Table 2 Characteristics of the 76 endoscopic preoperative procedures carried out in the high-risk patient group (*n* = 99)

Type of procedure, *n* (%)	
Endoprosthesis	66 (86.8%)
Sphincterotomy	6 (7.9%)
Nasobiliary drain	1 (1.3%)
Ampullectomy	2 (2.6%)
Attempt to endoscopic procedure, *n* (%)	4 (5.3%)
Two endoscopic procedures, *n* (%)	3 (3.9%)

Overall postoperative outcomes

Postoperative outcomes are detailed in Table 3. There was no difference in postoperative mortality, overall morbidity, rates of Grade B or C pancreatic fistula or DGE. The median LoS in the intensive care unit (ICU) was significantly shorter in the high-risk group (1.0 day versus 2.5 days; $P = 0.032$), but there was no significant difference in median hospital LoS (21.0 days versus 21.0 days; $P = 0.750$).

Infectious complications and microbial aetiology

Postoperative infectious complication was found in 37% (*n* = 64) of patients (Table 4).

Table 3 Intraoperative and postoperative characteristics of the patients

	Total cohort (*n* = 175)	High-risk group (*n* = 99)	Low-risk group (*n* = 76)	*P*-value[a]
Intraoperative bile contamination, *n* (%)	89 (50.9%)	80 (80.8%)	9 (11.8%)	**0.001**
Operative time, min, median (range)	450 (380–540)	460 (390–540)	430 (360–512.5)	0.270
Intraoperative blood loss, ml, median (range)	410 (300–600)	400 (300–625)	475 (300–600)	0.910
Transfusions of red blood cells, units, median (range)	0 (0–0)	0 (0–0)	0 (0–2)	**0.015**
Mortality, *n* (%)	6 (3.4%)	1 (1.0%)	5 (6.6%)	0.117
Overall morbidity, *n* (%)	122 (69.7%)	67 (67.7%)	55 (72.4%)	0.250
Major morbidity, *n* (%)	40 (22.9%)	20 (20.2%)	20 (26.3%)	0.404
Infectious complications, *n* (%)	64 (36.6%)	29 (29.3%)	35 (46.1%)	**0.018**
Pancreatic fistula (Grades B + C), *n* (%)	24 (13.7%)	17 (17.2%)	7 (9.2%)	0.179
Associated with infected collection	7	5	2	1
Delayed gastric emptying, *n* (%)	18 (10.3%)	12 (12.1%)	6 (7.9%)	0.506
Haemorrhage, *n* (%)	14 (8.0%)	7 (7.1%)	7 (9.2%)	0.799
Clostridium difficile colitis, *n* (%)	1 (0.6%)	1 (1%)	0	1
Length of stay, days, median (range)				
Intensive care unit	1.0 (0–5.0)	1.0 (0–4.0)	2.5 (0.8–6.3)	**0.032**
Hospital stay	21 (16–28)	21 (15–28)	21 (16–27)	0.750

[a]Values in bold are significant at $P < 0.05$.

Table 4 Detailed postoperative infectious complications

	Total cohort (*n* = 175)	High-risk group (*n* = 99)	Low-risk group (*n* = 76)	*P*-value[a]
Infectious complications, *n* (%)	64 (36.6%)	29 (29.3%)	35 (46.1%)	**0.018**
Surgical site infection, *n* (%)	19 (10.8%)	10 (10.1%)	9 (11.8%)	0.729
Abscess, *n* (%)				
Wound	7 (4.0%)	3 (3.0%)	4 (5.3%)	0.639
Intra-abdominal	12 (6.9%)	7 (7.1%)	5 (6.6%)	0.886
Pneumonia, *n* (%)	14 (8.0%)	2 (2.0%)	12 (15.8%)	**0.001**
Bacteraemia, *n* (%)	27 (15.4%)	11 (11.1%)	16 (21.1%)	**0.030**
CRBSI, *n* (%)	10 (5.7%)	4 (4.0%)	6 (7.9%)	0.370
Urinary tract infection, *n* (%)	18 (10.3%)	4 (4.0%)	14 (18.4%)	**0.002**
Antibiotherapy > 7 days, *n* (%)	41 (23.4%)	18 (18.2%)	23 (30.3%)	0.081

[a]Values in bold are significant at $P < 0.05$.
CRBSI, catheter-related bloodstream infection.

Positive bile culture was found in 51% of patients ($n = 89$). Patients considered at risk for PIBC (high-risk group) showed a positive bile culture more frequently (81%, $n = 80$) than patients in the low-risk group (12%, $n = 9$) ($P < 0.001$). Of patients who did not undergo a preoperative endoscopic procedure, patients with an ampullary carcinoma were significantly more likely to have a PIBC than patients with an adenocarcinoma [34 of 46 (74%) patients versus nine of 76 (12%) patients; $P < 0.001$]. The microorganisms most commonly isolated in the bile culture were *Enterococcus* species (48%), *Escherichia coli* (42%) and *Klebsiella* species (28%); their sensitivities to different antibiotherapy regimens are shown in Table 5. In more than half of patients (66%, $n = 59$), more than one pathogen was identified in the bile culture. This did not differ according to tumour histology [20 of 34 (59%) patients with ampulloma versus 39 of 55 (71%) patients with adenocarcinoma; $P = 0.241$].

The empirical AMT in the high-risk group (ticarcillin + clavulanic acid or piperacillin + tazobactam) was appropriate in 67% ($n = 66$) of patients. The initial regimen was found to be inappropriate in patients with infections caused by *E. coli* (14%, $n = 14$) and *Staphylococcus* species (14%, $n = 14$). In patients with a PIBC who developed a postoperative infectious complication, pathogens found in the intraoperative bile culture were identified as responsible for bacteriologically proven postoperative infection in 11 of

Table 5 Microbial aetiology and antibiotic sensitivity in positive intraoperative bile cultures in 89 patients

Germs	Patients, *n* (%)	Antibiotic sensitivity rate, %							
		Amoxicillin	Amoxicillin + clavulanic acid	Ticarcillin + clavulanic acid	Piperacillin + tazobactam	Cefoxitin	Gentamicin	Amikacin	Ciprofloxacin
Enterococcus sp.	43 (48%)	90%	90%	90%	90%	0%	0%	0%	0%
Escherichia coli	37 (42%)	60%	80%	80%	90%	90%	90%	100%	90%
Klebsiella sp.	25 (28%)	0%	90%	90%	90%	100%	100%	100%	90%
Hafniae alvei	10 (11%)	0%	0%	100%	100%	90%	100%	100%	100%
Enterobacter sp.	9 (10%)	0%	0%	90%	90%	90%	100%	100%	90%
Streptococcus sp.	8 (9%)	60%	60%	60%	60%	80%	0%	0%	0%
Pseudomonas aeruginosa	8 (9%)	10%	10%	60%	90%	50%	60%	90%	80%
Staphylococcus sp.	7 (8%)	0%	70%	70%	70%	70%	90%	90%	70%
Proteus sp.	6 (7%)	0%	100%	100%	100%	100%	100%	100%	100%
Morganella morganii	4 (5%)	0%	0%	100%	100%	100%	100%	100%	100%

32 patients. Among patients who developed a bacteriologically proven postoperative infectious complication, the analysis of bacteriological samples revealed similar rates of antibiotic-resistant microorganisms in the high- and low-risk groups [in eight of 29 (28%) patients and eight of 35 (23%) patients, respectively; $P = 0.664$]. In the high-risk group, half of the antibiotic-resistant germs responsible for infectious complications were already present in the bile culture. No late resistant infection was observed in the high-risk group.

Among low-risk patients, 12% ($n = 9$) had PIBC. No predictive factors for PIBC in the low-risk group were identified. Patients with PIBC received, in addition to the one-shot antimicrobial cefoxitin prophylaxis, a 5-day AMT course started on PoD 2 and adapted to the antibiogram. These patients did not develop postoperative infectious complications more frequently than low-risk patients with negative bile culture [five of nine (56%) patients versus 30 of 67 (45%) patients; $P = 0.542$].

Discussion

If the study of targeted strategies to prevent the occurrence of pancreatic fistula[7,8] and DGE[9] after PD had not produced uneven results, such an approach might make sense in the prevention of postoperative infectious complications. In the present study, the authors observed that a 5-day postoperative course of AMT in patients at high risk for biliary contamination was associated with a significant decrease in the overall occurrence of postoperative infectious complications compared with that in patients considered to be at low risk for biliary contamination. With reference to surgical site infection, high-risk patients presented a non-significantly different rate of infection, whereas a higher rate had been expected in line with previous reports.[11,16–18] Identified risk factors for biliary contamination (i.e. malignant ampulloma and subjection to preoperative endoscopic procedures) appeared to be accurate as >80% of patients in whom these risk factors were present had a positive bile culture. Furthermore, the AMT protocol for high-risk patients appeared to be bacteriologically appropriate in >80% of cases. The present study justifies the application of a specific AMT policy in patients undergoing PD and suspected to have a bile duct contamination in order to decrease the overall rate of postoperative infectious complications.

Bile contamination from the digestive tract is a well-known risk factor for postoperative infectious complications.[1,11,14,18,36,37] This condition is usually asymptomatic, is only diagnosed on intraoperative positive bile culture, and occurs frequently in patients who undergo preoperative endoscopic procedures[15,21] and in patients with ampullary carcinoma.[18] Indeed, rates of bile contamination in patients with biliary drainage range from 30% to 98%.[3,15,38,39] However, despite strong evidence of the negative impact of preoperative biliary drainage if serum bilirubin is <250 μM/l,[22] most patients with pancreatic head adenocarcinoma are still referred to surgery with biliary drainage in place. Ampulloma is frequently associated with bile contamination as indicated by the occurrence of cholangitis in up to 20% of patients.[18–20] This is likely to reflect sphincter dysfunction,[18,19,40–42] as well as the need for numerous preoperative endoscopic procedures in the preoperative workup of ampulloma.[41]

In order to prevent the occurrence of postoperative infectious complications associated with bile contamination, the present authors propose the specific administration of a 5-day course of postoperative AMT in high-risk patients. The rationale for this treatment is firstly that the frequent bile leakage in the operative field after common bile duct section is likely to contaminate the postoperative fluid collection that is frequently observed after pancreatic surgery. Overall, this surgical procedure can be viewed as an Altemeier class 3 procedure,[43] which justifies the provision of AMT as previously shown with other procedures such as colorectal surgery.[44] Secondly, pathogens responsible for bile contamina-

tion in high-risk patients have been shown to differ from pathogens isolated from bile culture in non-health care-associated biliary infections.[18,45,46] These pathogens must be targeted appropriately. The systematic policy evaluated in the present study was found to be associated with a reduced rate of infectious complications after PD in selected patients (i.e. patients who underwent preoperative endoscopic procedures or patients with ampullary carcinoma). Interestingly, as a result of this active prevention strategy, high-risk patients demonstrated an even lower overall rate of infectious complications than patients without risk. Rates of wound and intra-abdominal infections, which, on the basis of previous evidence,[11,15–18] were expected to be higher in the high-risk group, were similar across the two groups, confirming the efficacy of this preventive strategy. This efficient preventive strategy may prove even more interesting when PD is performed without postoperative drainage, as the potentially intraoperatively infected fluid remains intra-abdominal. This decrease in postoperative infectious complications was also associated with a shorter stay in the ICU.

The microorganisms most frequently isolated in bile samples were *Enterococcus* species, *E. coli* and *Klebsiella* species; this is similar to findings reported in previous studies.[3,45–47] A comparison of the microorganisms identified in bile cultures and those identified in cultures obtained from postoperative wound and intra-abdominal infections showed identical microorganisms in about half of cases, which suggests that at least a third of overall infectious complications are caused by preoperatively contaminated bile. Interestingly, in the no-risk group, 12% of patients had a positive bile culture. No risk factor for this finding could be identified and thus routine intraoperative bile sampling in all patients undergoing PD is justified.

The national French guidelines for surgical AMP recommend the use of only second-generation cephalosporin for PD.[24] Based on pathogens isolated in bile culture in high-risk patients, this treatment would have led to inappropriate AMP in 57% of patients. Similarly, in a high-volume North American centre, the use of second-generation cephalosporin as AMP was not associated with a lower rate of infectious complications in high-risk patients.[15] Results demonstrated that other antimicrobial agents and administration should be considered.[15] In view of the local microbial ecology, the combination of carboxy or ureido penicillin and gentamicin was considered suitable for the most frequently isolated pathogens (i.e. ampicillin-sensitive *enterococcus* and Gram-negative bacteria). Extended-spectrum beta-lactamase (ESBL) pathogens were infrequent and did not appear to justify a further enlargement of this protocol.[15]

The authors are aware of some limitations of the current study. Firstly, from a methodological point of view, only a four-arm, randomized controlled study (which also tested standard AMP in high-risk patients and broad AMT in low-risk patients in an intent-to-treat analysis) would support the drawing of definitive conclusions. Nevertheless, such a trial cannot occur without results from preliminary studies such as this. Secondly, the present study design cannot determine whether the decrease in infection rate relates to the initial broad empiric ABT or to the subsequent adaptation. The duration of ABT should also be investigated because of its potential impact on microbial ecology and strain resistance, even if this was not observed in the present experience. From this perspective, as previously reported,[3] intraoperative bile culture and antibiogram should only be used to treat postoperative symptomatic infection. This latter policy is theoretically less likely to influence the respective bacteriological ecology, but it remains a therapeutic and not a preventive strategy. It is important to note that the present policy was also associated with a decrease in non-bile-related infections such as urinary tract infections and pneumonia, which resulted in an overall clinical benefit to patients. A last option for the prevention of postoperative infectious complications in patients at risk would involve the use of AMP[45] guided by preoperative bile culture. However, this policy is only possible in patients in whom percutaneous or endoscopic nasobiliary drains are placed and these are used less frequently than endoscopic biliary stenting because of the associated increase in morbidity.[48]

In conclusion, bile contamination is frequent in patients with periampullary neoplasm, especially following preoperative biliary drainage, and in patients with malignant ampulloma. This justifies the routine intraoperative sampling of bile for bacteriological documentation in all patients undergoing PD. Specific postoperative AMT seems to be efficient in preventing infectious complications in these high-risk patients. The benefits and consequences of such a policy should be evaluated prospectively on a larger scale, with specific attention to its impact on bacteriological ecology and resistance.

Conflicts of interest

None declared.

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