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## **Title**

High incidence of postoperative infections after pancreaticoduodenectomy: a need for perioperative anti-infectious strategies.

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## **Abstract**

**Objectives:** Postoperative infections occur frequently after pancreaticoduodenectomy, especially in patients with bile colonization. Recommendations for perioperative anti-infectious treatment are lacking, and clinical practice is heterogenous. We have analyzed the effects of bile colonization and antibiotic prophylaxis on postoperative infection rates, types and therapeutic consequences.

**Methods:** Retrospective observational study in patients undergoing pancreaticoduodenectomy with intraoperative bile culture. Data on postoperative infections and non-infectious complications, bile cultures and antibiotic prophylaxis adequacy to biliary bacteria were collected.

**Results:** Among 129 patients, 53% had a positive bile culture and 23% had received appropriate antibiotic prophylaxis. Postoperative documented infection rate was over 40% in patients with or without bile colonization, but antibiotic therapy was more frequent in positive bile culture patients (77% vs 57%,  $p=0,008$ ). The median duration of antibiotic therapy was 11 days and included a broad-spectrum molecule in 42% of cases. Two-thirds of documented postoperative infections involved one or more bacteria isolated in bile cultures, which was associated with a higher complication rate. While bile culture yielded Gram-negative bacilli (57%) and Gram-positive cocci (43%), fungal microorganisms were scarce. Adequate preoperative antibiotic prophylaxis according to bile culture was not associated with reduced infectious or non-infectious complication rates.

**Conclusion:** Patients undergoing pancreaticoduodenectomy experience a high rate of postoperative infections, often involving bacteria from perioperative bile culture when positive, with no preventive effect of an adequate preoperative antibiotic prophylaxis. Increased post-operative complications in patients with bile colonization may render necessary a perioperative antibiotic treatment targeting bile microorganisms. Further prospective studies are needed to improve the anti-infectious strategy in these patients.

## **Keywords**

Perioperative infection

Surgical site infection

Cephalic pancreaticoduodenectomy

Antimicrobial prophylaxis

Bile colonization

## **Introduction**

Cephalic pancreaticoduodenectomy (CPD) is major surgery whose main indication is the treatment of pancreatic adenocarcinoma [1]. Progress in perioperative management has reduced mortality to less than 5% in expert centers [2-4]. However, postoperative morbidity remains high (30-60%), mainly attributed to infections with reported incidences of approximately 40-75% and 10-50% for all types of infections and surgical site infections (SSI) respectively [5-9].

Currently, only preoperative, single-dose surgical antibiotic prophylaxis with cefazolin or ceftiofloxacin is recommended by the French Society of Anesthesia and Resuscitation (SFAR) [4]. The recommendations have recently evolved to exclude patients with preoperative biliary drainage and stenting, that is to say half of the patients. These patients frequently present bile colonization with bacteria that are resistant in more than 2/3 of cases to the molecules recommended in surgical antibiotic prophylaxis [5,6]. Multiple retrospective studies report an over 50% increase in the incidence of postoperative infections in this specific population, and suggest a benefit of broad-spectrum perioperative probabilistic antibiotic therapy rather than surgical antibiotic prophylaxis [2,3,5-11]. Some physicians have adopted this strategy in clinical practice.

The main objective of this retrospective study is to describe the nature and incidence of postoperative infections after CPD according to bile culture and the adequacy of surgical antibiotic prophylaxis relative to microorganisms isolated in bile culture. The secondary objectives are to describe the incidence of non-infectious postoperative complications in the same study groups, and to describe bacterial and fungal microorganisms found in intraoperative bile cultures.

## **Patients and method**

### Patients

In this observational, retrospective, monocentric study conducted in a high-volume expert center, all patients aged 18 years or more undergoing elective CPD for benign or malignant peri-ampullary tumors in the Department of Digestive Surgery and Transplantation of the Lille University Hospital between January 2014 and December 2018 were included.

The exclusion criteria were age < 18 years, pancreatic resections other than CPD or extended to the entire pancreas (total pancreaticoduodenectomy) or to neighboring organs, emergency surgery, patients operated in another hospital and transferred for management of a complication.

### Method

The main demographic, clinical and biological preoperative characteristics of the patients were collected. All patients received surgical antibiotic prophylaxis administered 30 minutes before incision by cefazolin (2g then 1g every 4 hours, double dose if BMI > 35kg/m<sup>2</sup> and bodyweight > 100kg) according to the SFAR guidelines or by ceftiofloxacin (2g then 1g/2h, double dose if BMI > 35kg/m<sup>2</sup> and bodyweight > 100kg). In case of allergy to  $\beta$ -lactams, patients received a combination of clindamycin 600mg (reinjection 600mg if duration > 4h, induction dose modified to 900mg following the 2017 guidelines) and gentamicin 5 mg/kg as a single injection [4].

The surgical technique consisted, after midline laparotomy, of resection by a two-stage procedure of the head of the pancreas, gastric antrum, first jejunal loop, gall bladder, bile duct and duodenum. The excision step consisted of a single-piece resection with locoregional lymph node dissection in the case of pancreatic or periampullary malignancy. The reconstruction step consisted in restoring pancreatic, biliary and digestive continuity and it required anastomoses, which were most often

pancreatico-jejunal, hepatic and gastroenteroanastomoses. A feeding jejunostomy was performed as required case-by-case. Suction drainage of pancreatico-jejunal and biliodigestive anastomoses was performed systematically. A trans-wirsung drain was placed if patients had risk factors for pancreatic fistula (soft pancreas, small pancreatic duct diameter [1]). Surgery duration, blood loss, and volume of blood transfusion were recorded.

Intraoperative bile sampling by trans-vesicular route or after section of the main bile duct was systematically performed for bacteriological analysis by the Bacteriology Laboratory of the Lille University Hospital. In the presence of yeasts, the sample was sent to the Mycology Laboratory for identification and an antifongigram. The antibiograms of all bacteria isolated in bile samples were analyzed, thereby assessing the adequacy of surgical antibiotic prophylaxis relative to isolated biliary microorganisms. In case of polymicrobial bile culture, surgical antibiotic prophylaxis was deemed inappropriate if at least one of the isolated bacteria was resistant.

A postoperative infection was defined by isolation of a pathogen from a microbiological sample culture resulting in the prescription of antibiotic therapy (peritoneal fluid, abscess, collection, blood culture, catheter culture, sputum, urine culture), need for drainage of a superficial or deep collection and appearance of a pancreatic fistula within 30 days of surgery. SSIs were defined according to the CDC recommendations as the presence of a superficial or deep incisional infection, an intra-abdominal organ or space infection requiring surgery, or the presence of a pancreatic fistula, defined according to the recommendations of the International Study Group of Pancreatic Surgery (ISGPF) [12,13].

The frequency of postoperative antibiotic therapy and its main characteristics, including median duration of treatment, antibiotic therapies lasting more than 7 days, use of broad-spectrum molecules (piperacillin-tazobactam, carbapenem) and combinations with an aminoglycoside or a fluoroquinolone were noted. Isolation from a microbiological culture of the same microorganism as the one found in the bile was studied at different sampling sites (blood, peritoneal fluid or abscess, catheter culture, sputum, urine).

The severity of postoperative complications was assessed according to the Clavien-Dindo classification [14]. Serious complications were defined by a score  $\geq 3$ . Gastroparesis (defined according to ISGPS [15]), hemorrhage, surgical revision procedures as well as all surgical or radiological drainage procedures were systematically identified. Postoperative mortality was defined as death occurring within 90 days of the procedure. The need for intensive care and the total length of hospital stay were also recorded.

#### **Statistical analysis:**

Qualitative variables are expressed as percentages and quantitative variables as mean +/- standard deviation if the distribution is normal, median with interquartile range otherwise. A Chi-square test was used to compare the qualitative variables. A multinomial logistic regression was performed to explain the risk factors for serious complications. All p-values presented were bilateral and the significance level was set at  $p < 0.05$ . Statistical analyses were performed with STATA 13 (StataCorp, College Station, TX).

#### **Results**

One hundred and twenty-nine patients with available intraoperative bile sample culture results were included in the study among the 158 patients initially eligible. Two groups were constituted according to the presence ( $n=69/129$ , 53%) or absence ( $n=60/129$ , 47%) of bile colonization. In

patients with bile colonization, surgical antibiotic prophylaxis was adequate according to colonizing biliary microorganisms in 23% (16/69) of cases (Figure 1).

Study population. The pre- and intraoperative patient characteristics are presented in Table I according to the presence or absence of bile colonization. Preoperative biliary drainage was performed in 44% (57/129) of the patients. Bile colonization was significantly associated with preoperative biliary drainage, 88% (50/57) of drained patients had a positive bile culture versus 26% (19/72) of non-drained patients ( $p=0.001$ ).

Postoperative infections and antibiotic therapies. No significant difference was found between colonized patients and those with negative bile cultures in the incidence of documented SSI and other postoperative infections (Table II). The main characteristics of postoperative antibiotic therapies are reported in Table III. Patients with bile colonization more frequently received postoperative antibiotic therapy for documented or clinically suspected infection (77% vs. 57%,  $p=0.008$ ), with a non-significant trend towards longer treatment durations. The use of broad-spectrum molecules or a combination of antibiotics was similar between the two groups.

Involvement of biliary microorganisms in postoperative infections. Thirty-eight percent (26/69) of patients with bile colonization developed a documented postoperative infection, 65% (17/26) of whom were infected with at least one of the bacteria isolated in bile cultures. Biliary bacteria were found in 80% (8/10) of patients with intra-abdominal infection and 46% (5/11) of bacteremic patients (Appendix 1).

Non-infectious complications. No significant difference in the incidence of non-infectious complications was found between colonized patients and those with negative bile cultures (Appendix 2).

Impact of surgical antibiotic prophylaxis adequacy relative to biliary colonization on the incidence of complications. Surgical antibiotic prophylaxis with cefazolin or cefoxitin was adequate to biliary microorganisms in only 23% (16/69) of cases. There was no significant difference in the incidence of SSI, other postoperative infections, surgical morbidity or postoperative antibiotic therapies, regardless of adequacy relative to bile colonization (Table IV). The risk factors for presenting a severe complication (Clavien-Dindo score  $\geq 3$ ) in multivariate analysis are presented in Table V. Preoperative biliary drainage was a protective factor (OR=0.241 [0.063-0.919],  $p=0.037$ ), while postoperative infection involving bacteria found in bile cultures increased the risk of severe complications 7.7-fold (OR=7.66 [1.94-30.23],  $p=0.004$ ).

Microbiological analysis of bile cultures. Bacteriological analysis is detailed in Appendix 3. The samples were polymicrobial in 83% (57/69) of the patients. The most frequently isolated microorganisms were Gram-negative bacilli (GNB) (57%) with a predominance of *Escherichia coli* (19%) and *Klebsiella* spp. (14%), followed by Gram-positive cocci (GPC) (43%) with a predominance of *Enterococci* (29%) and *Streptococci* (10%). There was no significant difference in the distribution of GPC (42% vs 48% respectively) and GNB (58% vs 52% respectively,  $p=0.44$ ) between patients with and without preoperative biliary drainage, and the distribution of the main species was similar. In contrast, bile colonization was more frequently polymicrobial in patients with preoperative biliary drainage (90% vs 63%,  $p= 0.01$ ). There was no significant difference in antimicrobial resistance between drained and non-drained patients, the percentage of GNB resistant to third-generation cephalosporins being 11.7% vs 12.5% respectively. *Staphylococcus aureus*, only found in 3 drained patients, were all sensitive to methicillin. The proportion of *Enterococcus faecalis* and *Enterococcus faecium* was similar between the two groups. Four percent (5/129) of the patients had bile colonization with *Candida* spp.. This was always associated with a polymicrobial bacterial culture.

## **Discussion**

We report a high incidence of postoperative infections with a high consumption of antibiotics after CPD, confirming the need for a perioperative strategy designed to prevent infectious morbidity in this specific surgery. Postoperative antibiotic therapy for documented or clinically suspected infection was more frequent in patients with bile colonization, and 2/3 of documented postoperative infections involved one or more bacteria isolated in bile culture with an increased risk of severe complications. Taken together, these results suggest that perioperative antibiotic therapy may need to be adapted to biliary bacterial ecology. The high incidence of surgical site infections even when surgical antibiotic prophylaxis is deemed adequate relative to bile sampling suggests the ineffectiveness of this single-dose approach in CPD. The prevalence of *Enterococcus faecium* and yeasts remains low, suggesting that in the probabilistic treatment, they may not be necessary except in severe cases.

The reduction of postoperative infectious morbidity is a major issue in CPD, as it is associated with an increase in overall morbimortality and indirectly impairs long-term survival by delaying access to adjuvant therapies in the neoplastic context [16-18]. In our study, more than 60% of patients had a documented or suspected postoperative infection leading to the prescription of antibiotic therapy. These incidences are similar to those reported in the literature [3,7,8,16]. Postoperative infections are also responsible for antibiotic overuse, as observed in our work where the median duration of treatment was 11 days and included a broad-spectrum molecule in 40% of cases. These data suggest the need for a preventive anti-infectious strategy to reduce postoperative morbidity and to forestall extended exposure to antibiotics.

Preoperative biliary drainage is a known risk factor for bile colonization, and was found in 88% of drained patients compared with only 24% of non-drained patients in our study [7,10]. Numerous studies clearly identify drainage and the resulting bile colonization as risk factors for postoperative infections [2,10,17,19-21]. However, this association was not found in our study, in which preoperative biliary drainage appeared to be a protective factor against the occurrence of serious complications. The protective effect of bile drainage, also found by others [3,18,22], could be the consequence of various confounding mechanisms resulting from the reduction in preoperative jaundice. Indeed, jaundice promotes complications through various mechanisms such as malnutrition, altered immune function and renal or hepatic dysfunction [23,24]. However, bile colonization was associated with a higher rate of postoperative antibiotic therapy compared with patients with sterile bile culture (77% vs 57%,  $p = 0,008$ ), suggesting a higher incidence of clinically suspected although not microbiologically documented infection.

Other data argue for an association between bile colonization and postoperative infections. The involvement of bacteria isolated from bile cultures in postoperative infections has been reported by other teams [16,17,25]. In our study, biliary bacteria were found in two thirds of colonized patients with documented postoperative infection. Infections with biliary bacteria were associated with an increased risk of severe complications. In a randomized controlled trial, Okamura et al. showed that a 2-day postoperative antibiotic treatment targeting bacteria found in preoperative bile cultures reduced the incidence of SSIs by almost 50% [11]. Similarly, Mohammed and al. reported in retrospective work a reduction in the incidence of SSIs and in the severity of complications in patients receiving a 10-day postoperative antibiotic therapy targeting bacteria from intraoperative bile cultures [6]. Taken altogether, these results suggest a role for perioperative antibiotic therapy targeting biliary bacteria rather than narrow-spectrum, single dose antibiotic prophylaxis.

In our work, antibiotic prophylaxis as recommended by the SFAR was adequate relative to bile microorganisms in only 23% of cases, the biliary ecology being mainly composed of *Enterococci* and group 3 *Enterobacteria* naturally resistant to C1G and C2G. These results are consistent with data from the literature, in which antibiotics recommended in surgical antibiotic prophylaxis cover biliary bacteria in less than 30% of cases [26]. However, when adequate, surgical antibiotic prophylaxis was not associated with a reduction in SSIs or other complications. The failure of preoperative antibiotic prophylaxis to reduce SSIs may be due to an overly narrow spectrum and/or short duration of the treatment. Indeed, some studies have reported that changing surgical antibiotic prophylaxis from a narrow to a broad-spectrum antibiotic was associated with a reduction in SSIs, along with a reduction in postoperative antibiotic consumption [8,22]. Furthermore, compared with a 24-hour treatment, extending perioperative antibiotic therapy up to 72 hours reduced the occurrence of SSI [5].

Regarding the microbial ecology of our center, a probabilistic short-term per- and post-operative antibiotic therapy targeting GNB of groups 1 to 3, GPC including *Enterococcus faecalis* and anaerobes may be proposed. Bile colonization was polymicrobial in more than 80% of cases, similar to the incidence reported by others [26]. Biliary ecology was similar between drained and non-drained patients, suggesting a colonization mechanism “a retro” from the digestive tract to bile ducts by a community commensal flora. Although rarely isolated from cultures, the presence of anaerobic bacteria in the bile was confirmed in a study of the biliary microbiota by metagenomic analysis based on 16S RNA[27]. The pathogenicity of *Enterococci* is still uncertain. However, Belmouhand et al. found an increased incidence of postoperative fistulas in cases of intra-abdominal enterococcal infection, arguing for their consideration in the probabilistic treatment [28]. The probabilistic use of a molecule targeting *Enterococcus faecium* is debatable, this species being found in only 7% of the biliary samples and 8% of the postoperative infections documented in our study (3 intra-abdominal samples and one blood culture). This is also true for yeasts, whose prevalence was low in bile cultures (<7%) and in the documented postoperative infections (7%; 1 blood culture and 3 intra-abdominal samples). However, some teams have decided to include these microorganisms in their probabilistic perioperative antibiotic therapy, for example by using tigecycline as an alternative to piperacillin-tazobactam [22] or a combination of piperacillin-tazobactam and vancomycin [8]. Others have decided to add fluconazole to the antibiotic treatment [5].

The target population for this perioperative anti-infectious strategy has yet to be defined. It could preferentially be applied in patients with biliary stenting, considered to be at higher risk of infections. In this group of patients with a high rate of bile colonization, pancreaticoduodenectomy may be considered as a class 3 surgery of the Altemeier surgical wound classification. All in all, a probabilistic perioperative antibiotic therapy rather than prophylaxis may be more suitable when bile is colonized. This strategy has been studied retrospectively and prospectively in observational works in France in comparison with the preoperative surgical antibiotic prophylaxis proposed by the SFAR. An antibiotic therapy with piperacillin-tazobactam, started preoperatively and continued for 5 days if bile cultures were positive, reduced the incidence of SSIs and other postoperative infections. It also reduced the length of hospital stay [9]. The same strategy, including an adaptation of antibiotic therapy to bile cultures at 48 hours, showed comparable results [7]. A third retrospective tricentric study (oral communication) compared the use of piperacillin-tazobactam associated with gentamicin as a perioperative antibiotic therapy, continued for 5 days and adapted to biliary sampling, to the conventional antibiotic prophylaxis. This antibiotic regimen was associated with decreased incidence of postoperative intra-abdominal infections, surgical revision and length of hospital stay in the “at-risk” drained patients [26]. In addition, other studies have reported a decrease in the total duration of postoperative antibiotic therapy when using broad-spectrum perioperative molecules instead of



narrow-spectrum preoperative antibiotic prophylaxis [2,8]. While the exact modalities of perioperative antibiotic therapy have yet to be defined, shorter durations and narrower spectrum should be preferred in order to limit the emergence of bacterial resistance and the occurrence of adverse events [29,30]. Finally, molecules with a good penetration into the biliary tract may be preferred, although this has not specifically been studied [31]. To date, this strategy has not been assessed in patients without preoperative biliary drainage, who are considered to be at lower risk. The rationale for antibiotic therapy rather than single surgical prophylaxis is more debatable in this class 2 surgery of the Altemeier classification. However, several studies, including ours, have reported an incidence of postoperative infections close to "at risk" patients, suggesting that non-drained patients may also benefit from an optimized anti-infectious strategy.

This study has many limitations due to its observational, retrospective and monocentric nature with the bacterial and fungal ecologies specific to our center. Postoperative morbidity, defined as the occurrence of at least one complication, is higher than reported in the literature, concerning more than 70% of the patients. This difference may be explained by our population with more comorbidities, suggested by an ASA 3 score 25% higher than in similar studies [2,9]. Postoperative therapeutic management, including the collection of microbiological samples and the decision to administer documented or probabilistic antibiotic therapy, may vary from one physician to another and influence patient prognosis. Finally, there is a lack of statistical power, particularly for the study of the effect of an adequate, single dose antibiotic prophylaxis on SSIs incidence.

## **Conclusion**

The findings of this study provide insights that may improve the infectious management of patients undergoing CPD. Postoperative infections after CPD occur in more than 50% of patients, leading to a high consumption of broad-spectrum antibiotics. Antibiotic therapy for clinically suspected or documented infections is more common in patients with bile colonization, reaching 75% of cases. In these patients, 2/3 of documented postoperative infections involve a microorganism isolated from the bile and seem to be associated with higher occurrence of severe complications. Surgical antibiotic prophylaxis even when appropriate to biliary bacteria does not seem effective in preventing SSIs or other postoperative infections. These results support the use of short-term probabilistic perioperative antibiotic therapy adapted to the biliary bacterial ecology. Patients with sterile bile culture may also benefit from this strategy as their postoperative infection rate remains high. Bile colonization and postoperative infections with *Enterococcus faecium* and *Candida* remain scarce, suggesting that their consideration in the spectrum of the probabilistic antimicrobial therapy may not be necessary in non-severe patients. Prospective multicenter trials evaluating different therapeutic strategies are needed to improve global management of these patients.

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Figure 1.

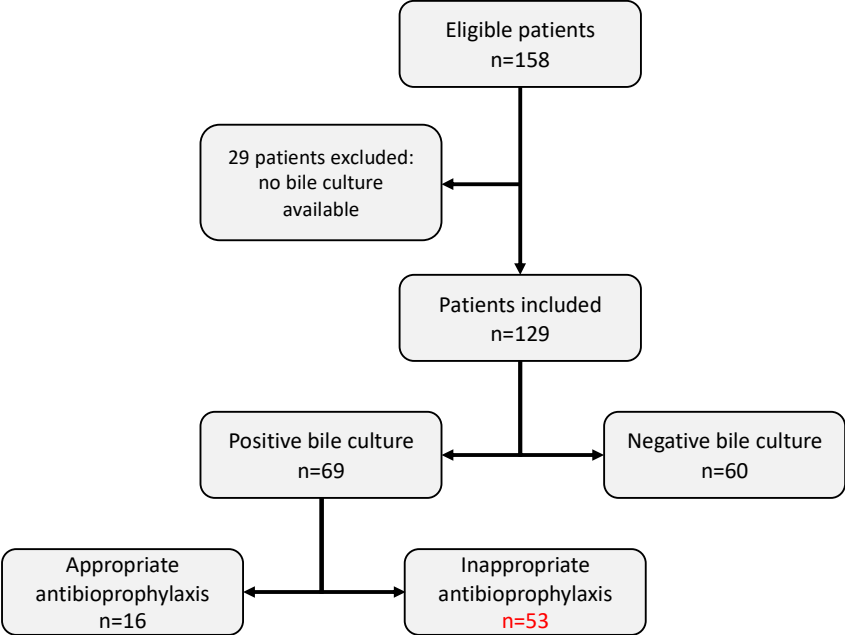


Figure 1. Study flowchart

# TABLES

**Table I. Preoperative and intraoperative patient characteristics**

	Global population (n=129)	Positive bile culture (n=69)	Negative bile culture (n=60)	p
<b>Sex ratio (M/W)</b>	72/57	39/30	33/27 1,22	0,862
<b>Age median [range]</b>	64 [29-83]	66 [33-83]	63 [29-82]	0,039
<b>ASA score n(%)</b>				
1	9 (7.0%)	2 (2.9%)	7 (11.7%)	0.141
2	87 (67.4%)	49 (71.0%)	38 (63.3%)	
3	32 (24.8%)	18 (26.1%)	14 (23.3%)	
<b>BMI* (kg/m<sup>2</sup>)</b>	25.4 ± 4.8	25.3 ± 4.9	25.6 ± 4.8	0.601
<b>Diabetes mellitus n(%)</b>	32 (24.8%)	18 (26.1%)	14 (23.3%)	0.759
<b>Renal failure n(%)</b>	8 (6.2%)	6 (8.7%)	2 (3.3%)	0.216
<b>Ischemic cardiomyopathy n(%)</b>	16 (12.4%)	8 (11.6%)	8 (13.3%)	0.38
<b>Histology n(%)</b>				
Adenocarcinoma	66 (51.2%)	42 (60.9%)	24 (40.0%)	
IPMN	12 (9.3%)	2 (2.9%)	10 (16.7%)	
Cholangiocarcinoma	19 (14.7%)	11 (15.9%)	8 (13.3%)	
Ampullary carcinoma	6 (4.7%)	3 (4.3%)	3 (5.0%)	
Duodenal carcinoma	9 (7.0%)	2 (2.9%)	7 (11.7%)	
Chronic calcific pancreatitis	9 (7.0%)	6 (8.7%)	3 (5.0%)	
Other	8 (6.4%)	3 (4.3%)	5 (8.4%)	
<b>Neoadjuvant chemotherapy n(%)</b>	19 (14.7%)	13 (18.8%)	6 (10.0%)	0.158
<b>Preoperative bile drainage n(%)</b>	57 (44.2%)	50 (72.4%)	7 (11.7%)	<0.001
<b>Operative time* (mn)</b>	440±102	452±102	427±81	0.351
<b>Blood loss* (ml)</b>	792±861	830±937	661±677	0.171
<b>Intraoperative transfusion n(%)</b>	25 (19.4%)	13 (18.8%)	12 (20.0%)	0.868

mean ± SD; ASA : score of the American Society of Anesthesiologists; BMI : body mass index; IPMN: intraductal papillary-mucinous neoplasm

**Table II. Incidence of postoperative infections**

	<b>Global population (n=129)</b>	<b>Positive bile culture (n=69)</b>	<b>Negative bile culture (n=60)</b>	<b>p</b>
<b>All documented postoperative infection n(%)</b>	52 (40.3%)	26 (37.7%)	26 (43.3%)	0.590
Intra-abdominal infection n(%)	18 (14%)	10 (14.5%)	8 (13.3%)	0.850
Abscess (wound and organ space) n(%)	1 (0.8%)	0 (0%)	1 (1.7%)	-
Bacteremia n(%)	21 (16.3%)	12(17.4%)	9 (15%)	0.714
CLABSI n(%)	7 (5.4%)	3 (4.3%)	4 (6.7%)	-
Respiratory tract infection n(%)	7 (5.4%)	4 (5.8)%	3 (5%)	-
Urinary tract infection (%)	20 (15.5%)	8 (11.6%)	12 (20%)	0.188
<b>Collection drainage n(%)</b>	20 (15,5%)	10 (14.5%)	10 (16.7%)	0.734
<b>Pancreatic fistula n(%)</b>	65 (50.4%)	32 (46.4%)	33 (55.0%)	0.329

CLABSI: central line associated bloodstream infection



**Table III. Characteristics of postoperative antibiotic therapies**

	<b>Global population (n=129)</b>	<b>Positive bile culture (n=69)</b>	<b>Negative bile culture (n=60)</b>	<b>p</b>
<b>Postoperative antibiotic therapy n (%)</b>	87 (67%)	53 (77%)	34 (57%)	0,008
<b>Median duration (j)</b>	11[7 - 17]	10[7 – 14]	14[7 – 22]	0,132
<b>Duration &gt;7days n(%)</b>	63 (49%)	38 (55%)	25 (42%)	0,129
<b>Antibiotic combination (%)</b>	19 (15%)	11 (16%)	8 (13%)	0,678
<b>Broad-spectrum antibiotic therapy n (%)</b>	54 (42%)	29 (42%)	25 (42%)	0,967

Broad spectrum: piperacillin-tazobactam or carbapenem ; Antibiotic combination : a  $\beta$ -lactam associated with aminoglycoside or fluoroquinolone

**Table IV. Impact of surgical antibiotic prophylaxis adequacy relative to biliary colonization on the incidence of complications**

	Positive bile culture (n=69)		p
	Appropriate antibioprophylaxis (n=16)	Inappropriate antibioprophylaxis (n=53)	
<b>Infections</b>			
<b>Documented postoperative infection n(%)</b>	7 (43.7%)	19 (35.8%)	0.570
<b>Collection drainage n(%)</b>	2 (12.5%)	8 (15.1%)	1
<b>Fistula n(%)</b>	8 (50.0%)	24 (45.3%)	0.740
<b>Antibiotic therapy</b>			
<b>Postoperative antibiotic therapy n (%)</b>	13 (81.3%)	40 (75.5%)	0.746
<b>Median duration (d)<sup>§</sup></b>	9 [7-14]	10 [7-17]	0.402
<b>Duration &gt;7days n(%)</b>	12 (92.3%)	35 (87.5%)	1
<b>Surgical complications</b>			
<b>Gastroparesis n(%)</b>	8 (50.0%)	17 (32.1%)	0.191
<b>Hemorrhagic complication n(%)</b>	5 (31.3%)	7 (13.2%)	0.095
<b>Reintervention under GA n(%)</b>	5 (31.3%)	11 (20.8%)	0.383
<b>Pronostic du patient</b>			
<b>Hospital length of stay (d)*</b>	24,31±12	24,12±19	0.623
<b>Hospitalisation in ICU n(%)</b>	1 (6.3%)	4 (7.5%)	0.861
<b>Death n(%)</b>	1 (6.3%)	3 (5.7%)	0.930
<b>Clavien Dindo ≥ 3 n(%)</b>	6 (37.5%)	13 (24.5%)	0.309

\*mean ± SD ; <sup>§</sup> median and interquartile interval; GA: general anaesthesia

**Table V. Multivariate analysis of risk factors for severe postoperative complications (Clavien-Dindo  $\geq 3$ )**

	OR	p	95%CI	
<b>Preoperative drainage</b>	0.241	<b>0.037</b>	0.063	0.919
<b>Neoadjuvant chemotherapy</b>	1.243	0.783	0.264	5.851
<b>Inappropriate antibioprophylaxis</b>	0.419	0.208	0.108	1.624
<b>Postoperative infection with bile microorganism</b>	7.659	<b>0.004</b>	1.941	30.228

OR : odds ratio, 95%CI : 95%-confidence interval

# APPENDICES

## Appendix 1. Involvement of biliary bacteria in postoperative infections

Site of infection	IAI	Bc	CLABSI	RTI	UTI	Total
<b>Number of documented infections</b>	23	20	3	6	9	61
<b>Similar bacteria isolated in bile</b>	11	6	0	2	5	24
<b>Postoperative infection with biliary bacteria (%)</b>	48	30	0	33	56	39

IAI : Intra-abdominal infection ; Bc : blood culture ; CLABSI : central-line associated bloodstream infection

## Appendix 2. Incidence of non-infectious postoperative complications

	Global population (n=129)	Positive bile culture (n=69)	Negative bile culture (n=60)	p
<b>Surgical complications</b>				
<b>Gastroparesis n(%)</b>	50 (38,8%)	25 (36,2%)	25 (41,7%)	0,527
<b>Hemorrhagic complication n(%)</b>	23 (17,8%)	12 (17,4%)	11 (18,3%)	0,889
<b>Reintervention under GA n(%)</b>	29 (22,5%)	16 (23,2%)	13 (21,7%)	0,836
<b>Prognosis</b>				
<b>Hospital length of stay (d)*</b>	24,1±15	24,2±17,6	23,9±11,3	0,555
<b>Hospitalisation in ICU n(%)</b>	10 (7,8%)	5 (7,2%)	5 (8,3%)	0,818
<b>Death n(%)</b>	8 (6,2%)	4 (5,8%)	4 (6,7%)	0,838
<b>Clavien Dindo ≥3 n(%)</b>	41 (31,8%)	19 (27,5%)	22 (36,7%)	0,267

\*mean ± SD; GA: general anesthesia

## Appendix 3. Microorganisms isolated in peroperative bile cultures

Microorganisms isolated in bile cultures	Positive bile culture (69 patients) n=168 bacteria	Without bile drainage (19 patients) n= 31 bacteria	With preoperative bile drainage (50 patients) n= 137 bacteria
<b>Gram Positive cocci</b>			
<i>Enterococcus</i>	48 (29%)	9 (29%)	39 (28%)
<i>Enterococcus faecalis</i>	29 (17%)	6 (19%)	23 (17%)
<i>Enterococcus faecium</i>	11 (7%)	2 (6%)	9 (7%)
Autres ( <i>avium, durans, gallinarum, hirae, spp</i> )	8 (5%)	1 (3%)	7 (5%)
<i>Staphylococcus</i>	6 (4%)	2 (6%)	4 (3%)
<i>Staphylococcus aureus</i>	3 (2%)	-	3 (2%)
Autres ( <i>epidermidis, haemolyticus, hominis</i> )	3 (2%)	2 (6%)	1 (1%)
<i>Streptococcus</i>	17 (10%)	3 (10%)	14 (10%)
<i>Streptococcus anginosus</i>	11 (7%)	1 (3%)	10 (7%)
Autres ( <i>constellatus, lutetiensis, oralis, salivarius, spp</i> )	5 (3%)	2 (6%)	3 (2%)
<i>Granulicatella Adiacens</i>	1 (1%)	1 (3%)	-
<b>Total GP</b>	<b>72 (43%)</b>	<b>15 (48%)</b>	<b>57 (42%)</b>
<b>Gram Negative bacilli</b>			
<i>Enterobacteriaceae</i>			
Group 1			
<i>Escherichia coli</i>	32 (19%)	7 (23%)	25 (18%)
Group 2			
<i>Klebsiella</i>	24 (14%)	1 (3%)	23 (17%)
<i>Klebsiella pneumoniae</i>	19 (11%)	1 (3%)	18 (13%)
<i>Klebsiella oxytoca</i>	4 (2%)	-	4 (3%)
<i>Klebsiella varicola</i>	1 (1%)	-	1 (1%)
<i>Proteus</i>	4 (2%)	1 (3%)	3 (2%)
<i>Proteus vulgaris</i>	2 (1%)	1 (3%)	1 (1%)
<i>Proteus mirabilis</i>	2 (1%)	-	2 (1%)
<i>Citrobacter koseri</i>	3 (2%)	-	3 (2%)
Group 3			
<i>Enterobacter</i>	11 (7%)	1 (3%)	10 (7%)
<i>Enterobacter cloacae</i>	7 (4%)	1 (3%)	6 (4%)
<i>Enterobacter aerogenes</i>	4 (2%)	-	4 (3%)
<i>Hafnia alvei</i>	5 (3%)	2 (6%)	3 (2%)
<i>Morganella Morganii</i>	2 (1%)	-	2 (1%)
<i>Serratia (marcescens, liquefaciens)</i>	2 (1%)	-	2 (1%)
<i>Citrobacter freundii</i>	4 (2%)	2 (6%)	2 (1%)
<i>Pseudomonas aeruginosa</i>	3 (2%)	1 (3%)	2 (1%)
<i>Acinetobacter ursingii</i>	1 (1%)	1 (3%)	-
<i>Aeromonas (caviae, hydrophila, spp)</i>	4 (2%)	-	4 (3%)
<i>Haemophilus influenzae</i>	1 (1%)	-	1 (1%)
<b>Total GN</b>	<b>96 (57%)</b>	<b>16 (52%)</b>	<b>80 (58%)</b>
<b>Polymicrobial culture, number of patients</b>	<b>57 (83%)</b>	<b>12 (63%)</b>	<b>45 (90%)</b>
<b><i>Candida</i>, number of patients</b>	<b>5 (7%) patients</b>	<b>2 (10%)</b>	<b>3 (6%)</b>