Improving outcomes of pancreatic surgery

Groen, J.V.

CHAPTER 11

Clinical implications of bile cultures obtained during pancreatoduodenectomy: a cohort study and meta-analysis

J.V. Groen*, D.H.M. Droogh*, M.G.J. de Boer, S.A.V. van Asten, J. van Prehn, A. Inderson, A.L. Vahrmeijer, B.A. Bonsing, J.S.D. Mieog

* Both authors contributed equally and share first authorship

HPB (Oxford). 2021 Jul;23(7):1123-1133. doi: 10.1016/j.hpb.2020.10.028. Epub 2020 Dec 10. PMID: 33309165.

ABSTRACT

Background: The association between intraoperative bile cultures and infectious complications after pancreatoduodenectomy remains unclear. This cohort study and meta-analysis aimed to determine the predictive role of intraoperative bile cultures in abdominal infectious complications after pancreatoduodenectomy.

Methods: The cohort study included 114 patients undergoing pancreatoduodenectomy. Regression analyses were used to estimate the odds to develop an organ space infection (OSI) or isolated OSI (OSIs without a simultaneous complication potentially contaminating the intraabdominal space) after a positive bile culture. A systematic review and meta-analysis was performed on abdominal infectious complications (Mantel-Haenszel fixed-effect model).

Results: The positive bile culture rate was 61%, predominantly in patients after preoperative biliary drainage (98% vs 26%, $p<0.001$). OSIs occurred in 35 patients (31%) and isolated OSIs in nine patients (8%) and were not associated with positive bile cultures (OSIs: odds ratio=0.6, 95% CI=0.25-1.23, isolated OSIs: odds ratio=0.77, 95% CI=0.20-3.04). In the meta-analysis, 15 studies reporting on 2 047 patients showed no association between positive bile cultures and abdominal infectious complications (pooled odds ratio=1.3, 95% CI=0.98-1.65).

Discussion: Given the rare occurrence of isolated OSIs and similar odds for patients with positive and negative bile cultures to develop abdominal infectious complications, routine performance of bile cultures should be reconsidered

INTRODUCTION

Pancreatoduodenectomy remains a complex and technically demanding procedure with high rates of morbidity (25-52%) and mortality (1-3%).[1-4] Infectious complications, such as surgical site infections (SSIs) and organ space infections (OSIs), are reported as the most common complications following pancreatoduodenectomy besides pancreatic fistula and delayed gastric emptying.[5, 6] Previous studies showed an association between preoperative biliary drainage, contamination of intraoperative bile cultures (IOBCs) and the occurrence of postoperative infectious complications, particularly SSIs.[1, 7-10] Although biliary drainage is not routinely recommended, the number of patients requiring this preoperative procedure is expected to rise due to the increasing use of neoadjuvant chemotherapy in pancreatic cancer.[11, 12]

Patients with a biliary stent appear to have different IOBC contamination patterns.[3, 4, 8] Also, neoadjuvant treatment is associated with an alteration of the biliary microbiome.[13] A study in three centers (two USA, one Italian) showed interinstitutional variability in IOBCs and antibiotic resistance patterns, recommending institution-specific reviews to amend protocols for antibiotic prophylaxis.[14] A Dutch study showed appropriate antimicrobial coverage of IOBC microorganisms in 56% of the patients with biliary drainage and in 88% of the patients without biliary drainage.[15] These findings question whether coverage of biliary microorganisms by current antibiotic prophylaxis is sufficient.

The current perioperative antibiotic prophylaxis, generally cefazolin and metronidazole, is used by most centers to prevent SSIs.[16] However, different antibiotic regimens are used as postoperative prophylaxis to prevent OSIs. The clinical impact of bile culture based prophylactic antibiotic treatment, especially in OSIs, is questionable. Several studies concluded that the use of IOBCs does not offer additional information for postoperative infectious complications.[17, 18] Besides, poor concordance between bile cultures and cultures from infectious sites was observed, implicating that IOBC-targeted treatment could lead to the inappropriate use of antibiotics.[19]

Hence, no consensus is achieved about the predictive role of bile cultures in abdominal infectious complications after pancreatoduodenectomy. The primary objective of this study was to investigate the association between positive bile cultures and abdominal infectious complications after pancreatoduodenectomy. Secondary, the predictive role of IOBCs was evaluated by determining microorganism concordance in bile and OSI cultures. Additionally, a systematic review and meta-analysis was performed to place findings of the current study in perspective of the existing literature.

METHODS

Study design & patient selection

This study was a prospective single-center cohort study, reported according to the STROBE criteria.[20] All patients undergoing pancreatoduodenectomy at the Leiden University Medical Center (LUMC), a tertiary referral center, from June 2016 through October 2019 with an intraoperative bile culture were included. The need for informed consent was waived by the Medical Ethics Committee of the LUMC.

Data collection

Data was collected from the mandatory Dutch Pancreatic Cancer Audit.[21] Additional clinical outcomes were extracted from patient's medical records based on the clinical evaluation of physicians. Variables of interest included patient characteristics (age, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) score), surgical related information, postoperative complications (e.g. OSIs, SSIs and pancreatic fistula), preoperative biliary drainage and IOBC outcomes and peri- and postoperative antibiotic prophylaxis. Follow-up was up to 30 days after surgery. Two authors (JVG & DHMD) independently performed data collection for OSIs and SSIs; a third independent investigator (JSDM) was consulted in the event of disagreement.

Definitions

Pancreatoduodenectomy included classical Whipple procedures, pylorus-preserving and pylorus-resecting pancreatoduodenectomies. Positive IOBCs or postoperative cultures were defined as the presence of any cultivated microorganism. OSIs and SSIs, classified as superficial incisional SSI or deep incisional SSI, were defined by the Center of Disease Control definition and diagnosed up until 30 days after surgery (supplemental material 1).[22] Due to this comprehensive description, other complications with a non-infectious origin, for instance pancreatic fistula, interfere with the OSI definition by contamination of the intraabdominal space.[10] To decrease the interference of confounding complications, we formulated the concept of isolated OSI to identify 'isolated' abdominal complications such as abdominal abscesses. An isolated OSI was defined as a postoperative OSI occurring within 30 days after surgery without simultaneous occurrence of complications potentially contaminating the intraabdominal space, such as pancreatic fistula, biliary leakage, intestinal anastomotic leakage or gastro-intestinal perforation (defined as gastric or intestinal wall discontinuity confirmed by surgery). Pancreatic fistula and bile leakage were defined and classified according to the International Study Group of Pancreatic Surgery definition.[23, 24]

Microbiological procedures

IOBCs were perioperatively obtained directly after transection of the common bile duct. Assessment of the IOBCs was performed at the Medical Microbiology laboratory according to laboratory's standard operating procedure. In short, selective and nonselective media and broth enrichment were used for culture and incubated both aerobically and non-aerobically at 35°C. Bacteria were identified when less than two species were growing on the plates, when virulent bacteria were suspected (e.g. *Pseudomonas aeruginosa, Staphylococcus aureus, β-hemolytic Streptococci and Clostridium perfringens*) and if any colony grew on selective culture plates for resistant pathogens. Bacteria were categorized as mixed, fecal or skin flora in case of >2 species not suspected for clinical relevance and IOBCs as positive or negative. OSIs were often treated by placement of abdominal drains by a radiological intervention. Cultures of OSIs were obtained from these abdominal drains within 24h after placement to distinguish infection from colonization or contamination.[25, 26] OSI cultures were analyzed to identify clinically relevant microorganisms and determine resistance patterns.

Antibiotic prophylactic treatment

Standard antibiotic prophylaxis consisted of perioperatively intravenous (IV) cefazolin and 500 mg IV metronidazole, as proposed by Dutch antibiotics guidelines.[27] Due to a change in national protocol, patients undergoing surgery after October 2018 received 2 g instead of 1 g cefazolin every four hours. Doses of 3 g cefazolin were indicated for patients with a BMI >40. Standard postoperative prophylaxis contained five days of 750 mg IV cefuroxime and 500 mg IV metronidazole three times daily according to the local hospital protocol which conformed to the Dutch antibiotic guidelines.[27]

Outcomes and comparison

The main outcomes were the rate of OSIs and isolated OSIs stratified for IOBC status. Secondary outcomes were SSIs, timing of the infectious complications, amount (none, single or multiple) and concordance of microorganisms in IOBCs and postoperative cultures. A Dutch study showed that abdominal drain placement as treatment for pancreatic fistula is generally performed at median postoperative day 9 (interquartile range 7-11 days).[28] To diminish the interference of pancreatic fistula and other complications contaminating the intraabdominal space, analyses of the concordance between IOBCs and cultures from isolated OSIs and OSIs were limited to this time frame. Comparisons were made for patients with positive versus negative IOBCs with stratification for biliary drainage in subgroup analyses.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0. Continuous variables were presented as median with interquartile range, whereas categorical variables were expressed as absolute numbers and percentages. For comparison of continuous variables, the Mann-Whitney U test was performed. Categorical data were analyzed using the chi-squared test or the Fisher's exact test in case of small groups of <20 patients. Binary logistic regression analyses were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for OSIs, isolated OSIs within seven postoperative days and SSIs. A p-value <0.05 was considered statistically significant.

Systematic review of literature and meta-analysis

A systematic literature search was performed according to the PRISMA statement.[29] PubMed, Embase, Web of Science, COCHRANE Library, Academic Search Premier and PubMed Central were searched for full-text, English-written articles investigating the role of IOBCs in postoperative infectious complications. Titles, abstracts and full-text articles were screened by two independent authors (JVG & DHMD) for eligibility. Articles were selected if a comparison was made for patients with positive and negative IOBCs and study outcomes included postoperative infectious complications. Literature reviews, case reports and case series were excluded. Data extraction was performed using a standardized form with study characteristics, methods of IOBC assessment, number of patients with biliary drainage, IOBCs characteristics and postoperative infectious complications. The risk of bias was determined using the ROBINS-I tool for cohort studies.[30] Quantitative analysis on the primary outcomes (abdominal infectious complications such as OSIs, intraabdominal infections or abscesses and wound infections) was performed using Review Manager (RevMan version 5.3). To assess heterogeneity between studies, the I^2 statistic was used. An I^2 value of >50% was considered to represent substantial heterogeneity. The Mantel-Haenszel fixed-effect model was used to calculate pooled effects, represented as OR and 95% CI.

RESULTS

Patient characteristics

Of the 133 consecutive patients undergoing pancreatoduodenectomy from June 2016 until October 2019, 114 patients with an obtained IOBC were included (Table 1). Baseline characteristics (notably age, ASA score and BMI) of the nineteen patients without obtained bile cultures were comparable to the 114 included patients (data not shown). In nine patients, bile cultures were not performed because of robotic surgery. Preoperative biliary drainage was performed in 56 of the 114 patients (49%). A number of 103 patients received postoperative antibiotic prophylaxis by protocol, which was comparable in patients with and without biliary drainage (86% versus 95%). Reasons for adjustments in postoperative prophylaxis were postoperative fever or sepsis (n=7), preoperative infections (n=2), adjustments based on postoperative cultures (n=1) or allergies (n=1). Bile cultures were positive in 70 patients: 55 patients with and 15 patients without a biliary stent (98% versus 26%, $p<0.001$). Multiple microorganisms were cultured in 55 IOBCs; in 47 patients with and eight patients without biliary drainage (84% versus 14%, $p<0.001$). Of the 15 patients without biliary drainage and a positive IOBC, 12 patients underwent a preoperative endoscopic retrograde cholangiopancreatography (ERCP) or had a periampullary malignancy versus two of the 43 patients with a negative IOBC without biliary drainage (80% versus 0.05%, $p<0.001$).

Table 1. Baseline characteristics

		Total		Preoperative biliary drainage				
				No		Yes		
		N	%	N	%	N	%	P
Total		114	100	58	50.9	56	49.1	
Sex	**Male**	68	59.6	32	55.2	36	64.3	0.321
	Female	46	40.4	26	44.8	20	35.7	
Age (years), median (IQR)		68 (59-74)		68 (59-73)		68 (59-74)		0.766
BMI (kg/m²), median (IQR)		25.3 (23.1-28.4)		25.7 (23.0-28.1)		25.1 (23.3-28.6)		0.786
ASA groups	**I-II**	88	77.2	48	82.8	40	71.4	0.149
	III-IV	26	22.8	10	17.2	16	28.6	
Type of surgery	**Classical**	47	41.2	21	36.2	26	46.3	
	PPPD	65	57.0	35	60.3	30	53.6	0.237
	PRPD	2	1.8	2	3.4	0	0.0	
Blood loss (mL), median (IQR)		1000 (750-1400)		1000 (530-1250)		1000 (800-1400)		0.147
Duration of surgery (min), median (IQR)		261 (240-309)		253 (226-291)		273 (245-324)		0.005
Additional resection		8	7.0	6	10.3	2	3.6	0.157
Venous resection		15	13.2	6	10.3	9	16.1	0.366
Arterial resection		1	0.9	0	0.0	1	1.8	0.307
Postoperative antibiotics per protocol*		103	90.4	55	94.8	48	85.7	0.099
IOBCs	**Positive**	70	61.4	15	25.9	55	98.2	<0.001
	Negative	44	38.6	43	74.1	1	1.8	
Microorganisms in IOBC	**Multiple**	55	48.2	8	13.8	47	83.9	
	Single	15	13.2	7	12.1	8	14.3	<0.001
	None	44	38.6	43	74.1	1	1.8	

*Cefuroxime and metronidazole for five days. IQR: Interquartile range. BMI: Body Mass Index. ASA: American Society of Anesthesiologists. Classical: Whipple pancreatoduodenectomy. PPPD: pylorus preserving pancreatoduodenectomy. PRPD: pylorus resecting pancreatoduodenectomy. IOBC: intraoperative bile culture

Primary outcome

OSIs occurred in 35 patients (31%); 18 patients (26%) with positive and 17 (39%) with negative IOBCs (OR=0.6, 95% CI=0.25-1.23. Table 2). After stratification for biliary drainage, OSI rates remained comparable for positive and negative IOBCs in patients without a biliary stent (35% and 37%). Isolated OSIs occurred in nine patients (8%): five patients with positive and four with negative IOBCs (OR=0.77, 95% CI=0.20-3.04). OSIs were not isolated in 26 patients, mainly because of simultaneous occurrence of pancreatic fistula in 21 patients (81%).

Table 2. Infectious complications

		Total (n=114)		Intraoperative bile culture: Negative (n=44)		Intraoperative bile culture: Positive (n=70)		
		N	**%**	**N**	**%**	**N**	**%**	**P**
OSI		35	31	17	39	18	26	0.145
Timing	**1-7 Days**	15	13	5	11	10	14	0.076
	8-14 Days	9	8	7	16	2	3	
	>14 Days	11	10	5	11	6	9	
Isolated OSIs*		9	8	4	9	5	7	0.707
Timing	**1-7 Days**	4	4	1	2	3	4	0.316
	8-14 Days	2	2	2	5	0	0	
	>14 Days	3	3	1	2	2	3	
OSIs with simultaneous occurrence of confounding complications		26	23	*13*	*30*	*13*	*19*	0.774
	Pancreatic fistula	21	18	11	25	10	14	0.581
	Biliary leakage	3	3	2	5	1	1	0.512
	Enteric leakage or perforation	2	2	0	0	2	3	0.157
SSI		22	19	8	18	14	20	0.811
Location	**Superficial**	19	17	7	16	12	17	0.965
	Deep	3	3	1	2	2	3	
Timing	**1-7 Days**	8	7	3	7	5	7	0.947
	8-14 Days	7	6	2	5	5	7	
	>14 Days	7	6	3	7	4	6	

OSI: Organ Space Infection. SSI: Surgical Site Infection.
* OSIs in absence of confounding postoperative complications

Secondary outcomes

SSIs occurred in 22 patients (19%), of which 19 patients had superficial and three patients had deep incisional SSIs (Table 2). SSIs developed in 14 patients with positive and eight patients with negative IOBCs (OR=1.1, 95% CI=0.43-2.95). SSI rates remained comparable in patients with positive and negative IOBCs after stratification for biliary stenting (data not presented).

Isolated OSIs were not more observed in the first postoperative week compared to the second postoperative week or later after pancreatoduodenectomy. Isolated OSIs within seven days after surgery developed in three patients (4%) with positive and one (1%) with a negative IOBC (OR=1.9, 95% CI=0.19-19.10).

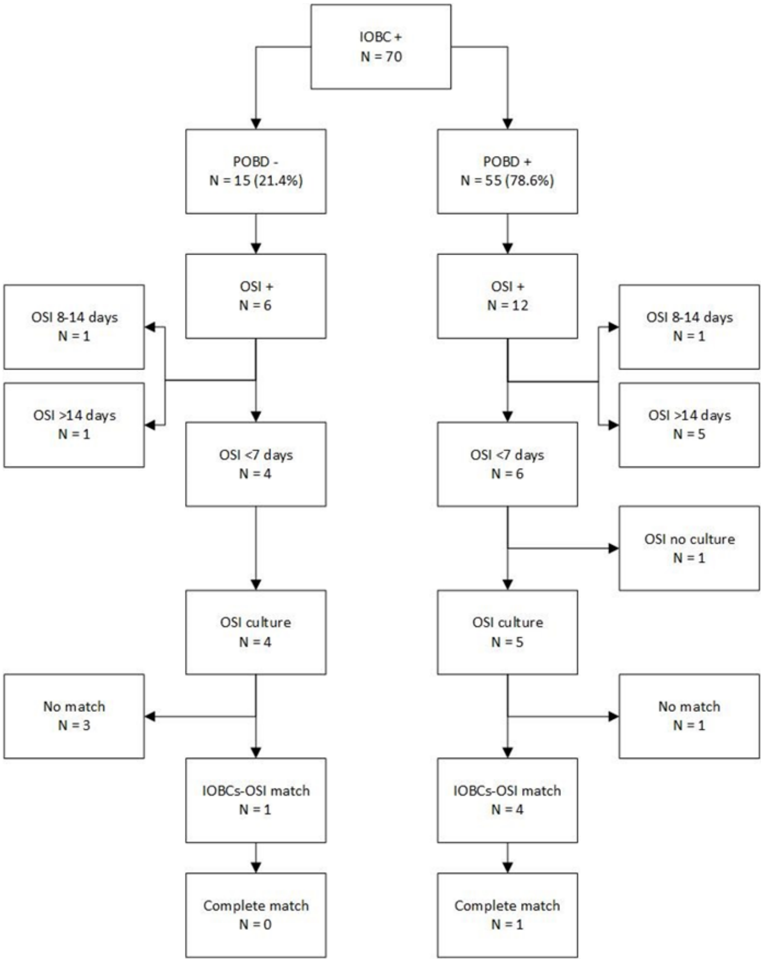


Figure 1. Culture concordance between bile and OSI cultures in patients with OSIs within seven days after pancreatoduodenectomy.

Multi-drug resistant organisms (MDRO) were cultivated from the IOBCs of three patients (3%). Detailed analysis of the microorganisms cultured from OSIs was performed in patients who developed an OSI or isolated OSI within seven days after surgery (n=15). Nine patients had both a positive IOBC and an obtained OSI culture (Figure 1). Partial microorganism concordance between bile and OSI cultures was observed in five of the nine patients. Complete concordance was seen in one out of nine patients.

Systematic review of literature and meta-analysis

The literature search identified 526 studies. After screening titles, abstracts and full-texts, 17 studies were included (Figure 2).[1, 6, 7, 9, 14, 19, 31-41] The selected studies included one prospective and 16 retrospective cohort studies evaluating IOBCs obtained during pancreatoduodenectomy (supplemental material 3). Three studies reported detailed information about the microbiological assessment of IOBCs[36, 38, 39], while the remaining 14 studies either did not report these methods or reported them as standard laboratory's procedures. Various definitions were used for wound infections, OSIs, abdominal infections and abscesses. The studies did not report on isolated abdominal infections or time-depending infectious complications after pancreatoduodenectomy. Most of the studies were qualified as having a moderate risk of bias, but four studies were assessed to have a serious risk of bias (supplemental material 4). Reasons for elevated risks of bias were mostly the absence of clear definitions for infectious outcomes or different antimicrobial regimes in the groups with positive and negative bile cultures.

The reported percentage of positive IOBCs varied from 40-90%.[1, 6, 7, 9, 19, 31-41] Positive IOBCs were more often observed in patients with biliary drainage (median 88%, range 47-100% versus median 29%, range 5-57%). The quantitative analysis included 15 of the selected studies and the current study (Figure 3). Fifteen studies, including the current study, reported on OSIs, abdominal infections or abdominal abscesses in 2 047 patients and showed comparable rates of abdominal infectious complications in patients with positive and negative IOBCs (OR=1.3, 95% CI=0.98-1.65, I^2=38%, figure 3A). Fourteen studies, including the current study, reported on surgical site infections or wound infections in 2 064 patients and observed an association between positive bile cultures and wound infections (OR=3.5, 95% CI=2.65-4.61. I^2=0%. Figure 3B). The funnel plots showed a nearly symmetrical scatter around the mean for all outcomes (supplemental material 5). Sensitivity analyses with a random-effects model showed similar results for both OSIs and SSIs (supplemental material 6).

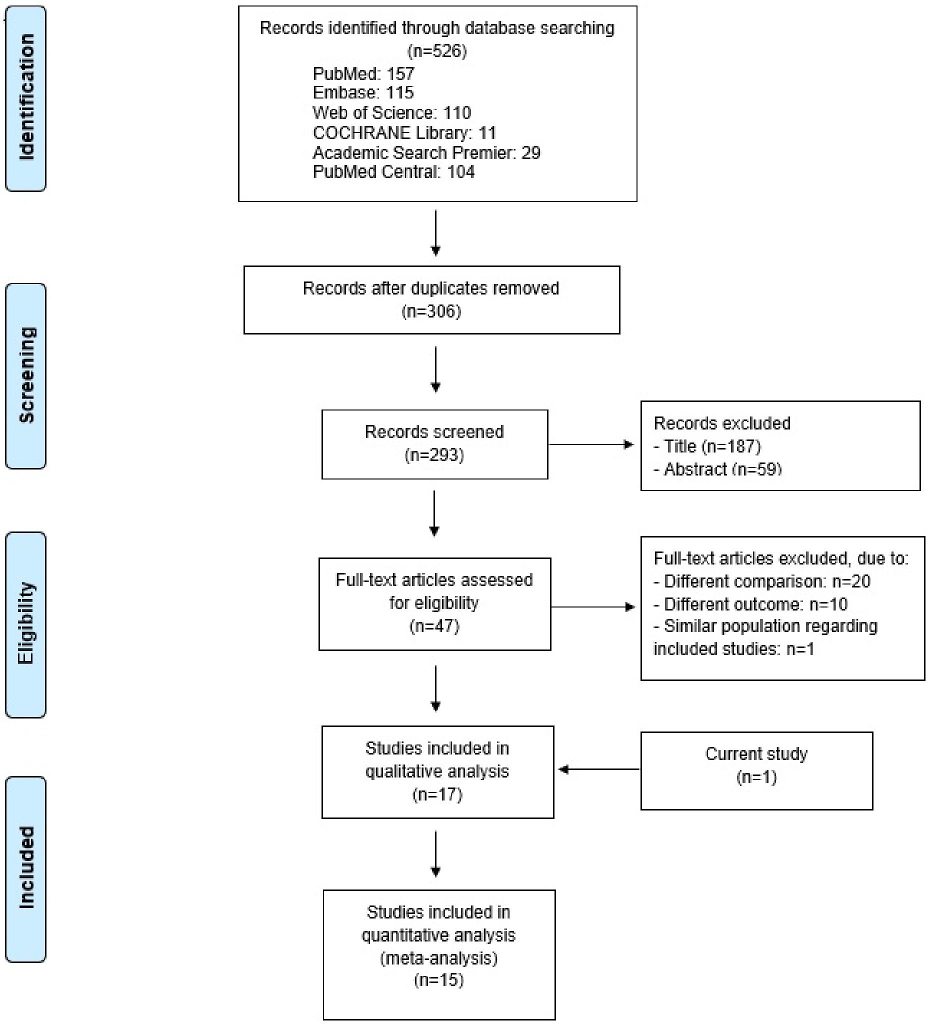
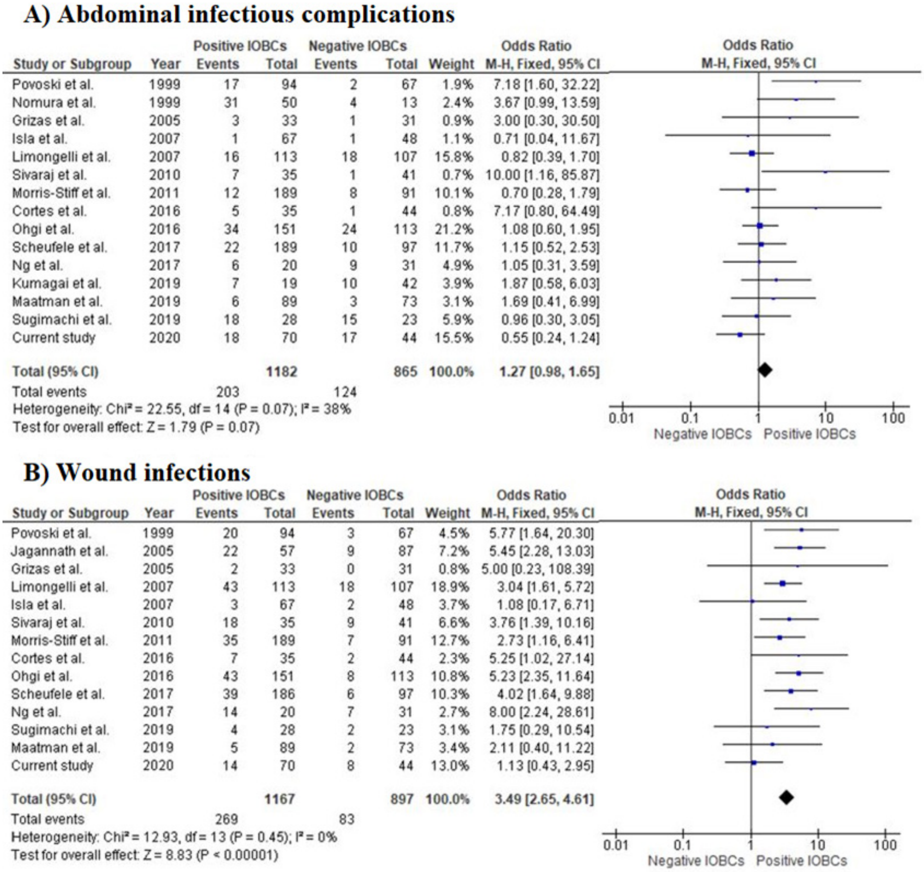


Figure 2. Study selection for the systematic review and meta-analysis



A) Abdominal infectious complications

Study or Subgroup	Year	Positive IOBCs Events	Positive IOBCs Total	Negative IOBCs Events	Negative IOBCs Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Povoski et al.	1999	17	94	2	67	1.9%	7.18 [1.60, 32.22]
Nomura et al.	1999	31	50	4	13	2.4%	3.67 [0.99, 13.59]
Grizas et al.	2005	3	33	1	31	0.9%	3.00 [0.30, 30.50]
Isla et al.	2007	1	67	1	48	1.1%	0.71 [0.04, 11.67]
Limongelli et al.	2007	16	113	18	107	15.8%	0.82 [0.39, 1.70]
Sivaraj et al.	2010	7	35	1	41	0.7%	10.00 [1.16, 85.87]
Morris-Stiff et al.	2011	12	189	8	91	10.1%	0.70 [0.28, 1.79]
Cortes et al.	2016	5	35	1	44	0.8%	7.17 [0.80, 64.49]
Ohgi et al.	2016	34	151	24	113	21.2%	1.08 [0.60, 1.95]
Scheufele et al.	2017	22	189	10	97	11.7%	1.15 [0.52, 2.53]
Ng et al.	2017	6	20	9	31	4.9%	1.05 [0.31, 3.59]
Kumagai et al.	2019	7	19	10	42	3.9%	1.87 [0.58, 6.03]
Maatman et al.	2019	6	89	3	73	3.1%	1.69 [0.41, 6.99]
Sugimachi et al.	2019	18	28	15	23	5.9%	0.96 [0.30, 3.05]
Current study	2020	18	70	17	44	15.5%	0.55 [0.24, 1.24]
Total (95% CI)			**1182**		**865**	**100.0%**	**1.27 [0.98, 1.65]**
Total events		203		124			

Heterogeneity: $Chi^2 = 22.55$, $df = 14$ ($P = 0.07$); $I^2 = 38\%$
Test for overall effect: $Z = 1.79$ ($P = 0.07$)

B) Wound infections

Study or Subgroup	Year	Positive IOBCs Events	Positive IOBCs Total	Negative IOBCs Events	Negative IOBCs Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Povoski et al.	1999	20	94	3	67	4.5%	5.77 [1.64, 20.30]
Jagannath et al.	2005	22	57	9	87	7.2%	5.45 [2.28, 13.03]
Grizas et al.	2005	2	33	0	31	0.8%	5.00 [0.23, 108.39]
Limongelli et al.	2007	43	113	18	107	18.9%	3.04 [1.61, 5.72]
Isla et al.	2007	3	67	2	48	3.7%	1.08 [0.17, 6.71]
Sivaraj et al.	2010	18	35	9	41	6.6%	3.76 [1.39, 10.16]
Morris-Stiff et al.	2011	35	189	7	91	12.7%	2.73 [1.16, 6.41]
Cortes et al.	2016	7	35	2	44	2.3%	5.25 [1.02, 27.14]
Ohgi et al.	2016	43	151	8	113	10.8%	5.23 [2.35, 11.64]
Scheufele et al.	2017	39	186	6	97	10.3%	4.02 [1.64, 9.88]
Ng et al.	2017	14	20	7	31	2.7%	8.00 [2.24, 28.61]
Sugimachi et al.	2019	4	28	2	23	3.1%	1.75 [0.29, 10.54]
Maatman et al.	2019	5	89	2	73	3.4%	2.11 [0.40, 11.22]
Current study	2020	14	70	8	44	13.0%	1.13 [0.43, 2.95]
Total (95% CI)			**1167**		**897**	**100.0%**	**3.49 [2.65, 4.61]**
Total events		269		83			

Heterogeneity: $Chi^2 = 12.93$, $df = 13$ ($P = 0.45$); $I^2 = 0\%$
Test for overall effect: $Z = 8.83$ ($P < 0.00001$)

Figure 3. Forest plots for abdominal infectious complications (A) and wound infections (B) in patients with positive versus negative intraoperative bile cultures

DISCUSSION

The primary aim of this study was to evaluate the predictive role of IOBCs in the occurrence of abdominal infectious complications in patients undergoing pancreatoduodenectomy. Positive IOBCs were not associated with the occurrence of OSIs, which was confirmed by the meta-analysis on abdominal infectious complications. Even more, only 8% of patients developed an isolated OSI, which was not associated with IOBC status.

The systematic review and meta-analysis included in this study confirmed the lack of correlation between IOBCs and abdominal infectious complications. Although some studies associated specific microorganisms (e.g. *Enterococcus* and *Enterobacter* species) with an increased risk for infectious complications, the clinical impact of these findings is questionable.[3, 7, 14, 36, 42] For example, empirical antibiotic therapy is often not directed at *Enterococcus* species.[43, 44] We found a complete concordance of bile and OSI cultures in only one of the nine patients with obtained OSI cultures and OSIs occurring within seven postoperative days. The polymicrobial origin of bile cultures in patients with biliary stents could account for the partial matches, by which the directive value of IOBCs would be negligible. These findings are in line with a recent study also demonstrating a poor concordance between IOBCs and postoperative cultures.[19] Taken together, a positive bile culture seems to be an inadequate predictor for the development of a postoperative infection as well as its causing pathogens.

In this study, the concept of isolated OSI was defined to account for the multifactorial origin of postoperative infections in pancreatic surgery and to rule out interference of confounding complications contaminating the intraabdominal space. Particularly, the occurrence of pancreatic fistula contributes to higher OSI rates as both definitions show considerable overlap. We observed a simultaneous occurrence of pancreatic fistula in 81% of the patients with OSIs. Besides, patients without preoperative biliary drainage generally have a smaller pancreatic duct and a soft pancreatic remnant, which is a risk factor for the development of pancreatic fistula. This is a likely explanation for the observed higher OSI rate in the patients without biliary drainage.[5, 10, 45] Isolated OSIs occurred in only nine patients and OSI rates were similar in patients with positive and negative IOBCs. Whether these low rates are attributable to the prolonged postoperative antibiotic prophylaxis of five days in this study, is subject of further investigation.

The use of postoperative prophylactic antibiotic treatment varies considerably between institutes since evidence for type and duration of postoperative prophylaxis is limited in this type of surgery.[6, 14] In our center, patients received standard antibiotic prophylaxis for five postoperative days. To our knowledge, only one study was conducted to evaluate the effect of prolonged antibiotic prophylaxis after pancreatoduodenectomy. This randomized controlled trial compared one-day to five-days postoperative antibiotic prophylaxis in only patients with preoperative biliary drainage and reported no benefit of prolonged postoperative prophylaxis regarding infectious complications in this group of patients.[46] However, the overall effect of standard prolonged antibiotic prophylaxis after pancreatoduodenectomy remains undetermined. As a more personalized alternative, several retrospective and one randomized controlled trial investigated the value of postoperative antibiotic prophylaxis based on IOBCs or even on preoperative cultures.[4, 5, 47-51] Most studies showed a decrease in wound infections in the IOBC-targeted group, but similar rates of abdominal infectious complications.[4, 48-51] However, type and duration of the antimicrobial prophylaxis varied largely. Also, the selection of the patients receiving the IOBC-targeted or prolonged prophylaxis differed between the studies. Furthermore, none of these studies used the concept of isolated OSIs and confounding complications could have interfered with the effect of the antibiotic prophylaxis. Altogether, the benefit of IOBC-targeted postoperative antibiotic prophylaxis remains disputable. However, standard use of postoperative antibiotic prophylaxis based on bile cultures will undoubtedly lead to the inappropriate use of broad-spectrum antibiotics.

Given the negligible predictive value of IOBCs and limited evidence for IOBC-based prophylactic antibiotic treatment, routine performance of IOBCs is questionable. Recently, updated recommendations from the Enhanced Recovery After Surgery guidelines stated that bile cultures should only be obtained in patients with biliary drainage and that postoperative antibiotic prophylaxis could be considered in patients with positive IOBCs.[52] The current study confirmed the high incidence of positive IOBCs in patients with a biliary stent. Moreover, performance of a preoperative ERCP without biliary drainage or the presence of periampullary tumors increased the risk of a positive IOBC. For that reason, performance of IOBCs could be considered in these patients if a positive IOBC leads to adequately adjusted postoperative antimicrobial prophylaxis. On the other hand, the high likelihood of a positive IOBC in patients after biliary stenting could be an argument to refrain from obtaining IOBCs, as culture results including specific microorganisms and their resistance patterns will be available after several days, most often coinciding with the end of prophylaxis.

Limitations of this study include the observational designs of the current study and the studies included in the meta-analysis, although results of the qualitative analysis did not change relevantly in a random-effects model. Furthermore, not all 133 consecutive patients were included because of not performed IOBCs, predominantly in patients undergoing robotic surgery. However, baseline characteristics and OSI occurrence of these patients were comparable to the study population. Another limitation is the standard use of postoperative antibiotic prophylaxis, which could have interfered with the development of OSIs. Besides, not all pathogens were identified in positive IOBCs, due to the microbiological assessment by standard laboratory's procedures. Although clinical relevant pathogens were individually evaluated, this factor might have complicated the concordance analysis for which these results were interpreted with a hypothesis-generating intention.

Despite these limitations, this study represents the use of IOBCs in a real-world clinical setting with comparable groups at baseline and clear definitions for OSIs, isolated OSIs and SSIs. Especially the concept of isolated OSI provided insight in the high frequency of confounding complications in patients with abdominal infections after pancreatoduodenectomy. Previous studies used various definitions for infectious complications leading to a disparity in reported abdominal infectious complications. For instance, Gavazzi et al reported 27% OSIs and 5% abdominal abscesses within the same population.[3] Combined with the systematic review and meta-analysis, an overview of the current knowledge about IOBCs was demonstrated in this study, resulting in a more critical note about the predictive role of IOBCs. With regard to expanding antibiotic resistance and stewardship[53, 54], the current postoperative prophylactic antibiotic treatment should be critically evaluated in a clinical trial to evade unnecessary use of antimicrobial prophylaxis.

In conclusion, similar rates of postoperative infections were observed in patients with positive and negative bile cultures in this study. Regarding the low pathogenicity of the cultured microorganisms and the substantial incidence of confounding non-infectious complications, the predictive value of IOBCs in infectious complications seems limited. Thus, the routine performance of IOBCs should be reconsidered and the efficacy of postoperative prophylactic antibiotic treatment after pancreatoduodenectomy needs further evaluation. The concept of isolated OSI in pancreatic surgery should be incorporated in future studies.

REFERENCES

1. Morris-Stiff G, Tamijmarane A, Tan YM, Shapey I, Bhati C, Mayer AD, et al. Pre-operative stenting is associated with a higher prevalence of post-operative complications following pancreatoduodenectomy. Int J Surg. 2011;9(2):145-9.
2. Kneuertz PJ, Pitt HA, Bilimoria KY, Smiley JP, Cohen ME, Ko CY, et al. Risk of morbidity and mortality following hepato-pancreato-biliary surgery. J Gastrointest Surg. 2012;16(9):1727-35.
3. Gavazzi F, Ridolfi C, Capretti G, Angiolini MR, Morelli P, Casari E, et al. Role of preoperative biliary stents, bile contamination and antibiotic prophylaxis in surgical site infections after pancreaticoduodenectomy. BMC Gastroenterol. 2016;16:43.
4. Sudo T, Murakami Y, Uemura K, Hashimoto Y, Kondo N, Nakagawa N, et al. Perioperative antibiotics covering bile contamination prevent abdominal infectious complications after pancreatoduodenectomy in patients with preoperative biliary drainage. World J Surg. 2014;38(11):2952-9.
5. Sourrouille I, Gaujoux S, Lacave G, Bert F, Dokmak S, Belghiti J, et al. Five days of postoperative antimicrobial therapy decreases infectious complications following pancreaticoduodenectomy in patients at risk for bile contamination. HPB (Oxford). 2013;15(6):473-80.
6. Ohgi K, Sugiura T, Yamamoto Y, Okamura Y, Ito T, Uesaka K. Bacterobilia may trigger the development and severity of pancreatic fistula after pancreatoduodenectomy. Surgery. 2016;160(3):725-30.
7. Ng ZQ, Suthananthan AE, Rao S. Effect of preoperative biliary stenting on post-operative infectious complications in pancreaticoduodenectomy. Ann Hepatobiliary Pancreat Surg. 2017;21(4):212-6.
8. Herzog T, Belyaev O, Akkuzu R, Holling J, Uhl W, Chromik AM. The Impact of Bile Duct Cultures on Surgical Site Infections in Pancreatic Surgery. Surg Infect (Larchmt). 2015;16(4):443-9.
9. Limongelli P, Pai M, Bansi D, Thiallinagram A, Tait P, Jackson J, et al. Correlation between preoperative biliary drainage, bile duct contamination, and postoperative outcomes for pancreatic surgery. Surgery. 2007;142(3):313-8.
10. Elliott IA, Chan C, Russell TA, Dann AM, Williams JL, Damato L, et al. Distinction of Risk Factors for Superficial vs Organ-Space Surgical Site Infections After Pancreatic Surgery. JAMA Surg. 2017;152(11):1023-9.
11. Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg. 2018;105(8):946-58.
12. van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362(2):129-37.

13. Goel N, Nadler A, Reddy S, Hoffman JP, Pitt HA. Biliary microbiome in pancreatic cancer: alterations with neoadjuvant therapy. HPB (Oxford). 2019;21(12):1753-60.
14. Fong ZV, McMillan MT, Marchegiani G, Sahora K, Malleo G, De Pastena M, et al. Discordance Between Perioperative Antibiotic Prophylaxis and Wound Infection Cultures in Patients Undergoing Pancreaticoduodenectomy. JAMA Surg. 2016;151(5):432-9.
15. Hentzen J, Smit MA, Bruins MJ, Rupert C, Schreinemakers J, Ruijs G, et al. Efficacy of Pre-Operative Antimicrobial Prophylaxis in Patients Undergoing Pancreatoduodenectomy: A Multi-Center Retrospective Analysis. Surg Infect (Larchmt). 2018;19(6):608-13.
16. Lassen K, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schafer M, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. World J Surg. 2013;37(2):240-58.
17. Sanchez Acedo P, Zazpe Ripa C, Eguaras Cordoba I, Herrera Cabezon J, Tarifa Castilla A, Camarero Triana B. The effect of a preoperative biliary prosthesis on the infectious complications of the pancreaticoduodenectomy. Rev Esp Enferm Dig. 2019;111(11):817-22.
18. Mussle B, Hempel S, Kahlert C, Distler M, Weitz J, Welsch T. Prognostic Impact of Bacterobilia on Morbidity and Postoperative Management After Pancreatoduodenectomy: A Systematic Review and Meta-analysis. World J Surg. 2018;42(9):2951-62.
19. Maxwell DW, Jajja MR, Ferez-Pinzon A, Pouch SM, Cardona K, Kooby DA, et al. Bile cultures are poor predictors of antibiotic resistance in postoperative infections following pancreaticoduodenectomy. HPB (Oxford). 2019.
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of clinical epidemiology. 2008;61(4):344-9.
21. van Rijssen LB, Koerkamp BG, Zwart MJ, Bonsing BA, Bosscha K, van Dam RM, et al. Nationwide prospective audit of pancreatic surgery: design, accuracy, and outcomes of the Dutch Pancreatic Cancer Audit. HPB (Oxford). 2017;19(10):919-26.
22. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Am J Infect Control. 1992;20(5):271-4.
23. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161(3):584-91.
24. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery. 2011;149(5):680-8.

25. Loos M, Strobel O, Legominski M, Dietrich M, Hinz U, Brenner T, et al. Postoperative pancreatic fistula: Microbial growth determines outcome. Surgery. 2018;164(6):1185-90.
26. Rasilainen SK, Juhani MP, Kalevi LA. Microbial colonization of open abdomen in critically ill surgical patients. World J Emerg Surg. 2015;10:25.
27. Antibioticabeleid SW. Richtlijn peri-operatieve profylaxe 2018.
28. Smits FJ, van Santvoort HC, Besselink MG, Batenburg MCT, Slooff RAE, Boerma D, et al. Management of Severe Pancreatic Fistula After Pancreatoduodenectomy. JAMA Surg. 2017;152(6):540-8.
29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 2009;339:b2535.
30. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ (Clinical research ed). 2016;355:i4919.
31. Cortes A, Sauvanet A, Bert F, Janny S, Sockeel P, Kianmanesh R, et al. Effect of bile contamination on immediate outcomes after pancreaticoduodenectomy for tumor. Journal of the American College of Surgeons. 2006;202(1):93-9.
32. Grizas S, Stakyte M, Kincius M, Barauskas G, Pundzius J. Etiology of bile infection and its association with postoperative complications following pancreatoduodenectomy. Medicina (Kaunas, Lithuania). 2005;41(5):386-91.
33. Isla AM, Griniatsos J, Riaz A, Karvounis E, Williamson RC. Pancreaticoduodenectomy for periampullary malignancies: the effect of bile colonization on the postoperative outcome. Langenbeck's archives of surgery. 2007;392(1):67-73.
34. Jagannath P, Dhir V, Shrikhande S, Shah RC, Mullerpatan P, Mohandas KM. Effect of preoperative biliary stenting on immediate outcome after pancreaticoduodenectomy. Br J Surg. 2005;92(3):356-61.
35. Kumagai YU, Fujioka S, Hata T, Misawa T, Kitamura H, Furukawa K, et al. Impact of Bile Exposure Time on Organ/space Surgical Site Infections After Pancreaticoduodenectomy. In Vivo. 2019;33(5):1553-7.
36. Maatman TK, Weber DJ, Qureshi B, Ceppa EP, Nakeeb A, Schmidt CM, et al. Does the Microbiology of Bactibilia Drive Postoperative Complications After Pancreatoduodenectomy? J Gastrointest Surg. 2019.
37. Nomura T, Shirai Y, Hatakeyama K. Impact of bactibilia on the development of postoperative abdominal septic complications in patients with malignant biliary obstruction. International surgery. 1999;84(3):204-8.
38. Povoski SP, Karpeh MS, Jr., Conlon KC, Blumgart LH, Brennan MF. Preoperative biliary drainage: impact on intraoperative bile cultures and infectious morbidity and mortality after pancreaticoduodenectomy. J Gastrointest Surg. 1999;3(5):496-505.

39. Scheufele F, Aichinger L, Jager C, Demir IE, Schorn S, Sargut M, et al. Effect of preoperative biliary drainage on bacterial flora in bile of patients with periampullary cancer. Br J Surg. 2017;104(2):E182-E8.
40. Sivaraj SM, Vimalraj V, Saravanaboopathy P, Rajendran S, Jeswanth S, Ravichandran P, et al. Is bactibilia a predictor of poor outcome of pancreaticoduodenectomy? Hepatobiliary & pancreatic diseases international : HBPD INT. 2010;9(1):65-8.
41. Sugimachi K, Iguchi T, Mano Y, Morita M, Mori M, Toh Y. Significance of bile culture surveillance for postoperative management of pancreatoduodenectomy. World journal of surgical oncology. 2019;17(1):232.
42. Sahora K, Morales-Oyarvide V, Ferrone C, Fong ZV, Warshaw AL, Lillemoe KD, et al. Preoperative biliary drainage does not increase major complications in pancreaticoduodenectomy: a large single center experience from the Massachusetts General Hospital. J Hepatobiliary Pancreat Sci. 2016;23(3):181-7.
43. Marcus G, Levy S, Salhab G, Mengesha B, Tzuman O, Shur S, et al. Intra-abdominal Infections: The Role of Anaerobes, Enterococci, Fungi, and Multidrug-Resistant Organisms. Open forum infectious diseases. 2016;3(4):ofw232.
44. Murray BE. The life and times of the Enterococcus. Clinical microbiology reviews. 1990;3(1):46-65.
45. Behrman SW, Zarzaur BL. Intra-abdominal sepsis following pancreatic resection: incidence, risk factors, diagnosis, microbiology, management, and outcome. The American surgeon. 2008;74(7):572-8; discussion 8-9.
46. Yamamoto T, Satoi S, Fujii T, Yamada S, Yanagimoto H, Yamaki S, et al. Dual-center randomized clinical trial exploring the optimal duration of antimicrobial prophylaxis in patients undergoing pancreaticoduodenectomy following biliary drainage. Ann Gastroenterol Surg. 2018;2(6):442-50.
47. Degrandi O, Buscail E, Martellotto S, Gronnier C, Collet D, Adam JP, et al. Perioperative antibiotherapy should replace prophylactic antibiotics in patients undergoing pancreaticoduodenectomy preceded by preoperative biliary drainage. J Surg Oncol. 2019;120(4):639-45.
48. Mohammed S, Evans C, VanBuren G, Hodges SE, Silberfein E, Artinyan A, et al. Treatment of bacteriobilia decreases wound infection rates after pancreaticoduodenectomy. HPB (Oxford). 2014;16(6):592-8.
49. Sano S, Sugiura T, Kawamura I, Okamura Y, Ito T, Yamamoto Y, et al. Third-generation cephalosporin for antimicrobial prophylaxis in pancreatoduodenectomy in patients with internal preoperative biliary drainage. Surgery. 2019;165(3):559-64.
50. Kondo K, Chijiiwa K, Ohuchida J, Kai M, Fujii Y, Otani K, et al. Selection of prophylactic antibiotics according to the microorganisms isolated from surgical site infections (SSIs) in a previous series of surgeries reduces SSI incidence after pancreaticoduodenectomy. J Hepatobiliary Pancreat Sci. 2013;20(3):286-93.

51. Okamura K, Tanaka K, Miura T, Nakanishi Y, Noji T, Nakamura T, et al. Randomized controlled trial of perioperative antimicrobial therapy based on the results of preoperative bile cultures in patients undergoing biliary reconstruction. J Hepatobiliary Pancreat Sci. 2017;24(7):382-93.
52. Melloul E, Lassen K, Roulin D, Grass F, Perinel J, Adham M, et al. Guidelines for Perioperative Care for Pancreatoduodenectomy: Enhanced Recovery After Surgery (ERAS) Recommendations 2019. World J Surg. 2020.
53. Center of Disease Control (CDC). *Antibiotic Resistance Threats in the United State.*, 2019. U.S. Department of Health and Human Services CDC.
54. World Health Organization (WHO). *Global Action Plan on Antimicrobial Resistance*. 2015. Switzerland. ISBN: 9789241509763.

Supplemental information 1. CDC definition for SSIs and OSIs

Table S1. Center for Disease Control and Prevention's Diagnostic Criteria for Surgical Site Infection (SSI)

Superficial Incisional SSI	
Criterion	Date of event for infection occurs within 30 days after any NHSN operative procedure. **AND** Involves only skin and subcutaneous tissue of the incision **AND** Patient has at least <u>**one**</u> of the following: a) Purulent drainage from the superficial incision. b) Organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiological testing method which is performed for purposes of clinical diagnosis or treatment (for example - not Active Surveillance Culture/Testing (ASC/AST) c) Superficial incision that is deliberately opened by a surgeon - attending physician** or other designee and culture or non-culture based testing is not performed. **AND** Patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat. d) Diagnosis of a superficial incisional SSI by the surgeon or attending physician** or other designee.
Reporting Instructions for Superficial SSI	<u>**The following do not qualify as criteria for meeting the NHSN definition of superficial SSI**</u> • Diagnosis/treatment of cellulitis (redness/warmth/swelling) - by itself - does not meet criterion "d" for superficial incisional SSI. Conversely - an incision that is draining or that has organisms identified by culture or non-culture based testing is not considered a cellulitis. • A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration). • A localized stab wound or pin site infection – Such an infection might be considered wither a skin (SKIN) or soft tissue (ST) infection - depending on its depth - but not an SSI. **Note:** A laparoscopic trocar site for an NHSN operative procedure is not considered a stab wound.
Deep Incisional SSI	
Criteria	Date of event for infection occurs within 30 days after the NHSN operative procedure. **AND** Involves deep soft tissue of the incision (for example - fascial and muscle layers) **AND** Patient has at least <u>**one**</u> of the following: a) Purulent drainage from the deep incision. b) A deep incision that spontaneously dehisces - or is deliberately opened or aspirated by a surgeon - attending physician** or other designee **AND** Organism is identified by a culture or non-culture based microbiologic testing method which his performed for purposes of clinical diagnosis or treatment (for example - not Active Surveillance Culture/Testing (ASC/AST) or culture or non-culture based microbiologic testing method is not performed **AND** Patient has at least <u>**one**</u> of the following signs or symptoms: • Fever (>38.0°C) • Localized pain or tenderness **Note:** A culture or non-culture based test that has a negative finding does not meet this criterion. c) An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam - or imaging test.
**The term attending physician for the purposes of application of the NHSN SSI criteria may be interpreted to mean the surgeon(s) - infectious disease - other physician on the case - emergency physician or physician's designee (nurse practitioner or physician's assistant). SSI denotes surgical site infection - NHSN denotes the National Healthcare Safety Network	

Supplemental information 1. CDC definition for SSIs and OSIs

“Organ/space SSIs must meet the following criteria:

- Infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place *and*
- The infection appears to be related to the operative procedure and infection involves any part of the anatomy (e.g., organs or spaces) other than the incision opened or manipulated during the operative procedure, and at least one of the following is present:
    - 1. Purulent drainage from a drain that is placed through a stab wound* into the organ/space.
    - 2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
    - 3. An abscess or other evidence of infection involving the organ/space on direct examination, during reoperation, or by histopathologic or radiologic examination.
    - 4. Diagnosis of an organ/space SSI by a surgeon or attending physician.”

Supplemental information 2. Literature search for PubMed

Combined search of two components (pancreatoduodenectomy and bile cultures): ((((“Pancreaticoduodenectomy”[Mesh] OR “pancreaticoduodenectomy”[tw] OR pancreaticoduodenectom*[tw] OR “pancreatoduodenectomy”[tw] OR pancreatoduodenectom*[tw] OR “duodenopancreatectomy”[tw] OR duodenopancreatectom*[tw] OR “pancreatico duodenectomy”[tw] OR pancreatico duodenect*[tw] OR “duodeno pancreatectomy”[tw] OR duodeno pancreatectom*[tw]) AND (“bile cultures”[tw] OR “bile culture”[tw] OR “bile duct cultures”[tw] OR “bile duct culture”[tw] OR “cultured bile”[tw] OR “bile analysis”[tw] OR “bile analyses”[tw])) OR (“Pancreaticoduodenectomy”[Mesh] OR “pancreaticoduodenectomy”[tw] OR pancreaticoduodenectom*[tw] OR “pancreatoduodenectomy”[tw] OR pancreatoduodenectom*[tw] OR “duodenopancreatectomy”[tw] OR duodenopancreatectom*[tw] OR “pancreatico duodenectomy”[tw] OR pancreatico duodenect*[tw] OR “duodeno pancreatectomy”[tw] OR duodeno pancreatectom*[tw]) AND (“Bile/analysis”[Mesh] OR “Bile/microbiology”[Mesh] OR “biliary stenting”[tw] OR “biliary stents”[tw] OR “biliary stenting”[tw] OR “bile duct stent”[tw] OR “bile duct stents”[tw] OR “bile duct stenting”[tw] OR “biliary duct stent”[tw] OR “biliary duct stents”[tw] OR “biliary duct stenting”[tw])) OR ((“Pancreatectomy”[Mesh] OR “pancreatectomy”[tw] OR pancreatectom*[tw] OR whipple procedure*[tw] OR whipple resect*[tw] OR whipple surger*[tw] OR “bile contamination”[tw] OR bile contamin*[tw] OR “Pancreatic Diseases/surgery”[Mesh] OR pancreatic surg*[tw] OR pancreas surg*[tw]) AND (“bile cultures”[tw] OR “bile culture”[tw] OR “bile duct cultures”[tw] OR “bile duct culture”[tw] OR “cultured bile”[tw] OR “bile analysis”[tw] OR “bile analyses”[tw] OR “biliary stenting”[tw] OR “biliary stents”[tw] OR “biliary stenting”[tw] OR “bile duct stent”[tw] OR “bile duct stents”[tw] OR “bile duct stenting”[tw] OR “biliary duct stent”[tw] OR “biliary duct stents”[tw] OR “biliary duct stenting”[tw]))) AND (english[la] OR dutch[la]) NOT ((“Case Reports”[ptyp] OR “case report”[ti] OR “Review”[ptyp] OR “review”[ti]) NOT (“Clinical Study”[ptyp] OR “trial”[ti] OR “RCT”[ti]))

Supplemental information 3. Study Characteristics

Result: 526 articles in six databases (10 Jan 2020)

						Number of patients (%)		Number of patients (%)		Included outcomes for quantitative analysis	
	Design	Country	Center	Inclusion period	MMB co-authors	Positive IOBCs	Negative IOBCs	Biliary drainage	No biliary drainage	SSIs or wound infections	Abdominal infectious complications
Current study	Prospective	NL	Single	2016-2019	X	70 (61)	44 (39)	59 (44)	74 (56)	X	X
Maxwell *et al.*[19]*	Retrospective	USA	Single	2014-2018		275 (90)	32 (10)	214 (41)	308 (59)		
Kumagai *et al.*[35]	Retrospective	Japan	Single	2015-2017		19 (31)	42 (69)	25 (41)	36 (59)		X
Sugimachi *et al.*[41]	Retrospective	Japan	Single	2014-2017		28 (55)	23 (45)	34 (49)	35 (51)	X	X
Maatman *et al.*[36]	Retrospective	USA	Single	2015-2017	X	89 (55)	73 (45)	89 (55)	73 (45)	X	X
Scheufele *et al.*[39]	Retrospective	Germany	Single	2007-2015		189 (65)	101 (35)	172 (59)	118 (41)	X	X
Ng *et al.*[7]	Retrospective	Australia	Single	2011-2015		20 (83)	4 (17)	31 (61)	20 (39)	X	X
Ohgi *et al.*[6]	Retrospective	Japan	Single	2010-2014		151 (57)	113 (43)	144 (55)	120 (45)	X	X
Fong *et al.*[14]*	Retrospective	USA	Multi	2008-2013		-	-	836 (52)	787 (48)		
Morris-Stiff *et al.*[1]	Retrospective	UK	Single	-		189 (68)	91 (33)	118 (42)	162 (58)	X	X
Sivaraj *et al.*[40]	Retrospective	India	Single	2007-2008		35 (46)	41 (54)	20 (26)	56 (74)	X	X
Limongelli *et al.*[9]	Prospective	UK	Single	-		113 (51)	107 (49)	102 (46)	118 (54)	X	X
Isla *et al.*[33]	Retrospective	UK	Single	1997-2002		67 (58)	48 (42)	52 (45)	63 (55)	X	X
Cortes *et al.*[31]	Case-control	France	Single	2002-2003		35 (44)	44 (56)	34 (43)	45 (57)	X	X
Grizas *et al.*[32]	Retrospective	Lithuania	Single	2002-2004		33 (52)	31 (48)	21 (33)	43 (67)	X	X
Jagannath *et al.*[34]	Retrospective	India	Single	1992-2001		57 (40)	87 (60)	74 (51)	70 (49)	X	
Povoski *et al.*[38]	Retrospective	USA	Single	1994-1997	X	94 (58)	67 (42)	125 (78)	36 (22)	X	X
Nomura *et al.*[37]	Retrospective	Japan	Single	1984-1995		50 (79)	13 (21)	-	-		X

*Studies only included in qualitative analysis.

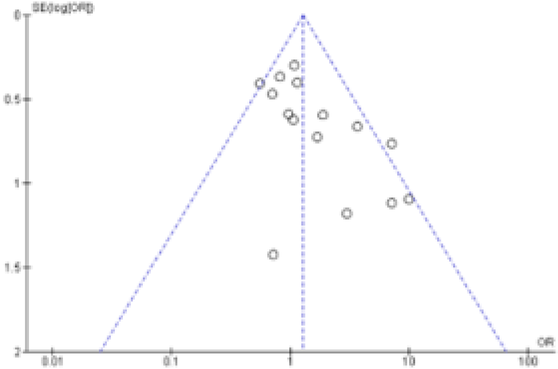
Supplemental information 4. Risk of bias table according to the ROBINS-1 tool[30]

	Confounding	Selection of participants	Classification of intervention	Deviations of intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Current study	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Maxwell *et al.*[19]*	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Kumagai *et al.*[35]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Sugimachi *et al.*[41]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Maatman *et al.*[36]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Scheufele *et al.*[39]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Ng *et al.*[7]	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate
Ohgi *et al.*[6]	Moderate	Low	Low	Low	Low	Serious	Low	Serious
Fong *et al.*[14]*	Moderate	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
Morris-Stiff *et al.*[1]	Moderate	Low	Low	Low	Low	Serious	Low	Serious
Sivaraj *et al.*[40]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Limongelli *et al.*[9]	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Isla *et al.*[33]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Cortes *et al.*[31]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Grizas *et al.*[32]	Moderate	Low	Low	Low	Serious	Serious	Moderate	Serious
Jagannath *et al.*[34]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Povoski *et al.*[38]	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Nomura *et al.*[37]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate

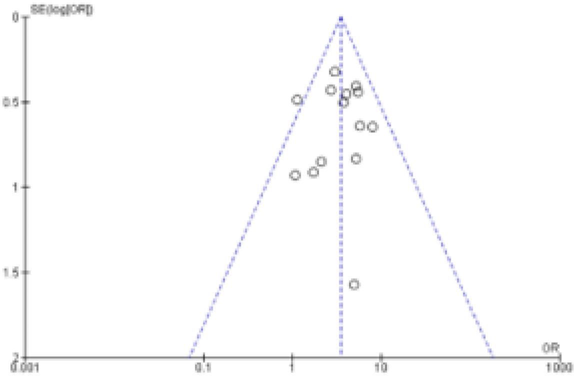
*Studies only included in qualitative analysis.

Supplemental information 5. Funnel plots for abdominal infectious complications (A) and wound infections (B)

A) Abdominal infectious complications



B) Wound infections

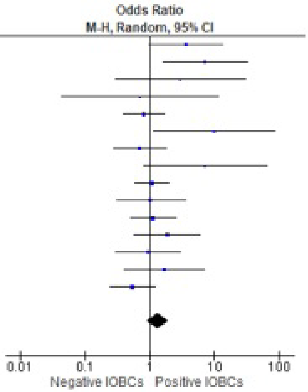


Supplemental material 6. Forest plots for postoperative abdominal infectious complications (A) and wound infections (B) in patients with positive versus negative intraoperative bile cultures, using the random-effects model.

A) Abdominal infectious complications

Study or Subgroup	Positive IOBCs Events	Positive IOBCs Total	Negative IOBCs Events	Negative IOBCs Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Nomura et al.	31	50	4	13	5.9%	3.67 [0.99, 13.59]	1999
Povoski et al.	17	94	2	67	4.8%	7.18 [1.60, 32.22]	1999
Grizas et al.	3	33	1	31	2.3%	3.00 [0.30, 30.50]	2005
Isla et al.	1	67	1	48	1.7%	0.71 [0.04, 11.67]	2007
Limongelli et al.	16	113	18	107	11.4%	0.82 [0.39, 1.70]	2007
Sivaraj et al.	7	35	1	41	2.7%	10.00 [1.16, 85.87]	2010
Morris-Stiff et al.	12	189	8	91	9.0%	0.70 [0.28, 1.79]	2011
Cortes et al.	5	35	1	44	2.6%	7.17 [0.80, 64.49]	2016
Ohgi et al.	34	151	24	113	13.4%	1.08 [0.60, 1.95]	2016
Ng et al.	6	20	9	31	6.4%	1.05 [0.31, 3.59]	2017
Scheufele et al.	22	189	10	97	10.6%	1.15 [0.52, 2.53]	2017
Kumagai et al.	7	19	10	42	6.8%	1.87 [0.58, 6.03]	2019
Sugimachi et al.	18	28	15	23	7.0%	0.96 [0.30, 3.05]	2019
Maatman et al.	6	89	3	73	5.2%	1.69 [0.41, 6.99]	2019
Current study	18	70	17	44	10.4%	0.55 [0.24, 1.24]	2020
Total (95% CI)		**1182**		**865**	**100.0%**	**1.32 [0.91, 1.93]**	
Total events	203		124				

Heterogeneity: Tau² = 0.19; Chi² = 22.55, df = 14 (P = 0.07); I² = 38%
Test for overall effect: Z = 1.46 (P = 0.15)



B) Wound infections

Study or Subgroup	Positive IOBCs Events	Positive IOBCs Total	Negative IOBCs Events	Negative IOBCs Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Povoski et al.	20	94	3	67	4.9%	5.77 [1.64, 20.30]	1999
Jagannath et al.	22	57	9	87	10.3%	5.45 [2.28, 13.03]	2005
Grizas et al.	2	33	0	31	0.8%	5.00 [0.23, 108.39]	2005
Isla et al.	3	67	2	48	2.3%	1.08 [0.17, 6.71]	2007
Limongelli et al.	43	113	18	107	19.6%	3.04 [1.61, 5.72]	2007
Sivaraj et al.	18	35	9	41	7.9%	3.76 [1.39, 10.16]	2010
Morris-Stiff et al.	35	189	7	91	10.7%	2.73 [1.16, 6.41]	2011
Ohgi et al.	43	151	8	113	12.2%	5.23 [2.35, 11.64]	2016
Cortes et al.	7	35	2	44	2.9%	5.25 [1.02, 27.14]	2016
Ng et al.	14	20	7	31	4.8%	8.00 [2.24, 28.61]	2017
Scheufele et al.	39	186	6	97	9.7%	4.02 [1.64, 9.88]	2017
Maatman et al.	5	89	2	73	2.8%	2.11 [0.40, 11.22]	2019
Sugimachi et al.	4	28	2	23	2.4%	1.75 [0.29, 10.54]	2019
Current study	14	70	8	44	8.4%	1.13 [0.43, 2.95]	2020
Total (95% CI)		**1167**		**897**	**100.0%**	**3.45 [2.60, 4.56]**	
Total events	269		83				

Heterogeneity: Tau² = 0.00; Chi² = 12.93, df = 13 (P = 0.45); I² = 0%
Test for overall effect: Z = 8.66 (P < 0.00001)