



Research article

Bacterial content of the human pancreatic duct: An observational study



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ABSTRACT

Background: Pancreatic fistula/PF is a challenging surgical complication. We could recently show that intestinal bacteria such as *Enterobacterales* colonize the PF fluid even after a “sterile” operation like distal pancreatectomy/DP. Therefore, we explored the bacterial flora of the human pancreatic duct in a patient collective undergoing pancreatic surgery.

Methods: In this observational study, upon transection of the pancreas during surgery, a swab was inserted into the main duct, and the micro-organismal content was correlated with clinical characteristics.

Results: Between February 2017 and February 2020, an intraoperative swab from the pancreatic duct was obtained from a total of 54 patients who underwent pancreatico-duodenectomy/PD or DP. The swabs were sterile in 39 cases (72.2%), detected intestinal bacteria in 10 cases (18.5%), and other bacteria in 5 cases (9.3%). There was no correlation of the micro-organismal content of the pancreatic duct swab with bacteria detected in the PF fluid or bile. Preoperative ERCP was associated with a higher frequency of bacterial colonization of the pancreatic duct (33.3% vs. 6.7%, $p = 0.005$). There was no correlation of the pancreatic duct swabs with postoperative complications.

Discussion: The human main pancreatic duct is usually sterile, and its bacterial colonization does not correlate with the occurrence of PF. Therefore, the mechanisms leading to infection of PF warrant in-depth, mechanistic investigation.

1. Introduction

Pancreatic fistula continues to be among the most feared complications after pancreatic surgery, reaching an incidence of 30–40% for clinically relevant Grade B/C fistula after distal pancreatectomy (DP) [1]. The pathophysiology behind pancreatic fistula formation is still not understood. Persistent leakage from the main pancreatic duct or from side branches, a high amount of acinar cells at the transection plane [2], postoperative pancreatitis [3], or dysfunction of the Sphincter of Oddi [4], are considered the probable underlying mechanisms.

In a recent study, we could show that the pancreatic fistula fluid (PFF) is frequently colonized by bacteria derived from the normal intestinal flora, particularly by *Enterobacterales* [5]. More importantly, such a

colonization of the PFF by *Enterobacterales* was present in 74% of cases after pancreatico-duodenectomy (PD), and in as high as 34% of cases after DP [5]. The latter finding was astonishing, when considering the fact that DP is an operation typically without opening of the intestinal lumen and also without anastomosis. This observation, therefore, raised the question of how intestinal bacteria such as *Enterobacterales* can colonize the PFF after a nearly sterile operation like DP.

For explaining the occurrence of *intestinal bacteria* in the PFF after DP, the following theoretical possibilities need to be considered: 1) Intestinal bacteria might translocate from neighbouring organs into the PFF, possibly induced by severe of postoperative pancreatitis [6,7], 2) Intestinal bacteria might translocate into the lymph fluid and reach the stump leakage site within clinically inapparent lymph fistula fluid near the

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stump, 3) Intestinal bacteria might ascend through a dysfunctional Sphincter of Oddi [4] along the pancreatic duct and reach the stump leak site, or 4) Intestinal bacteria might be among the natural flora/inhabitants of the normal pancreatic. Looking at the biomedical literature, investigations on the typical bacterial content of the normal pancreatic duct are currently lacking.

Therefore, to address this gap, we performed an observational study involving intraoperative swabs and subsequent bacterial cultures from the human main pancreatic duct upon transection of the pancreas during DP and PD, prior to any intestinal lumen opening. In addition, we correlated the detected bacteria with postoperative complications, including occurrence and infection of pancreatic fistula. Furthermore, we also analysed the impact of the preoperative performance of endoscopic retrograde cholangiography (ERCP) on the bacterial content of main pancreatic duct, as well as of bile fluid.

2. Methods

Consecutive patients who underwent pancreatic resection between 1st February 2017 and 1st February 2020 at the Department of Surgery, Klinikum rechts der Isar, Technical University of Munich, Germany were prospectively included in a departmental database for this observational study (cohort study). The study has been performed in line with the STROBE guidelines for observational studies [8]. The pancreatic resections were performed solely by six experienced pancreatic surgeons. During DP, the pancreatic stump was closed either via hand-sewn sutures or via stapler device or seldomly, a combination of both. No pancreatic anastomosis was performed for stump closure. The grade of PF was classified according to the current definition of the International Study Group on PF (ISGPF) [1]. The patient characteristics have been summarized in Table 1.

In all recruited cases (including total pancreatectomies), we performed the pancreatic transection at the level of porto-mesenteric junction, between the pancreatic head and body, with a scalpel, and hemostasis at the resection plane was achieved via selective suturing of the bleeding vessels with 5-0 or 6-0 monofilament sutures. Upon identification of the main pancreatic duct, a cotton swab was inserted into the main duct and then immediately immersed in agar-containing culture tubes and sent to the Institute for Microbiology for bacterial and fungal culturing.

Primary microbiological cultures of samples were performed on Columbia agar, Schaedler agar and Chocolate agar (prepared culture media, Becton Dickinson, Sparks, MD, USA). Species identification (Matrix Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry, Bruker Daltronics, Leipzig, Germany) and automated antimicrobial susceptibility testing (VITEK[®], bioMérieux, Marcy l'Etoile, France) were performed for all positive cultures. Anaerobic strains were tested using minimal inhibitory concentration (MIC) test strips (Liofilchem Inc., Waltham, MA, United States of America).

Microbiology reports were screened for every patient included in our database. A swab of the PF fluid was obtained in all patients with drain fluid suspicious for infection in conjunction with fever and/or elevation of blood leukocytes and/or C-reactive protein (CRP). In cases with clinically relevant PF, microbiological swabs were postoperatively obtained either from the drain fluid flowing over the intraoperatively placed abdominal drain, or from post-operatively, interventionally (e.g. CT-guided) placed abdominal drains (all passive drains). The drains were left in situ for a maximum of 6 days in cases without PF. All the documented bacteria species from the routine clinical microbiology reports of the main pancreatic duct, as well from the PFF, were collected in an additional database. Perioperative antibiotic prophylaxis was performed in every patient with single-shot ampicillin/sulbactam, and the patients who had preoperative ERCP received a combination of piperacillin/tazobactam instead.

The following microorganisms were classified as “intestinal” due to their typical presence in the normal intestinal flora: *Enterobacteriales* [i.e. *Escherichia coli* (*E. coli*), *Proteus spp.*, *Klebsiella spp.*, *Citrobacter spp.*], *Enterococcus spp.*, *Candida spp.*, and anaerobic bacteria (e.g. *Bacteroides spp.*, *Prevotella spp.*). The following microorganisms were considered as “not-primarily-

intestinal”: *Staphylococcus aureus*, *staphylococci* including *Staphylococcus epidermidis*, *Streptococcus spp.*, *Coagulase-negative*, *Haemophilus parainfluenzae*, *Corynebacterium spp.* The species *Streptococcus spp.* and *Haemophilus parainfluenzae* can be found in the digestive tract, but are also encountered on the skin and mucosa [9, 10]. The detection of bacterial strains was correlated with further complications such as intra-abdominal abscesses, haemorrhage, length of hospital stay and wound infections, and subanalysed according to the Clavien-Dindo classification of surgical complications [11]. We additionally analysed the presence of antibiotic resistance in the swabs from pancreatic duct and PFF. For this purpose, we applied the European Centre for Disease Prevention and Control (ECDC)-definitions for classification of bacterial resistance [12] for *Enterobacteriales*.

2.1. Study approval

The study was approved by the Ethics Committee of the Technical University of Munich, Germany (nr. 30/17s, as amended on 09th July 2021). Informed consent was obtained from all patients for biomaterial collection and intraoperative assessment of the pancreas.

2.2. Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics 25 software. Metric data were presented as medians with interquartile ranges or min.-max. Categorical data were shown as number and percentage. Correlations were tested with the Chi-square test or exact Fisher's test or Mann-Whitney U test. For correlation analyses, we calculated Odds ratios with the univariate and multivariate logistic regression model. A two-sided 95% confidence interval with a significance level (p-value) of 0.05 was generated for all calculations.

3. Results

3.1. Patient characteristics

In this observational study performed between 1st February 2017 and 1st February 2020, a total of 54 patients, who underwent pancreatic resection in our institution, were analysed for the microbiological spectrum of the pancreatic duct swabs (PD: 33, DP: 8, total pancreatectomy: 7, other: 6 cases). A bacterial swab was obtained from the pancreatic duct directly upon pancreatic transection (including total pancreatectomies). Clinically relevant PF was detected in 10 patients (18.5%) [Grade B: 7 (12.9%), Grade C: 3 (5.5%)]. The remaining patient characteristics are depicted on Table 1.

3.2. Bacterial spectrum of the pancreatic duct and the bile

The bacterial swabs from the duct were sterile in 39 cases (72.2%). In 10 cases (18.5%), the swabs detected intestinal bacteria, and in 5 cases (9.3%) other bacteria (Table 1). The detected bacterial species are depicted on Table 2.

The bacterial spectrum of the pancreatic fistula fluid (PFF) was distinct from that of the pancreatic duct. A bacteriological analysis of the PFF was performed in 16 cases. Here, the swabs of the PFF were sterile in 2 cases (12.5%), colonized by intestinal bacteria in 5 cases (31.2%), and by other bacteria in 9 cases (56.3%).

In comparison, the bacterial spectrum of the bile was also largely different. A swab from the bile was obtained intraoperatively from 65 cases. Here, the swabs of the bile were sterile in 32 cases (49.2%), colonized by intestinal bacteria in 24 cases (36.9%), and by other bacteria in 9 cases (13.9%).

3.3. Pancreatic duct obstruction & bacterial content of the pancreatic duct

We also explored the possibility that obstruction of the pancreatic duct due to a tumor or stone with subsequent dilation might also contribute to altered bacterial flora in the pancreatic duct. For this

Table 1. Patients with microbiological data - clinical characteristics.

	N
	54
Sex	
Male	31 (57.4%)
Female	23 (42.6%)
Age (median; min-max)	70.0 (33–87)
Operation	
Pancreatic head resection	33 (61.1%)
Distal pancreatectomy	8 (14.8%)
Total pancreatectomy	7 (13.0%)
Other	6 (11.1%)
Preoperative bile duct stenting	24 (44.4%)
Histopathology	
Ductal adenocarcinoma	27 (50.0%)
Distal bile duct/Papilla cancer	7 (13.0%)
Chronic pancreatitis	13 (24.1%)
Benign conditions	3 (5.6%)
IPMN	2 (3.7%)
Other	2 (3.7%)
Grade of pancreatic fistula	
Biochemical Leak	1 (1.9%)
B	7 (13.0%)
C	3 (5.6%)
Wound infections	4 (7.4%)
Clavien-Dindo Class	
0	25 (46.3%)
I	5 (9.3%)
II	7 (13.0%)
III	10 (18.5%)
IV	6 (11.1%)
V	1 (1.9%)
Bacterial spectrum in the pancreatic duct	
Sterile	39 (72.2%)
Intestinal bacteria	10 (18.5%)
Other bacteria	5 (9.3%)
Bacterial spectrum in the fistula/abscess (n = 7)	
Sterile	1 (14.3%)
Intestinal bacteria	2 (28.6%)
Other bacteria	4 (57.1%)

purpose, we compared the largest mean pancreatic duct diameter on the last preoperative computed tomography (CT) scan between patients with sterile vs. unsterile main pancreatic duct. Here, there was no obvious difference in the mean duct diameter (sterile: 4.8 ± 3.3 vs. unsterile: 6.7 ± 4.3 mm, $p = 0.1$, Mann-Whitney U test).

3.4. Impact of preoperative ERCP

A preoperative bile duct stenting was performed in 22 cases (40.7%, Table 1). As expected, patients with preoperative ERCP and bile duct stenting had a higher percentage of bacterial colonization of the pancreatic duct [with stent: sterile in 12 cases (50%), intestinal bacteria in 8 cases (33.3%), and other bacteria in 4 cases (16.7%); without stent: sterile in 27 cases (90%), intestinal bacteria in 2 cases (6.7%), and other bacteria in 1 case (3.3%); $p = 0.005$, Table 3].

Similarly, preoperative ERCP and bile duct stenting led to increased bacterial colonization of the bile [with Stent: sterile in 4 cases (23.5%), intestinal bacteria in 9 cases (52.9%), and other bacteria in 4 cases (23.5%); without Stent: sterile in 15 cases (50%), intestinal bacteria in 5 cases (21.7%), and other bacteria in 3 cases (13.0%); $p = 0.005$, Table 3].

In a cross-comparison of the bacterial species in the pancreatic duct versus bile, there was no correlation of the bacterial species between

Table 2. The detected bacterial species in the pancreatic duct.

Patient number	Bacterial species 1	Bacterial species 2	Bacterial species 3
1	<i>Enterococcus faecalis</i>	<i>Clostridium perfringens</i>	
2	<i>Streptococcus mitis</i>		
3	<i>Staphylococcus epidermis</i>		
4	<i>Enterococcus faecium</i>		
5	<i>Klebsiella pneumoniae</i>	<i>Proteus hauserin</i>	<i>Enterococcus faecalis</i>
6	<i>Escherichia coli</i>	<i>Klebsiella oxytoca</i>	
7	<i>Klebsiella pneumoniae</i>	<i>Enterobacter cloacae</i>	
8	<i>Klebsiella pneumoniae</i>		
9	<i>Klebsiella pneumoniae</i>		
10	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Enterococcus faecalis</i>
11	<i>Klebsiella pneumoniae</i>	<i>Enterococcus faecalis</i>	
12	<i>Klebsiella oxytoca</i>	<i>Enterobacter cloacae</i>	<i>Streptococcus anginosus</i>
13	<i>Klebsiella pneumoniae</i>		
14	<i>Escherichia coli</i>		
15	<i>Citrobacter koseri</i>		

these two localizations. Indeed, for example, presence of intestinal bacteria in the bile was associated with the presence of intestinal bacteria in the pancreatic duct in only 5 cases (35.7%), and with a sterile swab of the pancreatic duct in 8 cases (57.1%, $p = 0.24$, Table 4). There was further no significant difference in the colonization of the pancreatic duct depending on the type of operation (i.e., PD vs. DP, Table 5).

3.5. Pancreatic duct bacteria and clinically relevant pancreatic fistula

As an important aspect, the presence of bacteria in the pancreatic duct did not associate with pancreatic fistula or abscess formation (Table 6, $p = 0.19$). Here, among patients with a sterile pancreatic duct ($n = 39$), only 10 patients (25.6%) developed clinically relevant pancreatic fistula or abscess (Table 6). Among the 10 patients with intestinal bacteria in the pancreatic duct, no patient exhibited clinically relevant pancreatic fistula or abscess.

Similarly, among patients with a sterile pancreatic duct, 3 patients exhibited intestinal bacteria in the fistula/abscess fluid (75%). Among patients with intestinal bacteria in the pancreatic duct, only one patient had intestinal bacteria in the later pancreatic fistula fluid (Table 6).

3.6. Impact of pancreatic duct bacteria on postoperative complications

Finally, we analysed the potential correlation between the presence of clinically relevant surgical complications and the colonization of the pancreatic duct in our population (Table 6). Here, 33.3% of patients with a sterile pancreatic duct, and only 20% of patients with intestinal bacteria in the pancreatic duct suffered from higher grade (\geq Clavien-Dindo Grade 3) complications ($p = 0.65$), suggesting the lack of any association between pancreatic duct microorganisms and postoperative complications. Among the 11 patients with a fistula/abscess, 10 patients had a sterile pancreatic duct. Among patients with no clinically relevant pancreatic fistula or abscess ($n = 43$), the pancreatic duct swab was sterile in 29 cases (67.4%), and contained intestinal bacteria in 10 cases (23.3%).

4. Discussion

Microorganisms, especially bacteria, in the gastrointestinal tract are increasingly recognized as major promoters of postoperative complications in surgical patients. In the present observational study, we analysed the microorganism spectrum of the pancreatic duct as determined via intraoperative swabbing upon transection of the pancreas in a surgical population. Our findings underline that the pancreatic duct is frequently sterile and exhibits in general a limited microorganismal spectrum. As a

Table 3. Impact of preoperative ERCP/Stent on bacterial colonization of the pancreatic and bile duct.

	ERCP		p-value
	Yes	No	
	24	30	0.005
Pancreatic duct			
Sterile	12 (50%)	27 (90%)	
Intestinal bacteria	8 (33.3%)	2 (6.7%)	
Other bacteria	4 (16.7%)	1 (3.3%)	
	17	23	0.005
Bile duct			
Sterile	4 (23.5%)	15 (50%) ((65.2%) (81)	
Intestinal bacteria	9 (52.9%)	5 (21.7%)	
Other bacteria	4 (23.5%)	3 (13.0%)	

Table 4. Bile duct vs. Pancreatic duct colonization.

Bile duct	Sterile	Intestinal bacteria	Other	p-value
				0.24
Pancreatic duct				
Sterile	14 (73.7%)	8 (57.1%)	5 (71.4%)	
Intestinal bacteria	3 (15.8%)	5 (35.7%)	0	
Other bacteria	2 (10.5%)	1 (7.1%)	2 (28.6%)	

Table 5. Impact of the type of resection.

Bile duct	Pancreatico-duodenectomy	Distal pancreatectomy	p-value
			0.24
Pancreatic duct			
Sterile	24 (72.7%)	8 (100%)	
Intestinal bacteria	6 (18.2%)	0	
Other bacteria	3 (9.1%)	0	

secondary finding, we found that preoperative ERCP led to increased colonization of the pancreatic and bile duct. However, presence of bacteria in the pancreatic duct did not relate to the occurrence of infected pancreatic fistula or abscess in this observational study.

There has so far been only very scarce information on the usual microorganismal composition of normal main pancreatic duct. In a study limited to patients with chronic pancreatitis (CP), Parida et al. pursued a similar approach and intraoperatively collected the pancreatic juice from 26 patients who underwent resection for CP [13]. 11 of 26 patients (42%), and all the patients who had undergone preoperative ERCP had positive cultures from the pancreatic duct [13]. The most common

organisms in the duct were *Escherichia coli* (55%) and *Klebsiella pneumoniae* (3/11, 27%). The bacteria in the infected wounds of the patients were also similar to the bacterial spectrum of the pancreatic fluid [13]. However, the study by Parida et al. did not include specific information about the bacterial content of the pancreatic fistulas/leaks, when compared to the bacterial spectrum of the main pancreatic duct, which, in our view, is the clinically more relevant aspect. In another study, Yelamali et al. showed that the bacterial cultures from the pancreatic duct were positive in 64% of patients with CP who did not undergo any intervention (ERCP) prior to surgery [13, 14]. In their study, ERCP was performed in 15 patients and the bacterial positivity rate was 93% in this subgroup [13, 14]. Also here, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were the most frequent organisms [13, 14]. Based on our results and similar observations from other studies, it is obvious that ERCP constitutes a major factor leading to bacterial colonization of the pancreatic duct. However, ERCP itself does not seem to be a factor resulting in increased bacterial colonization of infected, clinically relevant pancreatic fistula.

The mechanism behind the rather infrequent, but still detectable, emergence of bacteria in the main pancreatic duct of patients who never underwent ERCP but resection, remains unclear. We speculate that three theories might explain the bacterial content of the main pancreatic duct in patients with no prior intervention. First, pancreatic tissues were shown to harbor bacteria, e.g., in patients with pancreatic cancer. Using 16S rRNA gene sequencing, Pushalkar et al. found high proportions of *Proteobacteria* (45%), *Bacteroidetes* (31%), and *Firmicutes* (22%) species in pancreatic cancer tissues [15]. They also showed that the microbiome constituents of the pancreatic cancer tissues are different and more abundant than those in the normal pancreatic tissue [15]. Thus, it is imaginable that a diseased pancreas, as encountered in patients who undergo resection for, e.g., CP or pancreatic cancer, is more prone to harbor bacteria. Second, we speculate that bacteria can occur in the main pancreatic duct of patients with a pancreatic disease through a Trojan horse-like mechanism, as suggested by Alverdy and colleagues [16]. Here, they postulated that during disease or surgical “injury”, bacteria in the intestinal tract can be taken up by neutrophils and then silently delivered to the operative site, resulting in an infection by intestinal bacteria [16]. It is conceivable that in patients with a diseased pancreas, such neutrophils carry intestinal bacteria into the disease sites, leading to detection of these bacteria during surgery. Finally, it is also possible that bacteria translocate into the pancreas from the intestine. This can be realized as either ascending colonization from the duodenum through the Vater’s papilla, or transmigration from the gut wall. Indeed, in acute pancreatitis, gut bacteria are known to translocate into the infected necrosis, and bowel decontamination with antibiotics appears to have protective effects in acute pancreatitis [17]. Interestingly, administration of fluorescently labeled *Enterococcus faecalis* or of GFP-labeled *Escherichia coli* to wild-type mice via oral gavage was shown to result in the detection of these fluorescent bacteria in the pancreas [15]. Therefore, these three

Table 6. Pancreatic duct bacteria and complications.

	Pancreatic duct			p-value
	Sterile	Intestinal bacteria	Other	
				0.19
Fistula/abscess				
Yes	10 (25.6%) (25.6%)	0	1 (20%) 1(71.4%)	
No	29 (74.4%)	10 (100%)	4 (80%)	
Fistula fluid				
Sterile	0	0	1 (50%)	0.3
Intestinal bacteria	3 (75%)	1 (100%)	0	
Other bacteria	1 (25%)	0	1 (50%)	
Complications				
< Clavien-Dindo 3	26 (66.7%)	8 (80%)	3 (60%)	0.65
≥ Clavien-Dindo 3	13 (33.3%)	2 (20%)	2 (40%)	

possibilities, i.e., the natural flora of the pancreatic tissue, the Trojan horse-mediated delivery of bacteria [16] into the pancreas from e.g. gut, or transmigration of bacteria from the intestine, can in our view account for the presence of bacteria in the main pancreatic duct in a surgical population, as in our study. Our study has some limitations. First of all, the sample size was rather low, limiting our ability to meaningfully differentiate between the impact of pancreatic duct bacteria on PD-vs. DP-associated complications. Second, the study was primarily an *observational* study, which was not primarily designed to discover the impact of pancreatic duct bacteria on fistula or other complications. However, the trends in the subgroup analyses were univocal, pointing out toward no effect of pancreatic duct bacteria on postoperative complications such as PF. Furthermore, our analysis of swabs reflects the “clinically detectable” bacteria through standard culture-based microbiological methods, and should not be seen equal to a genuine, sequencing-based “microbiome” analysis. As such, we do not exclude the role of the duct microbiome, but rather the impact of clinically detectable bacteria in the pancreatic duct, on the postoperative course of these patients.

5. Conclusion

In summary, we could show that the main pancreatic duct is frequently sterile in patients who undergo surgical resection for pancreatic disease. Detection of bacteria in the pancreatic duct is more common in patients after preoperative ERCP, but does not seem to constitute a risk factor for clinically relevant pancreatic fistula or other infectious complications. Based on our findings, the infection of pancreatic fistula fluids, or other surgical sites after pancreatic resection, seems to be derived from sources other than the main pancreatic duct. Pathomechanistic processes leading to transmigration or translocation of bacteria should be investigated in more detail for improved management of postoperative infectious fistulas or other complications after pancreatic surgery.

Declarations

Author contribution statement

IED and GOC conceived and designed the study. BSY, ED and CJ analysed and interpreted the data. KR, SS, OS, IP, RG, DW, MEM, ARN, GOC, HF and IED contributed analysis tools or data. ED, BSY, CJ and IED wrote the paper. All authors have worked on the draft and critically revised its important intellectual content. All authors have agreed on the final version of the manuscript.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

All affiliations for all co-authors are listed on the title page of the manuscript.

Additional information

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