




Association of bacteria in pancreatic fistula fluid with complications after pancreatic surgery

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Background: Pancreatic fistula (PF) is a common complication after pancreatic surgery. It is unclear how microbes in PF fluid affect outcomes and which microbes are present after pancreatoduodenectomy (PD) and distal pancreatectomy (DP). The aim of this study was to compare the microbiological spectrum of PF fluid after PD *versus* DP, and its association with postoperative complications.

Methods: Bacterial strains and antibiotic resistance rates of bacterial swabs obtained from the PF fluid of patients who underwent DP or PD were analysed. Cultured bacteria were classified as Enterobacterales and as 'other intestinal and non-intestinal microorganisms' based on whether they are typically part of the normal human intestinal flora.

Results: A total of 847 patients had a pancreatic resection (PD 600; DP 247) between July 2007 and December 2016. Clinically relevant PF was detected in 131 patients (15.5 per cent). Bacterial swabs were obtained from 108 patients (DP 47; PD 61), of which 19 (17.6 per cent) were sterile. Enterobacterales were detected in 74 per cent of PF fluid swabs after PD, and in 34 per cent after DP. Infected, polymicrobial or multidrug-resistant PF fluid was more common after PD (rates of 95, 50 and 48 per cent respectively) than after DP (66, 26 and 6 per cent respectively). Patients with higher grade complications (Clavien–Dindo grade IV–V) or grade C PF had more Enterobacterales and multidrug-resistant Enterobacterales in the PF fluid after DP.

Conclusion: Enterobacterales and multidrug-resistant bacteria are detected frequently after PD and DP, and are associated with more severe complications and PF in patients undergoing DP.

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Introduction

Pancreatic fistula (PF) continues to be among the most enigmatic complications after pancreatic surgery. Despite recent developments in surgical technique, its prevalence is still high, reaching 30–40 per cent after distal pancreatectomy (DP)¹. In comparison, the prevalence of PF after pancreatic head resection/pancreatoduodenectomy (PD) is somewhat lower, around 15 per cent². Several technical modifications have been tried to reduce the high PF rates after DP, including stapling, combination of suturing with stapling, patch application, stapler reinforcements, and pancreatojejunal anastomosis¹. To date, none of these

techniques has proven to reduce the incidence of PF consistently.

The leading reasons for PFs being a clinical problem are that they either become infected or cause erosive bleeding. In DP, surgeons typically do not open the intestinal lumen, in contrast to pancreatic head resection, which requires the creation of a pancreatojejunal or pancreatogastric anastomosis. Thus, it is unclear why PF after a sterile operation such as DP becomes infected, especially when most indications for DP are 'sterile' diseases such as pancreatic tail tumours.

To determine the reason behind the infection of PF after DP, the types of bacteria that are commonly detected in

the microbiological analysis of PF fluids after DP need to be analysed. Thus, the primary aim of this study was to compare the bacterial spectrum of PF fluid after DP and PD, and analyse its association with complications.

Methods

Data for patients who had surgery at the Department of Surgery, Klinikum rechts der Isar, Technical University of Munich, Germany, between 1 July 2007 and 31 December 2016 were obtained from a departmental database. Pancreatic resections were performed by seven experienced surgeons. Pancreatic stump closure during DP was performed by either hand-sewn sutures or a stapler device, or a combination of both, but not via anastomosis. PF grades were defined according to the definition of the International Study Group on Pancreatic Surgery³.

Microbiology reports were screened for every patient included in the database. The indication for obtaining a swab of the PF fluid in all patients was suspected infection in the drain fluid in conjunction with fever and/or increased blood leucocyte count and/or C-reactive protein concentration. Microbiological swabs were taken either from the drain fluid flowing over the abdominal drain placed during surgery, or after surgery from abdominal drains placed interventionally (for instance, CT-guided). All documented microorganisms from the microbiology reports were collected in a second database. Perioperative single-shot antibiotic prophylaxis with ampicillin plus sulbactam was given to every patient. No patient in the DP cohort had preoperative endoscopic retrograde cholangiopancreatography (ERCP) or preoperative transgastric biopsy.

The following microorganisms were classified as intestinal, based on their known presence in the normal intestinal flora: Enterobacterales (*Escherichia coli*, *Klebsiella* species (spp.), *Proteus* spp., *Citrobacter* spp.), *Enterococcus* spp., *Candida* spp., *Bacteroides* spp. and *Prevotella* spp.

The following strains were classified as 'not primarily intestinal': *Staphylococcus aureus*, coagulase-negative staphylococci including *Staphylococcus epidermidis*, *Streptococcus* spp., *Corynebacterium* spp. and *Haemophilus parainfluenzae*. *Streptococcus* spp. and *H. parainfluenzae* can be encountered in the gastrointestinal tract, but are typically associated with skin and mucosa^{4,5}.

The occurrence of bacterial strains was correlated with the presence and severity of further complications such as haemorrhage, intra-abdominal abscess, wound infection and length of hospital stay, and subanalysed based on the Clavien–Dindo classification of surgical complications⁶. The presence of antibiotic resistance in the collected

PF fluid was also registered, using European Centre for Disease Prevention and Control definitions for the classification of bacterial resistance for Enterobacterales⁷. The incidence of Enterobacterales and of multidrug-resistant Enterobacterales (MDRE) was compared between DP and pancreatic head resection.

Statistical analysis

Statistical analysis was performed using IBM SPSS® Statistics version 25 (IBM, Armonk, New York, USA). Continuous data are presented as median (range) or median (i.q.r.) values, and categorical data are given as numbers and percentages. Statistical significance was tested with the χ^2 test or Fisher's exact test, or with the Mann–Whitney *U* test, as appropriate. To identify risk factors, odds ratios (ORs) were calculated in univariable and multivariable logistic regression models. A two-sided 95 per cent confidence interval with a significance level (*P* value) of 0.050 was determined for all calculations.

Results

A total of 847 patients underwent pancreatic resection (PD, 600; DP, 247) between 1 July 2007 and 31 December 2016 in the authors' institution. Clinically relevant PF was detected in 131 patients, giving an overall fistula rate of 15.5 per cent (PD: biochemical leak 9 (1.5 per cent), grade B 25 (4.2 per cent), grade C 37 (6.2 per cent); DP: biochemical leak 17 (6.9 per cent), grade B 25 (10.1 per cent), grade C 18 (7.3 per cent)). Data for stiffness of the pancreas and pancreatic duct diameter in patients with PF are shown in *Table S1* (supporting information). Drains placed during surgery were left *in situ* for a mean of 7.9 (median 6) days. Interventionally placed drains stayed *in situ* for a mean of 14.1 (median 11) days.

An overview of patient characteristics is provided in *Table 1* and *Fig. 1*. A total of 108 patients were included in the final analysis.

Characteristics of pancreatic fistula fluid

Of the 108 patients from whom a PF fluid swab was taken for microbiology, 89 (82.4 per cent) had an infected PF and 19 (17.6 per cent) had a sterile fistula (*Table 1*). The rate of infected fistula was higher after PD (58 of 61 patients, 95 per cent) than after DP (31 of 47, 66 per cent) ($P < 0.001$). The infected fistulas were polymicrobial (contained more than 1 bacterial strain), especially after PD (29 of 58, 50 per cent) compared with DP (8 of 31, 26 per cent) ($P = 0.023$).

| Table 1 Clinical characteristics of patients with microbiological data | |
|---|-------------------------------|
| | No. of patients* (n = 108) |
| Age (years)† | 65.0 (31–85) |
| Sex ratio (M : F) | 70 : 38 |
| BMI (kg/m ²)‡ | 25.6 (23.4–28.1) |
| Diabetes | 8 (7.4) |
| Histopathology | |
| Ductal adenocarcinoma | 52 (48.1) |
| Distal bile duct cancer | 21 (19.4) |
| Chronic pancreatitis | 17 (15.7) |
| Benign condition | 12 (11.1) |
| IPMN | 4 (3.7) |
| Other | 2 (1.9) |
| Preoperative bile duct stenting | 16 (14.8) |
| Operation | |
| Pancreatic head resection | 61 (56.5) |
| Pylorus-preserving Whipple | 53 (49.1) |
| Classical Whipple | 3 (2.8) |
| DPPHR | 5 (4.6) |
| Distal pancreatectomy | 47 (43.5) |
| Duration of surgery (h)‡ | 5.5 (4.4–6.8) |
| Grade of pancreatic fistula | |
| Biochemical leak | 10 (9.3) |
| B | 49 (45.4) |
| C | 49 (45.4) |
| Wound infection | |
| | 9 (8.3) |
| Clavien–Dindo grade | |
| I | 3 (2.8) |
| II | 9 (8.3) |
| III | 53 (49.1) |
| IV | 32 (29.6) |
| V | 11 (10.2) |
| Relaparotomy | 33 (30.6) |
| Somatostatin administration | 29 (26.9) |
| Bacterial spectrum in fistula | |
| Sterile | 19 (17.6) |
| Non-intestinal bacteria (e.g. <i>Streptococcus</i> spp.) | 16 (14.8) |
| Enterobacterales | 29 (26.9) |
| MDRE | 32 (29.6) |
| Other intestinal bacteria (e.g. <i>Haemophilus parainfluenzae</i> , <i>Enterococcus</i> spp.) | 12 (11.1) |

*With percentages in parentheses unless indicated otherwise; †values are median (range) and ‡median (i.q.r.). IPMN, intraductal papillary mucinous neoplasm; DPPHR, duodenum-preserving pancreatic head resection; MDRE, multidrug-resistant Enterobacterales.

A large number of different bacterial species were detected in the drain fluid after both PD and DP (Table 2). Approximately 74 and 34 per cent of the microorganisms detected after PD and DP respectively were Enterobacterales, among which 64 per cent (29 of 45) and 19 per cent (3 of 16) respectively were MDRE ($P < 0.001$).

Fig. 1 Flow diagram showing the distribution of the different pancreatic fistula grades

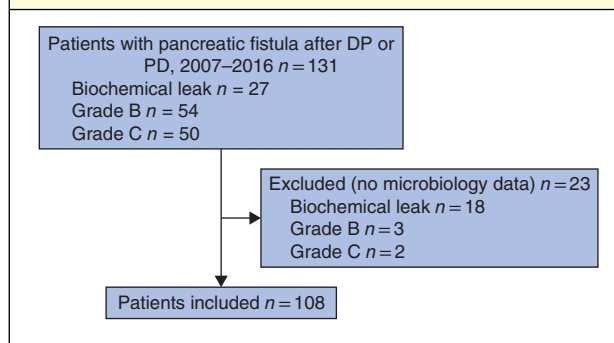


Table 2 Bacterial species and microorganisms in fistula fluid after pancreatoduodenectomy and distal pancreatectomy

| | PD (n = 61) | DP (n = 47) |
|-----------------------------------|-------------|-------------|
| Intestinal bacteria | | |
| Enterobacterales | 45 (74) | 16 (34) |
| MDRE | 29 (48) | 3 (6) |
| <i>Escherichia coli</i> | 23 (38) | 10 (21) |
| <i>Klebsiella</i> spp. | 19 (31) | 8 (17) |
| <i>Proteus</i> spp. | 6 (10) | 3 (6) |
| <i>Enterobacter</i> spp. | 13 (21) | 1 (2) |
| <i>Citrobacter</i> spp. | 5 (8) | 0 (0) |
| Other intestinal microorganisms | | |
| <i>Haemophilus parainfluenzae</i> | 2 (3) | 0 (0) |
| <i>Enterococcus</i> spp. | 40 (66) | 9 (19) |
| <i>Candida</i> spp. | 29 (48) | 5 (11) |
| <i>Bacteroides</i> spp. | 3 (5) | 3 (6) |
| <i>Prevotella</i> spp. | 3 (5) | 0 (0) |
| Non-intestinal bacteria | | |
| <i>Streptococcus</i> spp. | 10 (16) | 9 (19) |
| <i>Staphylococcus</i> spp. | 15 (25) | 28 (60) |
| <i>Corynebacterium</i> spp. | 0 (0) | 3 (6) |
| Other | 7 (11) | 8 (17) |

Values in parentheses are percentages. PD, pancreatoduodenectomy; DP, distal pancreatectomy; MDRE, multidrug-resistant Enterobacterales.

Postoperative complications

A higher rate of Clavien–Dindo grade IV–V complications was associated with the detection of both Enterobacterales and MDRE in PF fluid (Tables 3 and 4). In subgroup analysis, this association was significant in patients undergoing DP, but not in those having PD (Table 3).

In addition, a higher rate of clinically worse PF (grade C) was associated with both Enterobacterales and MDRE detected in PF fluid compared with non-Enterobacterales/sterile PF fluid (Tables 5 and 6).

Table 3 Complications according to bacterial spectrum and type of operation

| | Clavien–Dindo grade | | <i>P</i> * |
|---------------------|---------------------|------|------------|
| | I–III | IV–V | |
| All patients | | | 0.004 |
| No Enterobacterales | 35 | 12 | |
| Enterobacterales | 15 | 14 | |
| MDRE | 12 | 20 | |
| DP | | | 0.014 |
| No Enterobacterales | 24 | 7 | |
| Enterobacterales | 5 | 8 | |
| MDRE | 1 | 2 | |
| PD | | | 0.094 |
| No Enterobacterales | 11 | 5 | |
| Enterobacterales | 10 | 6 | |
| MDRE | 11 | 18 | |

Values in parentheses are percentages. MDRE, multidrug-resistant Enterobacterales; DP, distal pancreatectomy; PD, pancreatoduodenectomy. *Fisher's exact test.

Table 4 Univariable logistic regression analysis of complications: Clavien–Dindo grade I–III versus grade IV–V

| | Odds ratio | <i>P</i> |
|--|-------------------|----------|
| Bacterial spectrum | | |
| No Enterobacterales | 1.00 (reference) | |
| Enterobacterales | 2.72 (1.02, 7.25) | 0.045 |
| MDRE | 4.86 (1.87–12.85) | 0.001 |
| Parenchymal stiffness (soft versus hard) (<i>n</i> = 23)* | 1.71 (0.33–9.93) | 0.550 |
| Duct diameter (<i>n</i> = 76) | 0.96 (0.67–1.41) | 0.829 |
| BMI | 0.97 (0.84–1.07) | 0.974 |
| Age | 1.03 (0.93–1.06) | 0.092 |
| Duration of surgery | 1.08 (0.82–1.34) | 0.112 |
| PD versus DP | 1.60 (0.73–3.41) | 0.203 |

Values in parentheses are 95 per cent confidence intervals. MDRE, multidrug-resistant Enterobacterales; PD, pancreatoduodenectomy; DP, distal pancreatectomy.

In multivariable logistic regression analysis, only the presence of Enterobacterales and MDRE were independent risk factors for severe complications (OR 2.83, 95 per cent c.i. 1.04 to 7.87, $P=0.042$; and OR 5.53, 1.74 to 16.86, $P=0.003$, respectively) and grade C PF (OR 2.96, 1.05 to 8.15, $P=0.044$; and OR 3.46, 1.16 to 10.62, $P=0.033$, respectively).

The duration of drainage was not associated with the severity of PF ($P=0.902$), or with the presence of intestinal microorganisms ($P=0.441$) or multiresistant bacteria ($P=0.565$). In the multivariable logistic regression analyses, the emergence of Enterobacterales, rather than other

Table 5 Development of pancreatic fistula according to bacterial spectrum

| | Pancreatic fistula | | | <i>P</i> * |
|---------------------------|--------------------|---------|---------|------------|
| | Biochemical leak | Grade B | Grade C | |
| Bacterial spectrum | | | | 0.021 |
| No Enterobacterales | 6 | 28 | 13 | |
| Enterobacterales | 2 | 11 | 16 | |
| MDRE | 2 | 10 | 20 | |

MDRE, multidrug-resistant Enterobacterales. *Fisher's exact test.

Table 6 Univariable logistic regression analysis of pancreatic fistula: grade B versus grade C

| | Odds ratio | <i>P</i> |
|---|--------------------|----------|
| Bacterial spectrum | | |
| No Enterobacterales | 1.00 (reference) | |
| Enterobacterales | 3.13 (1.14, 8.65) | 0.025 |
| MDRE | 4.32 (1.58, 11.76) | 0.004 |
| Parenchymal stiffness (soft versus hard) (<i>n</i> = 23) | 0.71 (0.12–4.13) | 0.714 |
| Duct diameter (<i>n</i> = 76) | 1.03 (0.76–1.45) | 0.856 |
| BMI | 1.00 (0.82–1.13) | 0.698 |
| Age | 1.03 (0.99, 1.07) | 0.055 |
| Duration of surgery | 1.19 (0.96, 1.48) | 0.110 |
| PD versus DP | 2.36 (1.03, 5.39) | 0.045 |

Values in parentheses are 95 per cent confidence intervals. MDRE, multidrug-resistant Enterobacterales; PD, pancreatoduodenectomy; DP, distal pancreatectomy.

bacteria, was associated with patient age (OR 1.04 (95 per cent c.i. 1.00 to 1.08) per year; $P=0.029$) and type of surgery (OR 5.32 (2.28 to 12.53) for PD (compared with DP); $P<0.001$).

Discussion

This study has demonstrated that PF fluid has a distinct intestinal bacteriological spectrum after both PD and DP. The pathogenetic mechanism behind the colonization of pancreatic collections and PF with intestinal bacteria after DP is currently unknown. However, understanding this mechanism may have important implications for effective treatment of PF, especially as the present study showed an association between distinct intestinal bacteria (Enterobacterales) in the PF fluid and more severe complications after DP.

Peripancreatic collections due to leakage from the pancreatic resection plane are known to be infected frequently. After pancreatic head resection and subsequent pancreatojejunostomy, such infection is typically attributed

to the displacement of intestinal bacteria from the leaking anastomosis. However, why and how PFs and peripancreatic collections become infected after DP is unknown. At least in theory, haematoma at the resection plane may be a hotbed for bacterial growth. On the other hand, keeping the intra-abdominal drain *in situ* for longer periods may result in ascending intra-abdominal infection. However, in the absence of intraoperative damage to the intestine, neither theory can explain the occurrence of intestinal bacteria in PF fluid.

In the authors' view, one possible explanation for the presence of intestinal bacteria in PF-associated collections is the natural bacteriological flora of pancreatic juice. Information in the literature regarding the bacterial content or flora of normal pancreatic juice in the healthy pancreas is sparse. For a long time, researchers believed that, owing to the presence of aggressive proteases and digestive enzymes, pancreatic juice would actually have antibacterial activity⁸. This activity was demonstrated against *E. coli*, *Shigella* spp., *Salmonella* spp. and *Klebsiella* spp., but not against *Bacteroides fragilis* or *Streptococcus faecalis*, for example⁸. The present authors acknowledge that an ideal study would obtain bacteriology swabs prospectively from PF fluid, regardless of suspected clinical infection, at early and late time points. However, such a study would necessitate leaving the drain *in situ* for longer in a control group of patients with no sign of infection in the PF fluid. This potentially unnecessary drainage may similarly lead to secondary, unwanted infection/contamination of the fistula fluid.

Endoscopic therapies have been used increasingly to drain parapancreatic collections, and gastroenterologists are therefore interested in the microbiological spectrum of pancreatic fluid collections. In this regard, Mönkemüller and colleagues⁹ showed that bacteria are readily detectable in patients with acute or chronic pancreatitis-associated fluid collections. Furthermore, in a study of 26 patients who had surgery for chronic pancreatitis, Parida and co-workers¹⁰ found bacteria in the pancreatic duct fluid of 11 patients. Bacteria were, without exception, present in the pancreatic fluid cultures of patients who had preoperative ERCP, as a result of ascending contamination from the intestine¹⁰. The most common organism observed was *E. coli*, followed by *Klebsiella pneumoniae*, and bacteria isolated from the wound were similar to those in the pancreatic fluid¹⁰. Although the patient cohort was small, this study⁸ clearly showed that pancreatic juice is frequently infected in patients with chronic pancreatitis who had a previous endoscopic intervention.

In a study of patients with pancreatic cystic lesions that were drained endoscopically, Li *et al.*¹¹ also found intestinal bacterial strains, such as *Bacteroides* spp., *E. coli* and *Shigella*

spp., to be present in cyst fluid. In the present study, it was interesting that in patients with DP and no preoperative manipulation of the ampulla or main pancreatic duct, and no intraoperative opening of any intestinal lumen, half of all organisms present in infected PF fluid were intestinal bacteria.

Another explanation for the presence of intestinal bacteria in PF fluid after DP may be bacterial translocation, an event known to occur during acute or chronic pancreatitis^{12,13}. Infection of peripancreatic collections during acute pancreatitis is ascribed to such a translocation process from the surrounding intestinal loops, such as colon. It is possible that such translocation occurs due to surgery-induced, self-limiting, acute pancreatitis, which may result from DP. Indeed, in the authors' clinical experience, short-lived increases in serum amylase or lipase levels are common in the first 24 h after pancreatic resection, including resection of the tail. Such a translocation may be facilitated by disturbances in the microbiome of patients with pancreatic disease¹⁴, or by the presence of exocrine pancreatic insufficiency¹⁵.

What is the clinical consequence of the abundant presence of intestinal bacteria in PF fluid after DP? Undoubtedly, clinicians administer antibiotics to such patients with signs of sepsis or infection based on the antibiotic resistance profile of identified bacteria. An interesting question is whether bacterial translocation, which possibly occurs very early in the postoperative phase, may contribute to the generation of PF. Elucidating the potential impact of bacterial translocation on the healing process of the pancreatic resection plane may have key implications for preventing PF. Based on the present results, it is important to consider more aggressive therapeutic measures for patients with intestinal and/or multiresistant bacteria in the fistula fluid. Such measures could be more effective drainage of the peripancreatic collection and/or administration of antibiotics. However, antimicrobial therapy should be used only in the context of clinically suspected infection to avoid the emergence of multiresistant bacteria. Whether such an augmented intervention strategy would result in an improved clinical course needs to be analysed in future prospective studies.

This study has demonstrated that PF fluid after both PD and DP is frequently infected with intestinal bacteria. Understanding the pathogenetic mechanism behind the presence of intestinal bacteria in the fistula fluid after DP may help to improve the rate of infectious postoperative complications and contribute to knowledge on the development of PF.

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Supporting information

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