



# Effective Treatment of Biliopancreatic Fistulas due to Severe Leakage of the Pancreatojejunostomy Following Pancreatic Head Resection by Transhepatic Biliary Drainage: A Case Series of 17 Patients

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## Abstract

**Objective:** A combined biliopancreatic fistula due to severe leakage of the pancreatojejunostomy is a rare but clinically challenging postoperative complication after Partial Pancreatoduodenectomy (PPD). The aim of this study was to evaluate the therapeutic efficacy of placing a transhepatic biliary drain in this patient subgroup.

**Methods:** Patients were retrospectively analyzed according to postoperative complications, 30- and 90-day mortality as well as the rate of salvage pancreatectomy, postoperative hemorrhage, and length of hospital stay after treatment of biliopancreatic fistulas.

**Results:** 17 (5.5%) out of 310 patients developed a biliopancreatic fistula after PPD. All patients underwent transhepatic biliary drainage, either by radiological placement (PTBD, n=14) or during surgical re-exploration (STBD, n=3). No pancreatectomy or reoperation had to be performed after initial transhepatic biliary drainage. Postpancreatectomy hemorrhage occurred in 4/17 (23.5%) cases, major complications (Clavien-Dindo  $\geq$  IIIa) in 6/17 cases (35.3%). Median length of stay was 36 (18 to 71) days. 30-day mortality was zero and 90-day mortality 17.7%. No immediate procedure-related complication occurred.

**Conclusion and Advances in Knowledge:** The concept of transhepatic biliary drainage is feasible, effective and safe for the treatment of biliopancreatic fistulas. Separation of bile and pancreatic juice represents a novel therapeutic option in selected patients with severe leakage of the pancreatojejunostomy after PPD.

## OPEN ACCESS

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## Introduction

Pancreatic surgery is nowadays performed with better safety and lower mortality rates compared to the past [1]. Centralization strategies have been implemented and postoperative complication management after pancreatic surgery has advanced over the past two decades [2]. However, postoperative morbidity remains a challenge and occurs in up to 50% of patients after pancreatic head resections even in modern series [3]. A nationwide analysis revealed that overall mortality rates after pancreatic surgery are about 10% in Germany. Population-based data showed an approximately 50% reduction in the risk of postoperative mortality in very-low vs. very-high volume hospitals [4,5]. Studies investigating the reasons for this association identified a more effective management of severe complications rather than differences in the overall complication rates as the driving outcome-related variables [6]. One major advance in the management of postoperative complications has been a shift from operative to interventional treatment [1]. Today, the effective management of complications after pancreatic surgery is heavily reliant on the 24 h/7 days availability of an experienced interventional radiology unit [7].

Although complication patterns differ according to the type of pancreatic surgery performed, the most frequent and feared complication is the development of Postoperative Pancreatic Fistula

(POPF) after Partial Pancreaticoduodenectomy (PPD). The leakage of pancreatic secretion can result in a variety of conditions, from clinically non-relevant to severe systemic complications or even death [8]. Comparison of POPF rates, clinical outcomes and consequently study results was hampered in the past because the definition for POPF was not uniformly agreed-on [9]. This has changed with the implementation of an international and common POPF grading score by the International Study Group on Pancreatic Surgery (ISGPS) in 2005 [8]. ISGPS criteria have been revised in 2016 and since then, POPF severity is graded into three categories (biochemical leak, POPF type B or C) according to the change in clinical management as well as to the required therapeutic intervention [10]. A collective review of all reports using the standard POPF definitions found an overall POPF rate after PPD between 20% to 25% [11]. Clinically relevant POPF type B or C were found in 12% of patients after PPD [11]. However, the ISGPS criteria can only be applied retrospectively and classification of POPF is done after patient's hospital discharge. Standardized treatment algorithms for severe (grade B and C) POPF are scarce. The key management in clinically relevant POPF includes early recognition and prevention of severe sequela such as Post-Pancreatectomy Hemorrhage (PPH) and sepsis. Peripancreatic fluid collections need to be drained, either by percutaneous route if easily accessible or otherwise by re-laparotomy [12]. In the past, a wide range of patients with clinically relevant, especially grade C POPF (15% to 50%) have undergone completion pancreatectomy and as a consequence mortality rates were high (42%) [13]. Today, advances in interventional radiologic procedures have restricted salvage surgery to a small group of critically ill patients suffering from POPF [14]. In case of a combined biliopancreatic fistula, i.e. fistulas of the pancreaticojejunostomy containing pancreatic secretion and bile, consensus on the optimal treatment strategy is lacking. Therefore, we hypothesize that in case of an evident biliopancreatic fistula from the pancreaticojejunostomy, biliary drainage might reduce the severity of the anastomotic erosion due to the separation of bile and pancreatic secretions. This might prevent salvage completion pancreatectomy in this selected patient subgroup. As there is a need for more data, this study aimed at analyzing clinical outcome of patients with biliopancreatic fistulas after PPD treated by transhepatic biliary drainage.

## Material and Methods

### Patient population

All patients who underwent Partial Pancreaticoduodenectomy (PPD) at the University Hospital of Wuerzburg, Germany (UKW) between January 2009 and May 2019 were identified from the Wuerzburg Institutional Database (WID). Patient records were analyzed regarding the diagnosis and treatment of a Postoperative Pancreatic Fistula (POPF), defined as drainage of >50 ml/d of amylase-rich fluid (greater than a 3-fold elevation above the upper limit of normal in serum) through the operatively placed drains on or after postoperative day 3 and 7. POPF was classified as biochemical leak and grade B or C according to the updated International Study Group of Pancreatic Fistula classification after patient's discharge [10]. A biliopancreatic fistula was defined as drainage of pancreatic fluid together with biliary secretions on any postoperative day through the operatively placed drains. All patients with biliopancreatic fistulas, who received a transhepatic biliary drainage as a first-line treatment strategy, either by radiologic or surgical placement, were included into the analysis. Patients who showed insufficiency of the biliodigestive anastomosis as source of the biliary leakage were excluded from the

study. Primary and secondary endpoints in this study are referred to the procedure of biliary drainage in order to treat a biliopancreatic fistula. Primary endpoints of this study were defined as rate of post-interventional complications graded by Clavien and Dindo as well as 30 and 90 day mortality [15,16]. Secondary endpoints were re-operation, salvage completion pancreatectomy, postoperative hemorrhage, and length of hospital stay.

### Data source

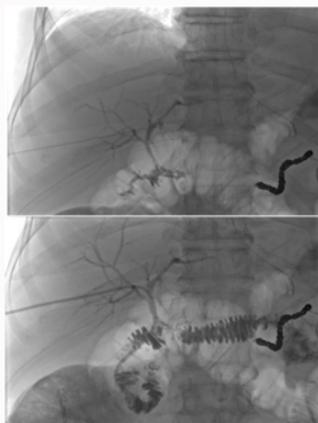
The Wuerzburg Institutional Database (WID) is a central prospective database with clinical and research data of patients, who were evaluated and treated at the UKW. It has been expanded on a daily basis since 1984. The collection of data and scientific analysis is approved by an institutional review board. The WID contains data on patient demographics, histological diagnosis based on International Classification of Disease coding standards, physician data, operative and interventional procedures, laboratory values and computerized medication records, inpatient admission and outpatients' registration data. Demographic details, clinical variables recorded at the time of primary diagnosis or during the initial surgery and histological details of the resected specimen were compiled.

### Treatment

All patients underwent Partial Pancreaticoduodenectomy (PPD), either pylorus-resecting according to Kausch/Whipple or pylorus-preserving according to Traverso/Longmire. In case of an evident postoperative biliopancreatic fistula, patients either underwent a radiologically placed Percutaneous Transhepatic Biliary Drainage (PTBD). In case of intra-abdominal fluid collections that could not be drained percutaneously by any reason, patients underwent reoperation with insertion of a Surgically placed Transhepatic Biliary Drainage (STBD) (Neuhaus Endless-Drainage, Waldemar Link, Hamburg, Germany), a lavage of the abdominal cavity and replacement of drains in order to achieve separation of pancreatic and biliary secretions [17].

### PTBD procedure

All interventions were performed under analgo-sedation and monitoring of vital signs by an intensive care physician as well as local anesthesia by the interventional radiologist. With the patient in supine position, a right liver lobe blind puncture (right middle axillary line between the intercostal space 9 to 11) was performed under fluoroscopic guidance (Axiom Artis Zee, Siemens, Germany) using a 22 G Chiba needle. As a dilated biliary tree had not been expected in the setting of a biliopancreatic fistula, the Chiba needle was navigated more centrally aiming the right main hepatic bile duct. Under slight and continuous retraction of the needle and simultaneous aspiration of bile secretion an entry into the bile duct was confirmed. Contrast agent was injected for a cholangiogram to assure the correct position of the needle. In this context, the absence of bile leakage over the biliodigestive anastomosis was evaluated. A further criterion was the proper runoff into the small intestine *via* the biliodigestive anastomosis. After that, a 0.018-inch nitinol guidewire (Nitrex, Medtronic's, Parkway, MN) was advanced through the Chiba needle via the biliodigestive anastomosis. Over the wire the needle was removed and a hydrophilic 4F sheath (Neff Percutaneous Access Set, Cook, Bjaaerskov, Denmark) with a flexible introducer and an inner stiffening cannula was carefully advanced towards the right main bile duct. During this maneuver the inner stiffening cannula was removed depending on the stability of the sheath-guidewire-system. After correct placement of the sheath within the bile duct, the



**Figure 1:** 63-year-old male patient 3 weeks after pylorus-preserving pancreaticoduodenectomy and 3 days after coil embolization due to active bleeding of the splenic artery.

a) The radiograph demonstrates percutaneous transhepatic cholangiography after successful puncture of the non-dilated left hepatic bile duct. Leakage from the bilioenteric anastomosis is excluded. b) Completion radiography showing successful PTBD via the hepaticojejunostomy.

flexible introducer was removed, and the 0.018-inch-guidewire was exchanged by a 0.035-inch-flexible guidewire (Radifocus, Terumo, Tokyo). The guidewire was directed beyond the biliodigestive anastomosis, and the sheath was removed. Over the wire a selective catheter (C1 Cobra catheter, Cook, Bjaeverskov, Denmark) was placed within the intestine and the flexible guidewire was exchanged for a stiff 0.035-inch-guidewire (Amplatz, Cook, Bjaeverskov, Denmark) in order to achieve more support. At least, the selective catheter was withdrawn and an 8.5F internal-external drainage system (Cook, Bjaeverskov, Denmark) was placed with the proximal holes close to and the distal holes beyond the hepaticojejunal anastomosis (Figure 1).

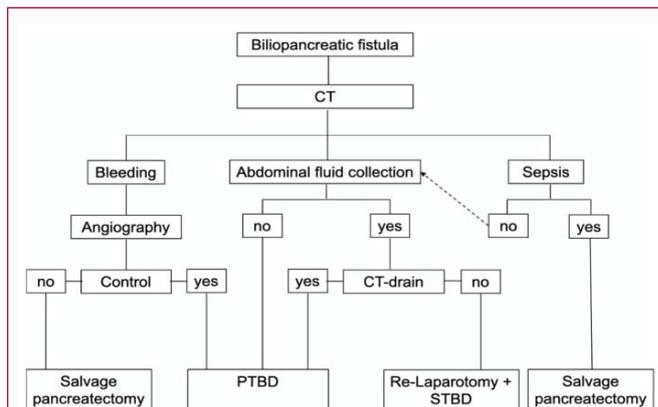
### Compliance with ethical standards

The retrospective analysis of patient data was approved by the institutional review board (approval number: 20190603 03) and in accordance with the 1964 Helsinki declaration and its later amendments. Informed consent for this study was not required according to the institutional review board. Informed consent for PPD, revision surgery and transhepatic biliary drainage was obtained from all patients included in the study.

## Results

### Patient characteristics

Between January 2009 and May 2019, 310 pancreatic head resections were performed at our center. Seventeen patients (5.5%) were identified from the WID who had developed a biliopancreatic fistula. The cohort consisted of 14 male and 3 female patients, with a median age of 67 [49 to 83] years and a median body mass index of 27 kg/m<sup>2</sup> (23-37). The most common classifications by the American Society of Anesthesiologists (ASA) were 2 and 3 (94%). The leading concomitant disease was arterial hypertension (70.6%), followed by coronary artery disease (35.3%). The preoperative serum bilirubin-level was 0.6 [0.2 to 26.5] mg/dl in the median. The median serum CA 19-9 level was 61.8 U/l [0.6 to 99.9]. All patients included received pylorus preserving PPD, with a median operation time of 357 [270 to 713] minutes. Pathological examination of specimens reported a malignancy in 14 patients, pancreatic ductal adenocarcinoma being



**Figure 2:** Proposed therapeutic algorithm for CPPF in case of biliary secretion.

the leading diagnosis. Each patient received a standardized treatment protocol of somatostatin analogo (Octreotide, 100 µl subcutaneously three times a day) until postoperative day 7. Major postoperative complications according to Clavien and Dindo ( $\geq$  grade IIIa) occurred in 14/17 patients (and median CCI was calculated 44.4 [26 to 100]). Three patients died within 90 days after surgery resulting in a 90-day mortality of 17.6%. Patient characteristics are listed in Table 1.

### Treatment of biliopancreatic fistulas and patient outcome

Biliopancreatic fistulas with an evident bile component in drainage fluids occurred on Postoperative Day (POD) 13 in the median (5 to 29 days). Affected patients received either interventional percutaneous (PTBD) or surgically placed Transhepatic Biliary Drainage (STBD). Of note, leakage of the hepaticojejunostomy was ruled out by either procedure. PPH was a frequent major complication and occurred in 12 out of 17 patients (70.5%) in total. Four patients (23.5%) developed PPH after placement of a biliary drainage. PPH was successfully treated in 10 patients by interventional covered stent implantation or coil embolization, two patients died subsequently due to multiorgan failure. Eleven patients received PTBD as a first-line treatment of a biliopancreatic fistula after relevant intra-abdominal fluid-collections had been ruled out by Computed Tomography (CT). Indication for re-laparotomy was based on acute changes in clinical examination and laboratory results or insufficient drainage of intra-abdominal fluid collections in CT scans, without a chance of percutaneous drain placement. Three of these six patients received simultaneous STBD during re-laparotomy and the remaining three patients underwent abdominal lavage with replacement of intra-abdominal drains receiving PTBD by the interventional radiologist postoperatively. None of these patients required repeated laparotomy. No salvage completion pancreatectomy was required to control persistent biliopancreatic leakage from the pancreaticojejunostomy. No immediate periinterventional complication was observed after PTBD. Six patients developed major postoperative or post-interventional complications (grade  $\geq$  IIIa according to Clavien and Dindo) following transhepatic biliary drainage during the subsequent hospital stay. Median length of hospital stay was 36 days (18 to 71 days). Thirty-day mortality was zero. Three out of 17 patients died within 90 days (17.6%). Treatment related outcome parameters are shown in Table 2.

## Discussion

POPF represents a major source of morbidity and mortality after PPD. Although overall mortality after PPD has decreased to

**Table 1:** Patient characteristics.

Variable	Patients
Age (years, median (range))	67 (48.7-83.0)
Gender male, n (%)	14 (82.4)
BMI (kg/m <sup>2</sup> ), median (range)	27 (22.8-37.0)
ASA score, n (%)	
1	0 (0)
2	7 (41.2)
3	9 (52.9)
4	1 (5.9)
Arterial Hypertension, n (%)	12 (70.6)
Diabetes, n (%)	5 (29.4)
Coronary Heart Disease, n (%)	6 (35.3)
Increased cardiovascular risk, n (%)	13 (76.5)
Bilirubin (mg/dl), median (range)	0.6 (0.2-26.5)
Preoperative CA19-9, median (range)	61.8 (0.6-99.9)
Type of surgery, n (%)	
Traverso-Longmire	17 (100)
Kausch-Whipple	0 (0)
Total operation time, median (range)	357 (270-713)
Postoperative somatostatin analogs, n (%)	17 (100)
Histology, n (%)	
Benign lesions	3
Malignant lesions	14
- PDAC	5
- NET	3
- Periampullary	3
- Other	3
Overall postoperative complications (CD), n (%)	17 (100)
I	
II	5 (29.4)
IIIa	5 (29.4)
IIIb	14 (82.4)
IVa	7 (41.2)
IVb	2 (11.8)
V	1 (5.9)
	3 (17.7)
CCI, median (range)	44.4 (26-100)

less than 5% in high-volume centers, the rate of POPF has remained high [2]. International consensus has been found on classification of POPF [10]. This classification system is based on retrospective grading according to the patients' clinical condition, and the required interventions to treat POPF. It is perfectly designed for comparative outcome analysis, but it does not represent a therapeutic algorithm in the event of POPF. Moreover, in the rare case of a biliopancreatic fistula, which we defined as leakage of pancreatic juice and bile from the pancreatojejunostomy in this study, agreed-on treatment strategies are lacking. Completion pancreatectomy should only be performed as a rescue procedure in patients with signs of severe sepsis or hemorrhage that cannot be managed by other means. Postoperative morbidity rates are high and mortality in this selected

**Table 2:** Treatment-related Outcome.

Variables	Transhepatic bile drainage (n=17)
Time to biliopancreatic fistula, median (range)	13 (5-29)
Treatment of biliopancreatic fistula	
PTBD, n (%)	11 (64.8)
STBD, n (%)	3 (17.6)
Reoperation + PTBD, n (%)	3 (17.6)
Reoperation after PTBD, n (%)	0 (0)
PPH, n (%)	12 (70.5)
PPH after transhepatic bile drainage, n (%)	4 (23.5)
CD ≥ IIIa after transhepatic bile drainage, n (%)	6 (35.3)
Completion pancreatectomy, n (%)	0 (0)
Length of stay, median (range)	36 (18-71)
30d mortality, n (%)	0 (0)
90d mortality, n (%)	3 (17.6)

patient group is reported to be 40% to 50% [13]. Furthermore, brittle diabetes-associated quality of life is significantly impaired and diabetes-associated morbidity increased in patients after total pancreatectomy compared to the general population [18]. In this case series we provide evidence that Transhepatic Biliary Drainage either by radiological (PTBD) or surgical (STBD) placement represents a safe, effective, and feasible procedure for the treatment of biliopancreatic fistulas. Procedure-related acute complication rate after PTBD was zero percent; the overall post-interventional/-operative major complication rate was 35.3% for the whole study group. None of the 17 patients required a reoperation or a salvage completion pancreatectomy. In-house mortality following this new treatment approach was 17.6%, which is low compared to patients who undergo salvage pancreatectomy as a first-line treatment for severe biliopancreatic fistulas (43 %, unpublished own data and 42% [13]). POPF grading according to ISGPS is applied after a patient's discharge. Therefore, it is not a helpful tool to guide clinicians in their management of severe POPF. Consensus on the optimal treatment strategy is lacking as national as well as international guidelines to not provide recommendations for these common and dreaded complication after Partial Pancreatoduodenectomy PPD [19]. For decades, treatment was performed through direct re-laparotomy with high morbidity rates [20]. However, management of postoperative complications has shifted over time towards a more frequent use of minimally invasive techniques. Percutaneous drainage of intra-abdominal peripancreatic fluid collections as well as angiographic stenting and/or embolization of PPH has been proven effective and safe [14,21]. Moreover, the evolution of interventional radiology has dramatically reduced the need for unplanned re-laparotomy [22]. Even in the case of non-dilated bile ducts, we have shown that PTBD is a safe procedure in the hand of well-trained interventional radiologists. We have developed a treatment algorithm for patients with biliopancreatic fistulas after PPD which favors the placement of a percutaneous transhepatic biliary drainage. It starts at the time the fistula first becomes clinically evident. It considers the patient's clinical condition and the presence of a peripancreatic fluid collection in computed tomography (Figure 2). In the absence of sepsis and abdominal fluid collections, the patient should directly undergo PTBD. In case a CT scan detects peripancreatic fluid collection, placement of a percutaneous drainage should be performed whenever possible and the patient referred to PTBD placement subsequently.

Otherwise, patients should undergo re-laparotomy, abdominal lavage, drain replacement and STBD if feasible. Damage control completion pancreatectomy should be restricted to patients with complete dehisence of the pancreatojejunostomy, sepsis or life-threatening PPH. Formation of the pancreatojejunostomy is the Achilles heel of PPD. Drainage of the pancreatic remnant to the gastrointestinal tract remains a crucial step, but it runs the risk of anastomotic breakdown. In conventional loop reconstruction, the pancreatojejunostomy is performed using the same jejunal loop as for the hepaticojejunostomy. Both anastomoses are placed close to each other. As a consequence, activation of pancreatic enzymes by bile is not obviated. This might promote tissue erosion at the pancreatojejunostomy, thereby increasing the risk of biliopancreatic fistula formation. The concept of separation of pancreatic juice and bile in order to reduce fistula sequela such as life-threatening hemorrhage was first applied by using two jejunal loops for reconstruction forty years ago [23]. Use of Roux-en-Y reconstruction with isolated pancreatic drainage is a technique that has been suggested to reduce POPF-related morbidity and mortality in patients undergoing PPD in retrospective studies [24]. However, results from a multicenter randomized study have demonstrated no benefit of dual loop vs. conventional loops reconstructions in terms of overall POPF rates, although in subgroup analysis there was a significantly reduced rate of clinically-relevant fistulas in the group of dual loop reconstruction [25]. It is known from pancreaticobiliary maljunction-associated pancreatitis that activation of phospholipase A2 by bile acids plays a crucial role in the etiology of this form of acute pancreatitis [26,27]. We hypothesized that the diversion of bile from pancreatic secretions might minimize the erosion from activated pancreatic enzymes in case of a biliopancreatic fistula. With this novel therapeutic concept of placing a transhepatic biliary drain, we aimed to reduce the rate of salvage completion pancreatectomies needed to control this situation. Indeed, in all patients treated with PTBD or STBD, biliary secretions were efficiently drained. Daily drain amounts consistently decreased and biliopancreatic fistulas finally suspended with a median time range of 13 days. PTBD is a minimally invasive technique. However, potential complications such as bleeding, cholangitis, biliary leak, duodenal perforation and death may occur. In some series, procedure-related death has been reported to range from 0.6% to 5.6% [28,29]. The periinterventional complication rate after PTBD in our series was zero percent although PTBD had to be set up into non-dilated bile ducts. PTBD in patients without intrahepatic bile duct dilatation is often very demanding because the drainage catheter has to be inserted into the very small-caliber bile duct [30]. In this context, the small-caliber bile duct has to be targeted more centrally so that complications with or without portal vein involvement are more likely. Procedure-related major complications rates in patients with non-dilated intrahepatic bile ducts have been shown to be significantly higher compared to patients with dilated intrahepatic bile ducts [30]. Consequently, 24 h/7 days availability of specialized or board-certified interventional radiologists is needed for the successful management of biliopancreatic fistulas after PPD. This is supported by the fact that postoperative mortality after PPD is substantially dependent on the presence of specialized radiology teams [4,5]. There were two main limitations to our study. First, the sample size was small, preventing us from generalizing the results and therefore considering them preliminary. Second, the study was retrospective. A prospective trial would be beneficial to determine the exact value of this modified drainage strategy.

In conclusion we provide evidence that the concept of

transhepatic biliary drainage is feasible, effective, and safe for the treatment of clinically demanding postoperative biliopancreatic fistulas. Separation of bile from pancreatic secretions represents a novel therapeutic option in selected patients with sufficiently drained biliopancreatic fistulas after PPD.

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