

# Is bactibilia a predictor of poor outcome of pancreaticoduodenectomy?

Sivanpillay Mahadevan Sivaraj, Velayutham Vimalraj, Palanichamy Saravanaboopathy, Shanmugasundaram Rajendran, Sathyanesan Jeswanth, Palaniappan Ravichandran, Rosy Vennilla and Rajagopalan Surendran

Chennai, India

**BACKGROUND:** Although bile infection has been proposed to increase infective complications following pancreaticoduodenectomy, its association with infective complications and non-infective complications like pancreatic fistula is still controversial.

**METHODS:** Seventy-six patients who had undergone pancreaticoduodenectomy between July 2007 and December 2008 were included in a prospective database and their data analyzed. In all patients intraoperative bile from the bile duct was cultured. Preoperative, intra-operative, and post-operative variables were recorded and analyzed.

**RESULTS:** Bile culture showed positive growth in 35 patients and negative growth in 41. Twenty patients in the positive group underwent ERCP and stenting. The patients with a positive bile culture had a higher incidence of infective complications including intra-abdominal abscess ( $n=8$ ), wound infection ( $n=27$ ), bacteremia ( $n=10$ ), and renal insufficiency ( $n=9$ ). There was no increase in the rate of non-infective complications of pancreaticoduodenectomy including pancreatic fistula ( $n=7$ ), delayed gastric emptying ( $n=9$ ), and post-operative hemorrhage ( $n=3$ ). The hospital stay was significantly prolonged in the patients with a positive bile culture ( $P=0.0002$ ).

**CONCLUSIONS:** Pre-operative biliary drainage is significantly associated with bile infection, and bile infection increases the overall rates of infective complications and renal

insufficiency. Because of the high incidence of complications is associated with infected bile, routine intra-operative bile culture is recommended in patients undergoing pancreaticoduodenectomy. Pre-operative prophylaxis is dependent on sensitivity of cases to perioperative antibiotics and intra-operative bile culture report. Because of its significant association with infected bile, biliary stenting should be used in strictly selected cases.

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**KEY WORDS:** bactibilia; Whipples pancreaticoduodenectomy; perioperative outcomes

## Introduction

Although bile infection has been proposed to increase infective complications following pancreaticoduodenectomy,<sup>[1]</sup> its association with infective and non-infective complications like pancreatic fistula is still controversial.<sup>[2-8]</sup> Jagannath et al<sup>[4]</sup> in a study on the outcome of pancreaticoduodenectomy following stenting concluded that biliary stenting was not significantly associated with a positive culture. But others<sup>[2, 3, 5-8]</sup> suggested preoperative biliary drainage was associated with bile infection. Some studies<sup>[2, 6-8]</sup> associated infected bile with increased incidence of post-operative infective complications, whereas other studies<sup>[3, 5]</sup> did not record such an association. Recently few studies have related the higher incidence of pancreatic fistula with bile infection.<sup>[5]</sup> Hence, the aim of this study was to analyze the effect of bile infection in the immediate outcome of pancreaticoduodenectomy, both infective and non-infective.

## Methods

Seventy-six patients who had undergone pancreatico-

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**Author Affiliations:** Institute of Surgical Gastroenterology and Liver Transplantation, New Gastroenterology Block, Government Stanley Medical College Hospital, Chennai 600 001, India (Sivaraj SM, Vimalraj V, Saravanaboopathy P, Rajendran S, Jeswanth S, Ravichandran P, Vennilla R and Surendran R)

**Corresponding Author:** Rajagopalan Surendran, Professor, Institute of Surgical Gastroenterology and Liver Transplantation, New Gastroenterology Block, Government Stanley Medical College, Royapuram, Chennai 600 001, India (Tel: 0091-44-25289595; Fax: 0091-44-25289595; Email: Stanleygastro@yahoo.com)

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duodenectomy between July 2007 and December 2008 were included in a prospective database, and their data were analyzed. The patients were given prophylactic antibiotics. Intravenous injection of Cephazolin 2 g was given before induction of anesthesia. All patients underwent standard Whipple pancreaticoduodenectomy,<sup>[9]</sup> after which, the pancreatic remnant was mobilized proximally, a posterior gastrostomy was made, and a pancreaticogastrostomy was performed to invaginate the remnant into the stomach. Anastomosis was made with 3-0 polyglactin (vicryl). Gastrojejunostomy and hepaticojejunostomy were performed on the same jejunal loop. Two drains were placed to drain the pancreatic and biliary anastomosis. In all patients, intra-operative bile culture from the bile duct was collected.

The preoperative variables analyzed were age, gender, serum bilirubin, serum albumin, and diabetes mellitus, which are associated with post-operative complications.<sup>[5, 8]</sup> Intra-operatively, the nature of the pancreatic remnant, the size of the main pancreatic duct, operative time, blood loss, and transfusions were recorded. Post-operatively, also recorded were death caused by complications, pancreatic fistula, hemorrhage, delayed gastric emptying, intra-abdominal abscess, wound infection, septicemia, renal insufficiency, and pulmonary complications. Post-operative hospital stay was also observed.

Pancreatic fistula was defined by the level of drained fluid amylase more than three times the level of serum amylase 3 days after operation.<sup>[10]</sup> Delayed gastric emptying was defined by drainage with a nasogastric tube for more than 10 days after operation with one of the following signs: emesis after removal of the nasogastric tube, reinsertion of a nasogastric tube, use of prokinetic agents after post-operative day 10, or failure to progress with diet.<sup>[11]</sup> Wound infection, intra-abdominal abscess, and bacteremia were recognized as infectious complications, which were confirmed by microbial cultures. Complications other than wound infection (death, pancreatic fistula, hemorrhage, delayed gastric emptying, intra-abdominal abscess, bacteremia, renal insufficiency, and pulmonary complications) were considered as major complications.

Values were expressed as median and ranged appropriately. Discrete variables were analyzed statistically using the two-tailed Fisher's exact test, and continuous variables using Student's *t* test. A difference was considered statistically significant when  $P < 0.05$ .

## Results

Bile culture showed positive growth in 35 patients and

negative one in 41. Twenty patients in the positive group underwent ERCP and stenting.

The mean age of patients was 53.42 years in the positive group and 52.24 in the negative group. No significant difference was seen in sex distribution in the two groups. The distribution of diabetes mellitus in both groups was not different significantly. No significant difference was observed in the levels of serum bilirubin and albumin between the two groups (Table 1).

### Pre-operative biliary drainage

In our series, 20 patients underwent ERCP and sphincterotomy, 18 underwent the procedures before being referred to our centre; the indications were not unified. Of the 18 patients, 2 had a history of fever and rigor. Since preoperative drainage was performed selectively for those with cholangitis non-responding to medical management, only 2 patients underwent ERCP and stenting for cholangitis in our institution.

### Intra-operative variables

All of our patients underwent a standard pancreaticoduodenectomy. Their median operative time and blood loss were not different. No blood transfusion was given. There was no significant difference in the nature of the pancreatic remnant and main pancreatic duct size between the two groups (Table 2).

**Table 1.** Demography and preoperative variables

Characteristics	Positive group (n=35)	Negative group (n=41)	P value
Gender (M/F)	22/13	26/25	1
Mean age (years)	53.42	52.24	0.6266
Diabetes mellitus	11	13	1
Serum bilirubin (mg/dl)	9.6	9.7	0.4573
Serum albumin (g/dl)	3.2	3.4	0.0821
Pre-operative endoscopy			
ERCP	20	0	<0.0001
Sphincterotomy	20	0	<0.0001
Biliary stenting	20	0	<0.0001

ERCP: endoscopic retrograde cholangiopancreatography.

**Table 2.** Intra-operative variables

Intra-operative variables	Positive group (n=35)	Negative group (n=41)	P value
Soft pancreatic remnant	13	15	1
MPD >3 mm	25	26	0.4759
Operative time (min)	300	300	0.8873
Blood loss (ml)	300	350	0.7044
Blood transfusion (units)	0	0	0.08

MPD: main pancreatic duct.

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**Table 3.** Post-operative complications

Characteristics	Positive group (n=35)	Negative group (n=41)	P value
Mortality	1	1	1
Pancreatic fistula	4	3	0.69681
Hemorrhage	1	2	1
Delayed gastric emptying	6	3	0.16742
Infective complications	18	9	0.0148
Wound infection	18	9	0.0148
IAA	7	1	0.0002
Bacteremia	9	1	0.0043
Renal insufficiency	8	2	0.03746
Pulmonary complication	1	2	1
Hospital stay (days)	16	10	0.0002

IAA: intra-abdominal abscess.

**Table 4.** Preoperative biliary drainage and complications

Characteristics	Preoperative biliary drainage	No preoperative biliary drainage	P value
Mortality	1	1	0.9999
Pancreatic fistula	4	3	0.0733
Hemorrhage	0	3	0.5618
Delayed gastric emptying	6	3	0.0084
Infective complications	15	12	0.00003
Wound infection	15	12	0.00003
IAA	7	1	0.0002
Bacteremia	8	2	0.0002
Renal insufficiency	7	2	0.0008
Pulmonary complication	1	2	1
Hospital stay (days)	20.5	10.5	0.0004
Total	20	56	

### Mortality

One of the 35 patients died of pancreatic fistula and septicemia on postoperative day 35. One of the 41 patients died of polycystic kidney disease and chronic renal failure on postoperative day 16 after development of pulmonary edema (Table 3).

### Morbidity

In 20 patients of the positive group one or more postoperative complications developed, and infectious complications were seen in 18 of them. They included intra-abdominal abscess (n=8), wound infection (n=27), bacteremia (n=10), and renal insufficiency (n=9). The rates of non-infective complications such as pancreatic fistula, delayed gastric emptying, and postoperative hemorrhage were not increased in patients after pancreaticoduodenectomy. Hospital stay was prolonged in the positive group (Table 3).

**Table 5.** Microorganisms isolated from bile cultures

Organism	Number	Percentage
<i>Escherichia coli</i>	32	91
<i>Klebsiella</i>	8	23
<i>Pseudomonas</i>	4	11
Others	3	8
<i>Staphylococcus aureus</i>	2	6
Fungal	Nil	Nil

**Table 6.** Antibiotic sensitivity pattern of organisms isolated from bile

Antibiotic	Number	Percentage
Piperacillin-tazobactam	32	91
Amikacin	27	77
Gentamicin	24	68.5
Ciprofloxacin	21	60
Cefotaxime	13	37
Amoxicillin-clavulanic acid	13	37
Cefazolin	2	5

The rates of complications such as wound infection, intra-abdominal abscess, and septicemia in the patients who had undergone ERCP and preoperative drainage were significantly higher than in those who had undergone ERCP and biliary drainage. Other complications including pancreatic fistula, hemorrhage, and pulmonary complications were not significantly different in both groups, but delayed gastric emptying was found in the patients with biliary drainage (Table 4).

*Escherichia coli*, *Klebsiella* were commonly seen organisms. In stented patients *Pseudomonas* were isolated. About 91% of the isolates were sensitive to piperacillin-tazobactam, followed by amikacin, gentamicin, and ciprofloxacin. Only 6% of the organisms were sensitive to cefazolin (Table 5 and 6).

### Discussion

In our study, we did not find an association of bile infection with preoperative comorbid illness, biochemical parameters, or pathological type of malignancy as reported elsewhere.<sup>[3]</sup> It was reported that bile infection was associated with pathological type,<sup>[2, 8]</sup> age,<sup>[5]</sup> preoperative levels of serum bilirubin and albumin,<sup>[5]</sup> and coronary artery disease.<sup>[8]</sup> In the present study, bile infection was not significantly associated with pathologic types, because of few patients with ampullary carcinomas undergoing ERCP for diagnosis/drainage. During the operation, operative time and blood loss were not affected by bile infection. Postoperative mortality was not influenced by

bile infection.<sup>[2, 3, 5, 8]</sup> One study reported<sup>[4]</sup> positive intraoperative bile culture was related to operative mortality. The rate of infectious complications was significantly increased in the positive bile culture group,<sup>[2, 4, 6, 8]</sup> but few studies showed this relation insignificant.<sup>[1, 5]</sup> The specific complications of pancreaticoduodenectomy included pancreatic fistula, hemorrhage, and delayed gastric emptying, the rates of these complications were not increased by bile infection.<sup>[2, 3-8]</sup>

The sensitivity of organisms may underscore the need for routine bile culture as most of them are resistant to the commonly used antibiotics. Before a culture, perioperative antibiotic therapy must be dependent on the sensitivity of antibiotics.

In our study, preoperative biliary drainage was significantly associated with bile infection, which increased the rates of overall complications, infective complications, and renal insufficiency. There was no increase in the incidence of pancreatic fistula, hemorrhage, or delayed gastric emptying, but ERCP and biliary stenting contribute to delayed gastric emptying. In view of the high incidence of complications associated with infected bile, it is thus recommended to avoid bile spillage, take a routine intra-operative bile culture in all patients undergoing pancreaticoduodenectomy, preoperative antibiotic prophylaxis, and peri-operative antibiotic treatment depending on bile culture. Since biliary stenting is significantly associated with infected bile, it should be used only in strictly selected cases of cholangitis irresponsible to medical management.

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