IMPACT OF BACTIBILIA ON THE DEVELOPMENT OF POSTOPERATIVE SEPTIC COMPLICATIONS IN PATIENTS UNDERGOING PANCREATICODUODENECTOMY

Dissertation submitted to
The Tamil Nadu Dr. MGR Medical University
In partial fulfillment for the
Degree of M.S. Branch I General Surgery

CERTIFICATE

This is to certify that the dissertation titled ‘Impact of Bactibilia on the Development of Postoperative Septic Complications in Patients Undergoing Pancreatico duodenectomy’ is the bonafide work of Dr. Chithra Sugathan Sheela , in fulfillment of the rules and regulations for the M.S., Branch 1, General Surgery Examination of The Tamil Nadu Dr. M.G.R. University, to be held in April, 2014.

Principal

Dr. Alfred J. Daniel,
Professor,
Department of Orthopaedics,
Christian Medical College,
Vellore.

Head of the Department

Dr. Benjamin Perakath,
Professor and Head,
Division of General Surgery, Christian Medical College,
Vellore.

Guide

Dr. V Sitaram
Professor and Head
Department of HPB Surgery,
Christian Medical College,
Vellore.

ACKNOWLEDGEMENTS

It is with immense gratitude that I acknowledge the support and help of those with whom this work was possible.

I thank the Almighty God for his grace, guidance and strength.

I owe my sincere gratitude to Dr. V Sitaram, my guide for his help and encouragement in bringing this to completion.

I thank Dr. Benjamin Perakath, Head of the Division of General Surgery, for his help and advice.

I thank my statistician Mrs. Grace Rebekah for her help in analysis.

I would like to express my gratitude to all my teachers and patients in CMC, Vellore for making this study and this course a reality

turnitin

Your digital receipt

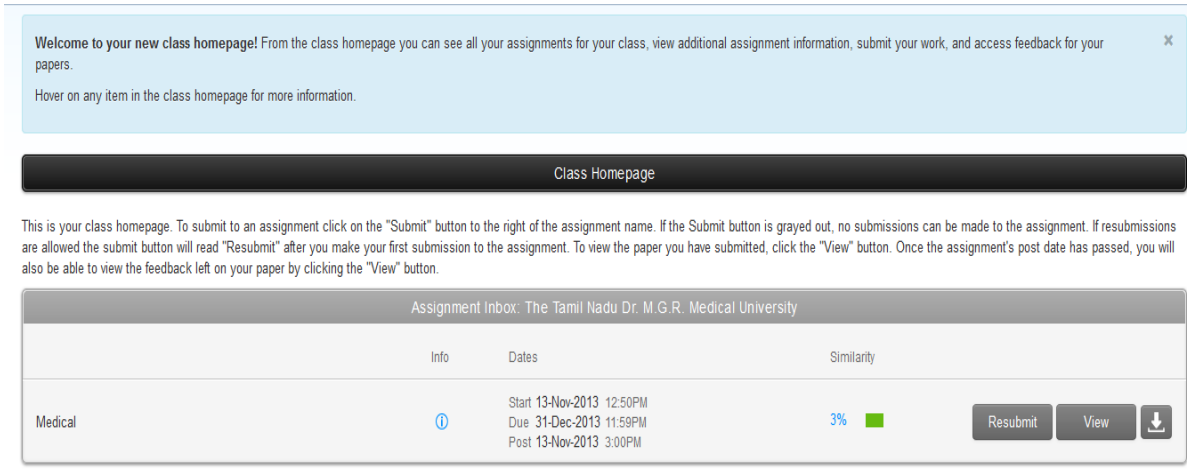
This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

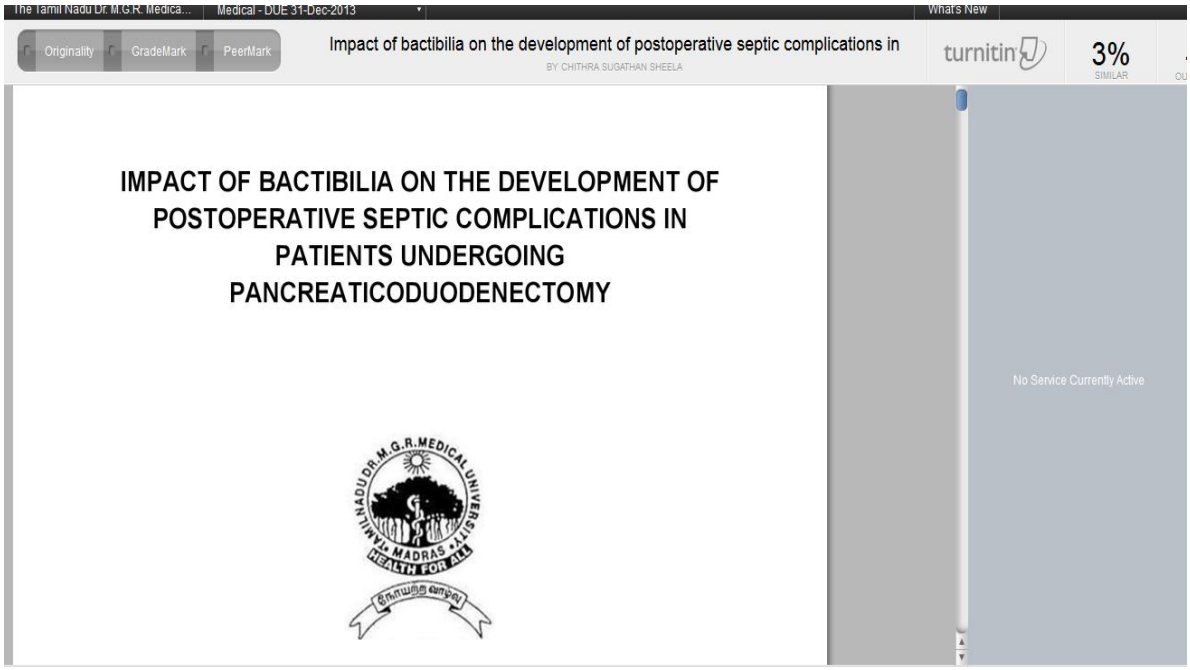
Paper ID	385255156
Paper title	Impact of bactibilia on the development of postoperative septic complications in patients undergoing pancreaticoduodenectomy
Assignment title	Medical
Author	Chithra Sugathan Sheela
E-mail	kannan12@hotmail.com
Submission time	19-Dec-2013 07:45PM
Total words	5771

First 100 words of your submission

IMPACT OF BACTIBILIA ON THE DEVELOPMENT OF POSTOPERATIVE SEPTIC COMPLICATIONS IN PATIENTS UNDERGOING PANCREATICODUODENECTOMY Dissertation submitted to The Tamil Nadu Dr. MGR Medical University In partial fulfillment for the Degree of M.S. Branch I General Surgery 1 CERTIFICATE This is to certify that the dissertation titled 'Impact of Bactibilia on the Development of Postoperative Septic Complications in Patients Undergoing Pancreatico duodenectomy' is the bonafide work of Dr. Chithra Sugathan Sheela , in fulfillment of the rules and regulations for the M.S., Branch 1, General Surgery Examination of The Tamil Nadu Dr. M.G.R. University, to be held in April, 2014. Principal Dr. Alfred J....

Plagiarism check





IRB Approval letter

Office of the Vice Principal (Research)

Christian Medical College
Vellore 632 002

Ref: 11/2011

February 2, 2012

The Treasurer
C.M.C.

Dear Mr. Denzil,

Sub: **FLUID Research grant project NEW PROPOSAL:**
Impact of bactibilia on the development of postoperative septic complications in patients undergoing pancreaticoduodenectomy
Dr. Chithra Sugathan Sheela (Emp. No. 20779), PG Registrar, General Surgery, Dr. John C Muthusami, General Surgery, Dr. Frederick L Vyas, Hepatopancreatobiliary Surgery, Dr. V. Sitaram, Surgery

Ref: IRB Min. No.7710 dated 12.12.2011

The Institutional Review Board at its meeting held on December 12, 2011vide Min. No 7710 accepted the project for 1 year at a total sanction of ₹ 2000/- (Rupees Two thousand only). Kindly arrange to transfer the sanctioned amount to a separate account to be operated by Dr. Chithra Sugathan Sheela and John C Muthusami.

Thank you.

Yours sincerely,

Dr.Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Chithra Sugathan Sheela, PG Registrar, Department of General Surgery, CMC
Dr. John C Muthusami, Professor , Department of General Surgery,CMC
File

Table of contents

1. Aims and objectives 5
2. Abstract 7
3. Literature review 11
4. Materials and methods 32
5. Results 52
6. Discussion 63
7. Conclusions 78
8. Limitations 80

Bibliography

Annexure

AIMS AND OBJECTIVES

1. To study the prevalence of positive bile cultures in patients undergoing pancreaticoduodenectomy

2. To assess if the organisms isolated from bile were sensitive to the commonly used intra-operative antibiotics and if a change in antibiotic practice was required

3. To compare the post-operative septic complications in bile culture positive and negative patients

4. To compare the organisms cultured from pus, intra-abdominal collections or blood in patients with complications, with the organisms grown from bile.

ABSTRACT

Background:

Bile is normally sterile, but stasis, presence of foreign body (stones, parasites, stents), predispose to bactibilia. Pancreaticoduodenectomy is the definitive procedure for cancer of the head of pancreas and periampullary cancers. It is a morbid procedure with high incidence of post-operative complications. Septic complications are the leading cause of post-operative morbidity. This study intends to determine any association between positive bile cultures and post-operative septic complications.

Methods:

Thirty consecutive patients undergoing pancreaticoduodenectomy in Christian Medical College, Vellore, were studied. Cefazolin, Amikacin and Metronidazole were given within 1 hour of skin incision in all patients. Cefazolin and Metronidazole were repeated at 4 hourly intervals during the operation. Patients, who had been stented previously or had any other biliary intervention, were given a single dose of Amikacin the day after the operation. This practice has since been discontinued. Intra-operatively, bile was sent was for culture, in a blood culture medium (BacT/ALERT FA Plus). Post-operatively, these patients were followed up for the

development of septic complications. Antibiotics were given if there was hemodynamic instability (attributed to sepsis) or organ dysfunction. Choice of antibiotics was dependent on bile culture report. Cultures from blood or intra-abdominal collections were compared with the intra-operative bile cultures. The overall development of complications in the post-operative period was compared between bile culture positive and negative patients.

Results

Bactibilia was present in 60% of the study population. Of these *Escherichia coli* (56.7%) and *Enterococci (*43.3%) were the most common organisms isolated. Sixty percent of patients developed septic complications post-operatively. Post-operative septic complications included wound infection, intra-abdominal collections and septicemia. Pre-operative biliary intervention did not have any statistically significant association with infected bile or septic complications. Pre-operative variables like history of cholangitis, intra-operative variables like hypotension, tachycardia or blood transfusion, did not have any association with post-operative septic complications. Four of the study patients succumbed to septic complications.

Conclusions

Pre-operative biliary intervention is not associated with increased incidence of infected bile. Bactibilia does not lead to infective complications post-operatively, in patients undergoing pancreaticoduodenectomy.

LITERATURE REVIEW

Bile is secreted from the hepatocytes and it travels along the bile canaliculi, hepatic ducts, and the common bile duct to reach the second part of duodenum through the duodenal papilla. Normally bile is sterile. This is maintained by defense mechanisms like normal flow, macrophages and secretory immunoglobulins, which do not allow bacterial growth. Presence of the sphincter of Oddi, which prevents bacterial migration from the duodenum, and secretory Immunoglobulin A in bile also protect against infection. Secretory immunoglobulin A, and mucus excreted by the biliary epithelium prevent microbial colonization, by functioning as anti adherence agents. (1)

In patients with biliary obstruction and bile stasis, there is bacterial overgrowth. (2)

Source of these bacteria is mainly ascending infection from the duodenum. In surgical or endoscopic sphincterotomy and with insertion of biliary stents, barrier mechanisms break down. Pathogenic bacteria enter the biliary system at high concentrations and take up residence on any foreign body. Hematogenous seeding from the portal circulation is also thought to play a role in this. Furthermore, the raised pressure in the biliary system

can cause reflux of bacteria into the blood stream, and increase the probability of septicemia. Gallstones, parasites and other foreign bodies act as a nidus for bacterial overgrowth.

Biliary obstruction raises the intra-biliary pressure. This adversely influences the defensive mechanisms such as the tight junctions, Kupffer cell function, bile flow, and secretory immunoglobulin A production. (3) This leads to changes in the bacterial flora, loss of mucosal integrity, and promotes bacterial overgrowth, portal bacteremia, endotoxemia and increased translocation of endotoxin to the liver, resulting in sepsis. Retrograde reflux from lymphatics into the blood stream, has also been demonstrated in causing systemic sepsis in patients with infected bile and an obstructed biliary system. (4)

Bile duct and sphincter pressure can be measured by endoscopic manometry. (5) Normal biliary ductal pressures usually range from 7 to 14 cm H_2O. Intraductal pressure can increase rapidly to 20-30 cm H_2O with either partial or complete obstruction. At biliary pressures greater than 15 cm H_2O, systemic reflux of radiolabelled biliary bacteria occurs. (6) This is referred to as cholangiovenous reflex. The reticuloendothelial system

within the liver normally kills most bacteria, with an estimated 10% entering the systemic circulation.

Bactibilia is a frequent accompaniment of obstruction in the biliary tract. Studies have shown that sterile bile cultures are found in normal subjects, but in obstructed systems, even in the absence of clinical signs of sepsis, cultures become positive. Patients with common bile duct stones have a higher probability of bile culture positivity than those with gallstones in the gallbladder or cystic duct. Bacteriological and morphological studies of 38 brown pigment common bile duct (CBD) stones were done in Prince of Wales Hospital Hong Kong. Positive cultures for bacteria were seen in 80.5%. Scanning electron microscopy showed the presence of bacteria in 84.2% of the CBD stones. (7)

Studies from San Francisco USA showed that bacteria were present in 68% of pigment stones and the pigment portions of 80% of composite stones. These gallstones were referred to as infectious stones. Bacteria were not found in cholesterol gallstones. Acute cholangitis was diagnosed in 52% of patients with infectious stones and only in 18% of patients with noninfectious stones. It was also demonstrated that infectious stones were

more commonly associated with history of biliary intervention, infected bile and emergency operative procedures. (8)

In a study of patients with brown pigment stones and paired bile cultures, 91% of bile and 99% of stone samples yielded positive cultures, with a total of 151 and 149 bacteria isolated from bile and stones respectively. (7) In 22 patients (33%), the bacteria isolated from the paired bile and stone samples were different. Even when the bacteria were similar, they often had different antibiotic sensitivities. This suggests that time was a factor in the evolution of bacterial flora in stones and bile cultures. (9) The choice of an antimicrobial regimen for biliary infection should take into account the expected antibiotic sensitivities of organisms colonizing bile, whether biliary obstruction or bacteremia is present, and the activity of the antibiotic in bile. (10)(11)

Most organisms isolated from infected bile were normal intestinal aerobes and anaerobes. Bacterial colonization of the bile may occur asymptomatically, may predispose to infection post-operatively, or may be associated with an attack of acute cholangitis, occurring secondary to obstruction. (10)

The organisms most often isolated from bile are the gram negative aerobes *Escherichia coli* and *Klebsiella pneumoniae*, gram-positive Enterococci, and the gram-negative anaerobe *Bacteriodes fragilis*. This has been established time and again by studies done on bile over the years. (11)

Patients admitted for cholangitis were studied over a six year period in Michigan and their bile cultures compared. (12) It was found that the most common isolates were *Enterococcus* > *Escherichia coli* > *Enterobacter* > *Klebsiella*. Sixty four percent of blood cultures and all but one of the bile cultures grew organisms. Seventy five percent of the organisms were resistant to the commonly used antibiotic. Inference from this data would be that antibiotic resistance is common among bacteria causing bile infection and so culture specific antibiotic should be instituted.

Obtaining bile samples in cholangitis was done based on the methods available and included direct aspiration of the gallbladder, by duodenal intubation or by T-tube drainage. (13) Optimal method to be adopted depends upon the clinical scenario and the most suitable methods available.

Patients with cholangitis, in sepsis require to be started on empirical antibiotics after drawing blood cultures, targeting the most commonly isolated organisms. Organisms isolated from blood culture have been found to correlate well with those isolated from bile cultures in patients with cholangitis. (11)(10) Anaerobic cover is reserved for patients who have undergone biliary enteric bypass, elderly and who are in florid sepsis or septic shock. (10)

Pancreaticoduodenectomy

Pancreaticoduodenectomy is a major operation, and is indicated in patients with malignancies of the head of pancreas, the duodenum or the distal common bile duct. It involves resection of the duodenum, with part of the stomach, the head of pancreas, the gall bladder and the common bile duct, along with removal of the regional lymph nodes, followed by reconstruction, which involves anastomosing the jejunum with the pancreatic duct, the hepatic duct and the remnant of the stomach. (14)

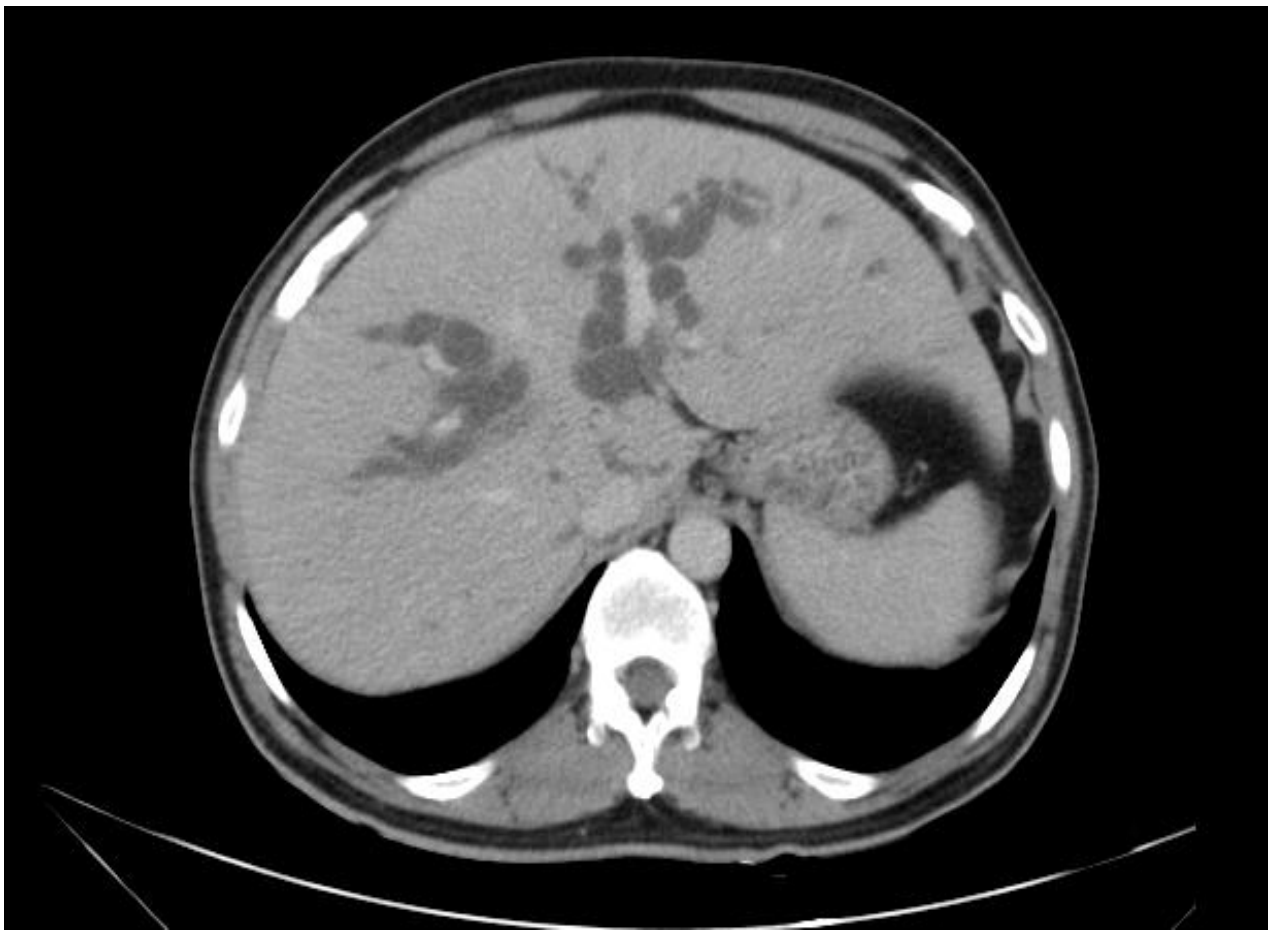


Figure 1 Contrast enhanced CT scan of the abdomen showing intrahepatic biliary radicle dilatation in a patient with periampullary carcinoma

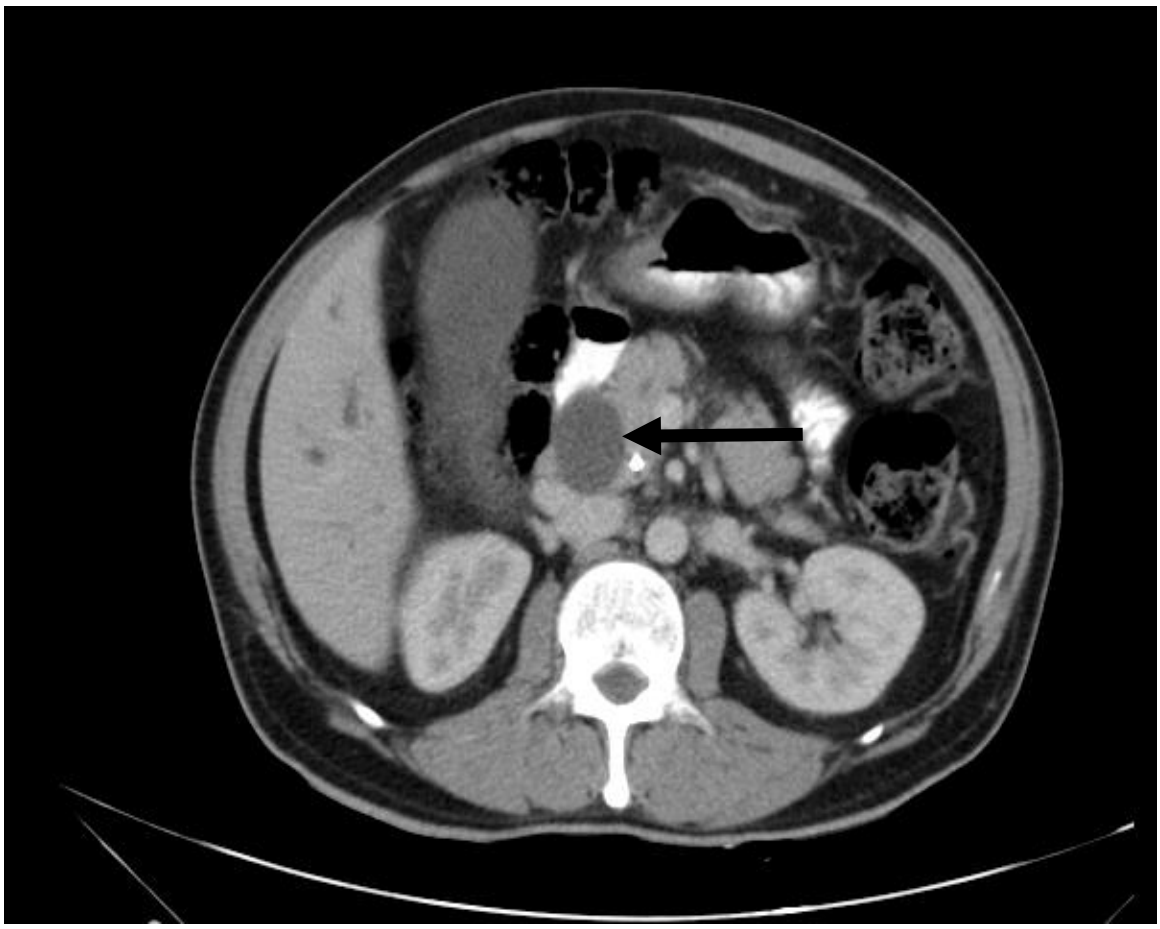


Figure 2 Another image from the same patient showing dilated common bile duct

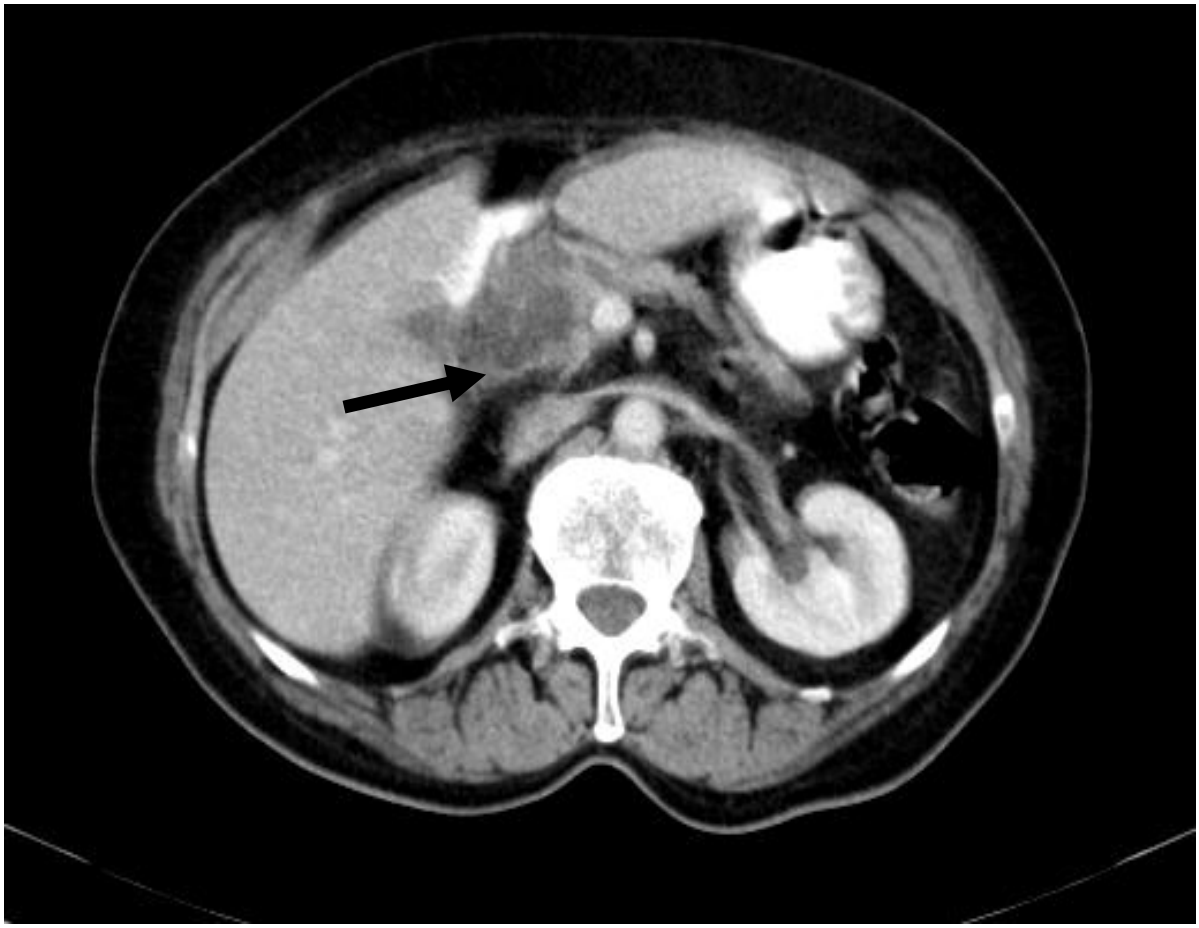


Figure 3 Contrast enhanced CT scan images showing cystic neoplasm in the region of the head of pancreas

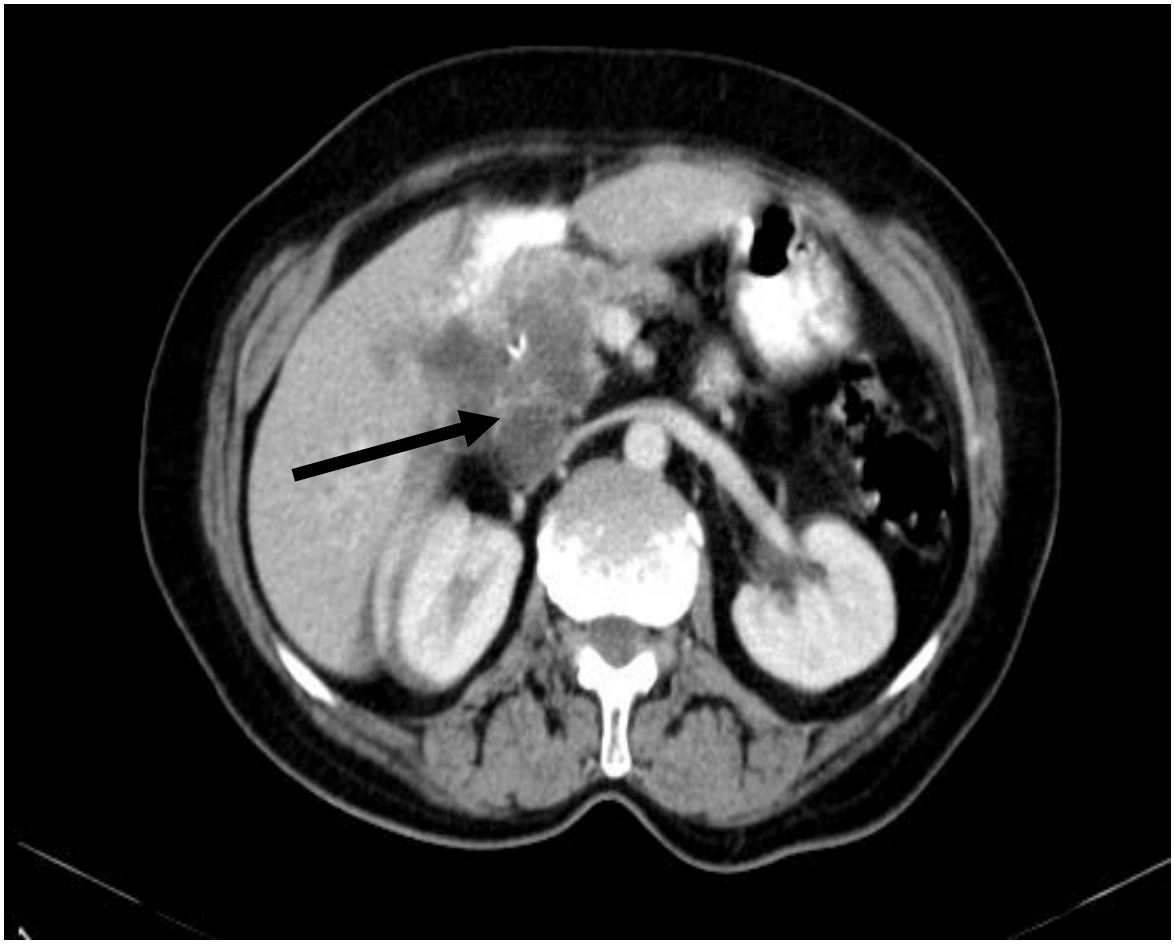


Figure 4 Contrast enhanced CT scan images showing cystic neoplasm in the region of the head and uncinate process of the pancreas

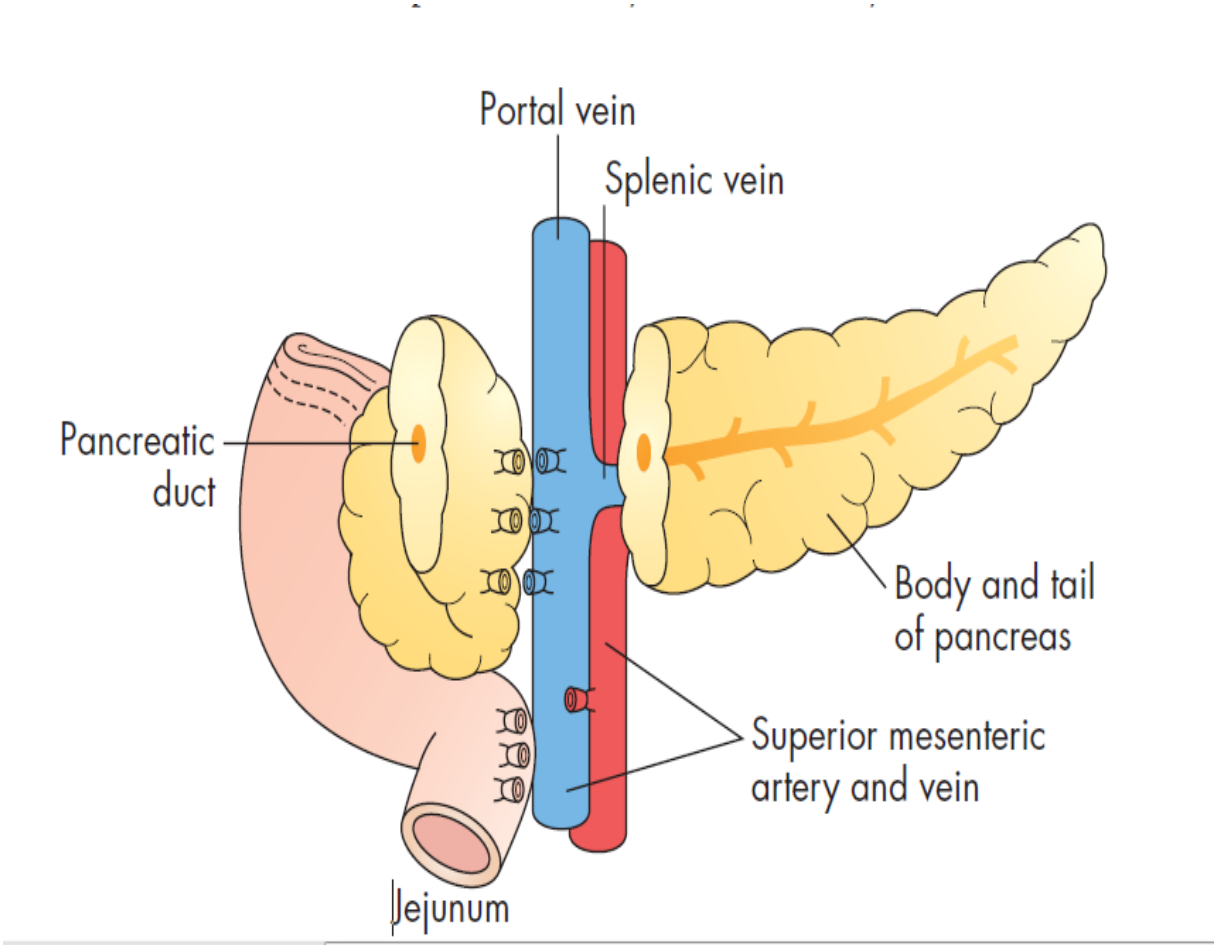


Figure 5 Pancreaticoduodenectomy specimen in situ

The procedure, when carried out at specialized centers, after careful patient selection and careful intra-operative and post-operative management, carries a mortality rate of only 2-3%. However post-operative morbidity is seen in 30-40% patients. (14) Most of the complications are septic in nature.

Post-operative complications encountered include pancreatic anastomotic failure, hemorrhage, and delayed gastric emptying. Septic complications like surgical site infection and septicemia are usually related to pancreatic anastomotic failure. Pancreatic anastomotic failure is diagnosed post-operatively by estimation of drain fluid amylase levels. Some centers however, do not recommend the routine placement of drains and practice post-operative drain placement under radiological guidance, should the need arise. (15) The various studies done in this field have established an association between infected bile and post-operative septic complications. (16) Some studies have also established that the same organism that produced bile infection has also produced bacteremia and wound infections. (17) Most of the organisms grown from the bile as well as the infected fluids were found to be resistant to the commonly used intra-operative antibiotic, hence raising the question of its efficacy. (18)

Bactibilia in pancreaticoduodenectomy

In a prospective study done by Sivaraj SM et al in Chennai (December 2008), in which 76 patients were studied, the prevalence of positive bile cultures was found to be 46%. Post-operative infective complications were found to be higher in patients with positive bile cultures. (16) Eight patients had intra-abdominal abscess,27 patients developed wound infection and bacteremia developed in 10 patients.

Occurrence of cholangitis pre-operatively has been found to correlate with post-operative septic complications (p=0.007). Contamination from ductal bile intra-operatively, was found to play an important role in the development of post-operative abdominal septic complications. Bacteria found in pre-operative ductal bile were also detected in infected intra-abdominal collections of 80% of patients with septic complications. Intra-operative contamination with infected bile was postulated to be the cause. (19)

Seventy nine patients, who underwent pancreaticoduodenectomy in a French center, were prospectively analyzed. (17) The post-operative course of 35 patients with infected bile (group B+) was compared with that of 44

patients with sterile bile (group B-). It was shown that 80% of patients with infected bile had undergone endoscopic biliary intervention pre-operatively. It was demonstrated that there was a statistically significant association between infected bile and post-operative infective complications. They also demonstrated that the organisms isolated from bile were also isolated from another culture 49% of the time. Other parameters like operating time, blood loss etc was comparable in both groups. This study explored the possibility of instituting specific antibiotic prophylaxis in patients who previously had biliary intervention, as a means to prevent post-operative sepsis.

Studies have shown that in patients, who have undergone pre-operative drainage procedures, bile cultures are polymicrobial, while in pancreaticoduodenectomy, *Escherichia coli* and *Enterococci* predominated. (13)

A study done in Memorial Sloan-Kettering Cancer Center, New York, established such a strong correlation between bactibilia and post-operative morbidity that they recommend that pre-operative stenting be altogether avoided in candidates for pancreaticoduodenectomy. (20)

According to Morris Stiff from Birmingham, pre-operative stent insertion prior to pancreaticoduodenectomy is associated with increased morbidity but not mortality and this is greatest for stents placed at Endoscopic Retrograde Cholangio Pancreaticogram (ERCP). (21)

A study from Lithuania showed that infected bile is found more often after pre-operative biliary interventions. Bile in these cases was more often found to be polymicrobial in nature. However, this did not translate to statistically significant post-operative septic complications. (22)

There have been studies from India that demonstrated that overall rates of septic complications following biliary surgery were low. Association between infected bile and post-operative septic complications could not be established. The inference was that judicious antibiotic use and good surgical technique could bring down post-operative complication rates markedly. However this was based on observations in patients undergoing cholecystectomy for gallstone disease. Extrapolating this to include all biliary tract operations would be misleading. (23)

A retrospective analysis of 228 patients who underwent pancreaticoduodenectomy in Louisville Kentucky (24), revealed no

statistically significant association between pre-operative biliary intervention and positive bile cultures or overall complications.

A study done at The Johns Hopkins Medical Institutions, Baltimore in 2000, claimed that pre-operative biliary stenting had an association only with post-operative wound infections and pancreatic fistula, both of which did not directly increase mortality rates. There is an increase in the rate of pancreatic fistula formation, possibly as a result of pancreatic inflammation related to the stenting procedure. Stenting also increases the rate of wound infection, possibly secondary to contaminated bile after the intervention. The conclusion being that pre-operative biliary stenting is safe but should be used selectively because of the associated risks. (25) Intra-operative bile cultures can be used to guide post-operative antibiotic treatment, if the need arises. (24)

Data from Indianapolis show that pre-operative biliary stenting increases the incidence of bactibilia, bacteremia, and wound infection rates but does not increase morbidity, mortality, or length of hospital stay. (26)

The impact of pre-operative biliary interventions in post-operative morbidity and mortality is controversial. It is uniformly accepted that they

cause positive bile cultures. It is not clear if this leads to an increase in morbidity and mortality.

With modern imaging techniques, it has become possible to manage post-operative intra-abdominal complications conservatively, with drainage procedures, thus bringing down overall mortality rates. (27)

Intra-operative tachycardia, blood loss and hypotension

Presence of systemic inflammatory response syndrome (SIRS) intra-operatively is found to correlate with poor surgical outcomes. (28) This is aggravated by intra-operative blood loss necessitating blood transfusion. Transfusion associated immunomodulation leads to altered immune response in the form of increased humoral immune response and downregulation of cellular immunity. This in turn leads to greater susceptibility to infections, longer hospital stay and post-operative mortality. (29)

Peri-operative tachycardia, an absolute increase in heart rate and heart rate lability are independent predictors of both short- and long-term adverse outcomes in patients undergoing major non-cardiac surgery. (30)

Clavien Dindo classification of post-operative complications

Post-operative complications were graded according to the Clavien Dindo classification. It is based on the treatment used to manage the post-operative complication. It was first introduced in 1992 to standardize the classification of surgical complications, to enable better interpretation of surgical outcome data.

A critical evaluation of the classification system found it to be valid and applicable worldwide. (31)

Grade Definitions

Grade I Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions

Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections, opened at the bedside.

Grade II Requiring pharmacological treatment with drugs other than such allowed for grade I complications

Blood transfusions and total parenteral nutrition are also included

Grade III Requiring surgical, endoscopic or radiological intervention

Grade IIIa Intervention not under general anesthesia

Grade IIIb Intervention under general anesthesia

Grade IV Life-threatening complication (including CNS complications)* requiring IC/ICU management

Grade IVa Single organ dysfunction (including dialysis)

Grade IVb Multi-organ dysfunction

Grade V Death of a patient

Suffix‘d’: If the patient suffers from a complication at the time of discharge, the suffix‘d’ (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

* Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks.

(CNS, central nervous system; IC, intermediate care; ICU, intensive care unit)

MATERIALS AND METHODS

Type of study: This is a cross sectional study.

Duration: January 2012-June 2013

Inclusion criteria: All patients undergoing pancreaticoduodenectomy at Christian Medical College, Vellore, a tertiary care centre in South India. The prevalence of bactibilia among patients undergoing pancreaticoduodenectomy was around 40% as estimated by studies done previously in this area. This value was used as the estimated proportion to calculate the sample size.

Formula

$$n = \frac{Z^{2}_{1-\alpha/2}\, p\,(1-p)}{d^{2}}$$

Where,

p : Expected proportion

d : Absolute precision

1- $\alpha/2$: Desired Confidence level

Using this formula and applying the numbers,

Expected proportion: 0.43

Precision: 15%

Desired confidence level (1-alpha): 95%

The required sample size was calculated as 43

Exclusion criteria: Nil

Methodology:

Informed consent was taken from the patients admitted for pancreaticoduodenectomy. A printed proforma was filled in with pre-operative, intra-operative and post-operative details. Pre-operative variables studied include socio demographic parameters, serum bilirubin, diabetic status, history of fever with chills and any intervention done to relieve biliary obstruction like ERCP or stenting. Intra-operatively, samples of their bile was collected and sent for culture. This is a routine practice at our institution and bile sample is collected by the operating surgeon from the common hepatic duct and sent for culture in blood culture bottles.

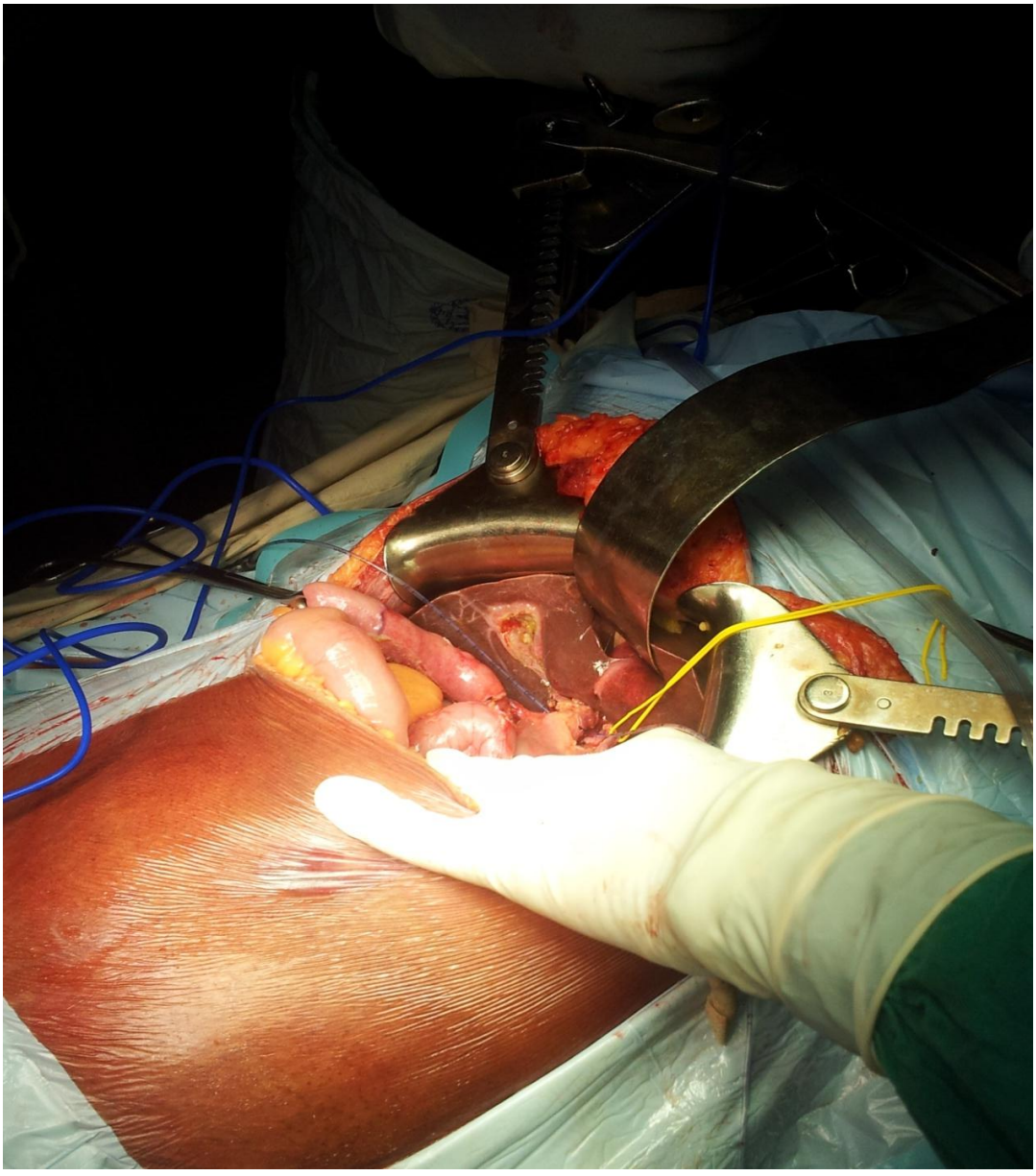


Figure 6 Yellow tape around the common bile duct

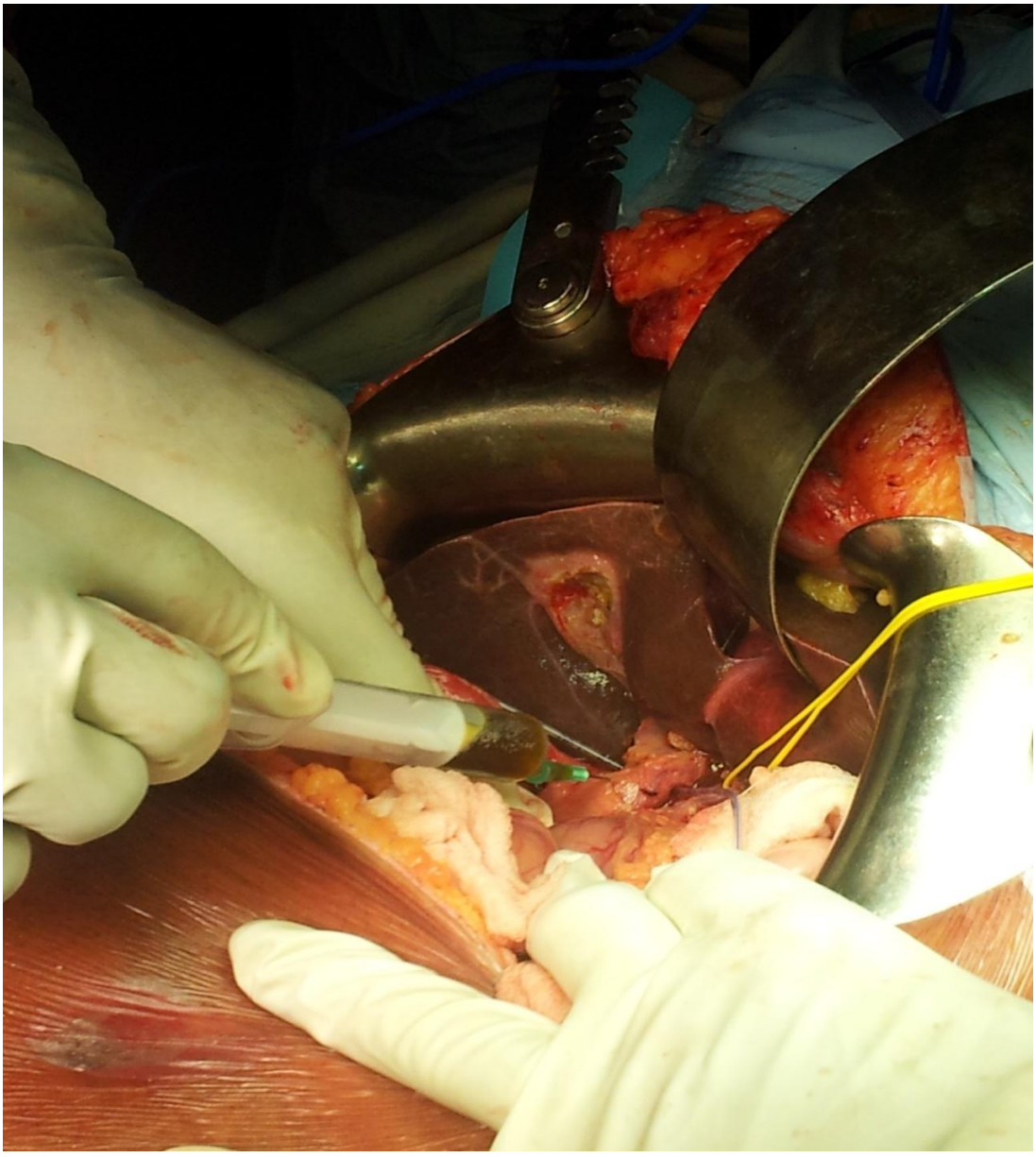


Figure 7 Aspirating bile from the common hepatic duct intra-operatively

Figure 8 Sterile vacuum sealed bottles containing nutrient medium, used for sending bile for culture

Figure 9 BacT/ALERT 3D machine used to detect growth of organisms in the nutrient medium

.

Figure 10 BacT/ALERT panels of machines, processing the samples

Figure 11 The colorimetric sensor in the machine detects the carbon dioxide gas produced in the culture medium, once every 10 minutes and indicates growth of organism

Figure 12 Blood culture bottles arranged in the wells within the BacT/ALERT 3D. Once growth is picked up, smears are prepared and subcultures done.

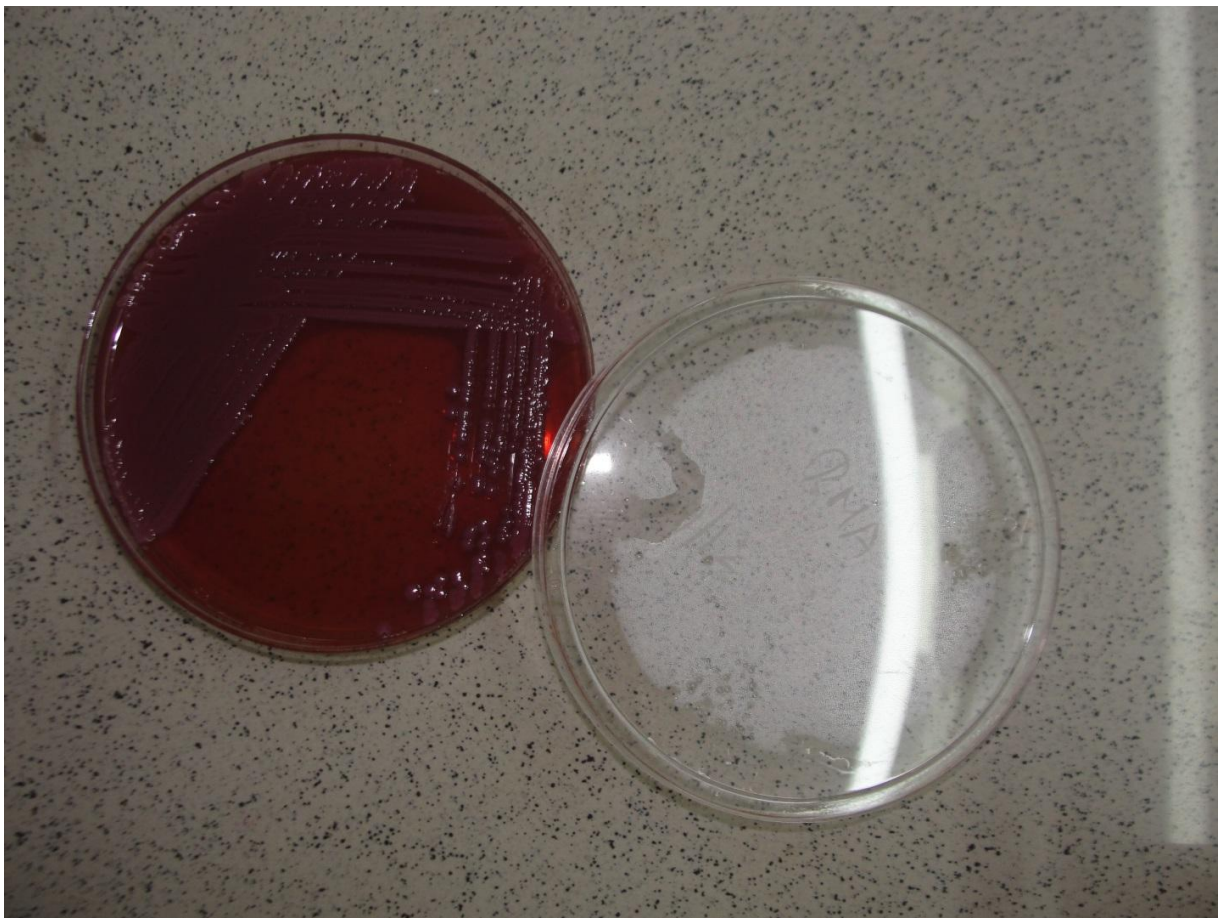


Figure 13 Gram negative bacilli (*Escherischia coli*) subcultured on Mac Conkey agar

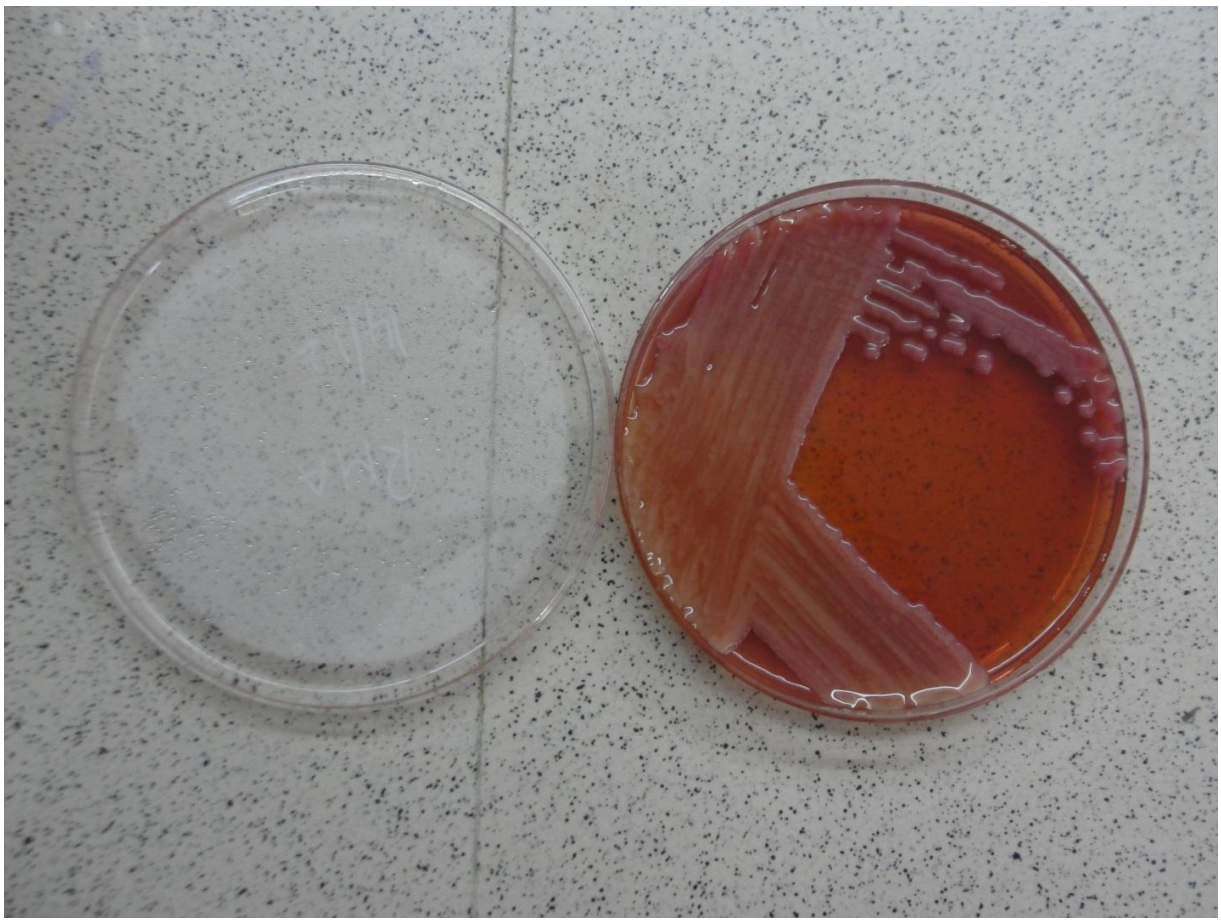


Figure 14 Mucoid colonies of *Klebsiella* species on MacConkey agar

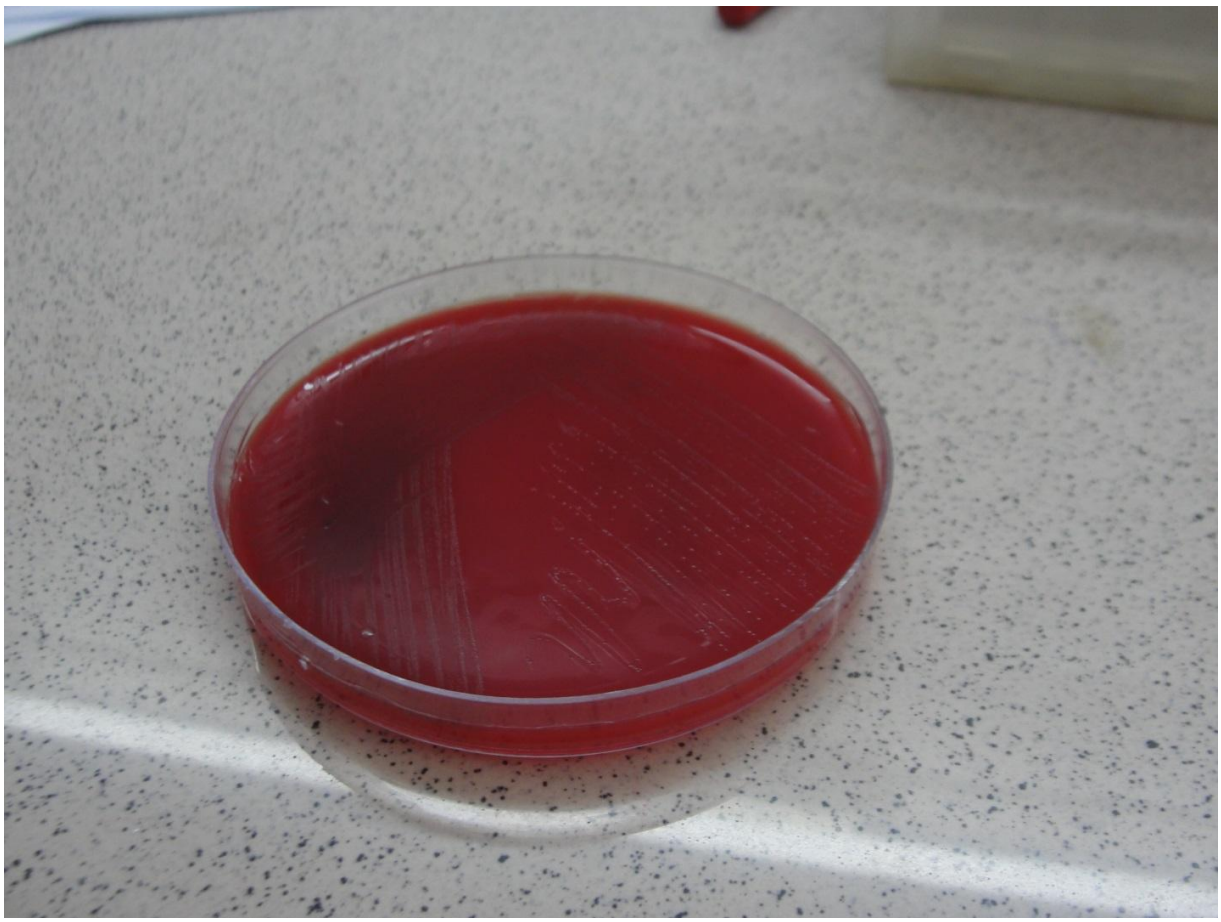


Figure 15 Gram positive organism subcultured on blood agar. Fine colonies of *Enterococci.*

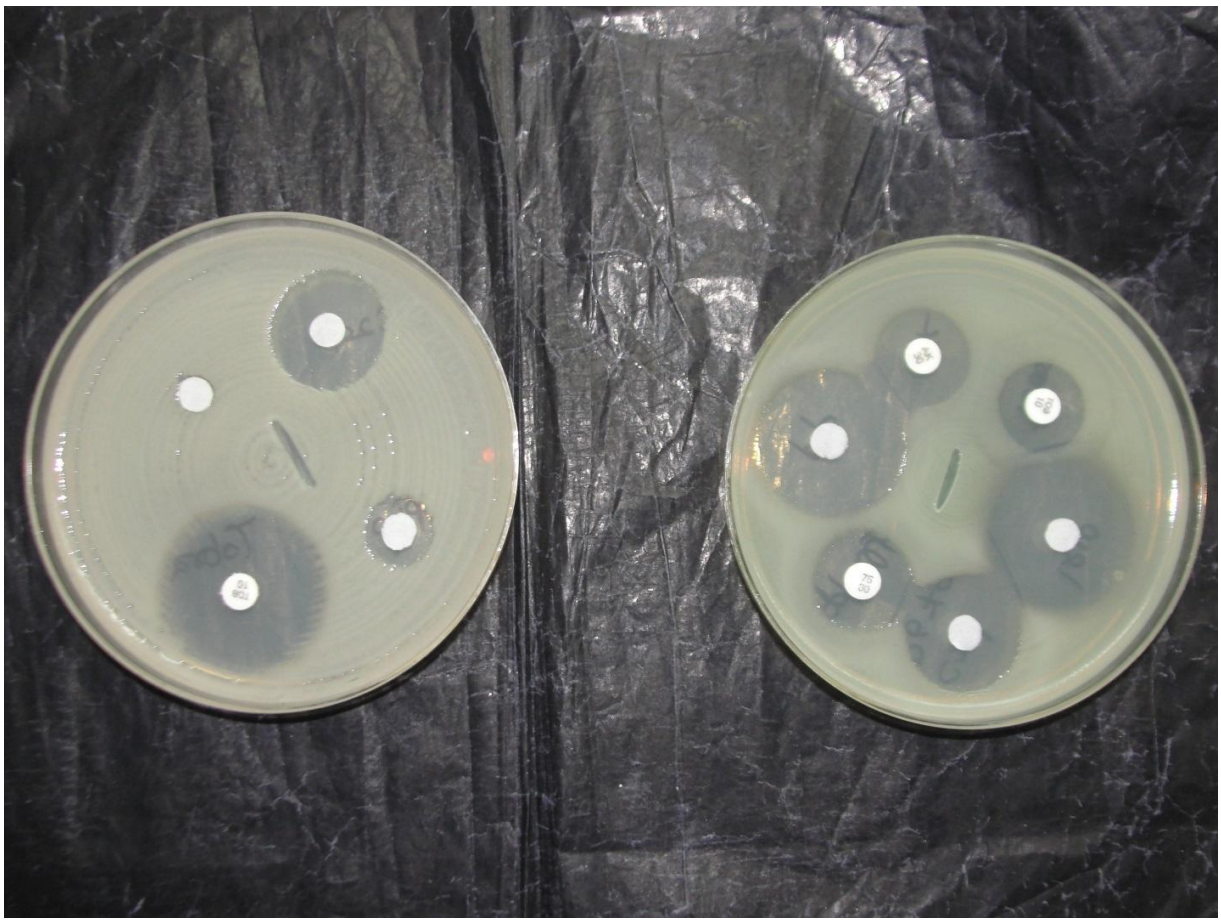


Figure 16 Antibiotic sensitivity testing done in Gram negative organisms.

Clear area around the antibiotic disc is indicative of antibiotic susceptibility

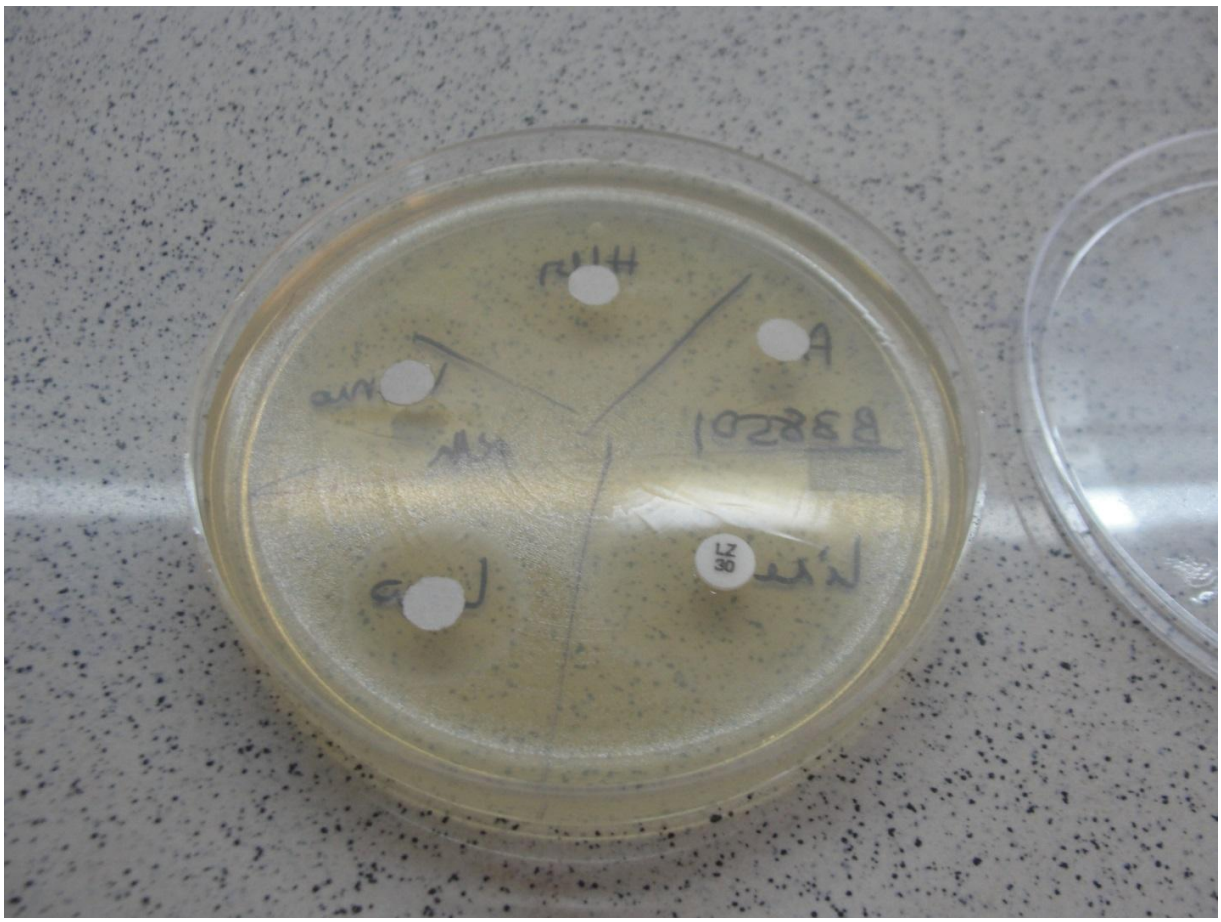


Figure 17 Antibiotic sensitivity testing done in Gram positive organisms.

Intra-operative blood transfusion, persistent tachycardia, intra-operative hypotension or fever and any change or escalation of antibiotic in the immediate post-operative period were recorded as intra-operative variables to be analyzed. During the post-operative period, they were monitored for the development of septic complications like wound infection, bacteremia, intra-abdominal abscesses, and pulmonary infection

Pus from wound infection or tissue sample from infected wound was used for culture. Intra-abdominal infected collections aspirated, either under radiological guidance or samples taken during reoperation were cultured. Sputum sample or endotracheal aspirates in intubated patients were cultured in case of pulmonary infections. Only documented positive cultures were considered as septic complications and the bacteria grown were compared with those grown from bile. Patients were followed up till discharge from hospital.

Data analysis: Data was analyzed using the SPSS 16 software.

Antibiotic policy:

All patients received Cefazolin, Amikacin and Metronidazole at induction. Cefazolin and Metronidazole were repeated every 4 hours intra-operatively. Patients, who had been stented previously or had undergone any other biliary intervention, were given a single dose of Amikacin the day after the operation. This practice has since been discontinued. In the presence of features of SIRS or sepsis, patients were empirically started on antibiotics, which were changed according to sensitivity patterns once the antibiogram became available. However, some patients received a full 7 day course of antibiotic in spite of negative cultures. This was based on clinical features as judged best by the treating team.

DEFINITIONS

Bactibilia: documented positive bile culture

SIRS: Systemic Inflammatory Response Syndrome

Two or more of the following

- Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F)
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) of less than 32mm Hg
- Abnormal white blood cell count (>12,000/µL or < 4,000/µL or >10% immature [band] forms)

Sepsis: Systemic Inflammatory Response Syndrome with source of infection. According to this study, only documented cultures are taken to mean sepsis.

Wound infection: Positive pus swab culture from wound

Pneumonia: Positive sputum culture or endotracheal aspirate culture in intubated patients

Bacteremia*:* Positive blood culture

Intra-abdominal abscess: Positive cultures of intra-abdominal fluids

Post-operative complications: The Clavien Dindo grading was used to quantify post-operative complications

RESULTS

Study period: January 2012 to June 2013

Number of patients: 30 consecutive patients who underwent pancreaticoduodenectomy. The sample size calculated at the start of the study was 43. The study is continuing in the unit to reach the calculated sample size.

Demographic characteristics:

Distribution of age:

Mean age = 48.97 years (range 24 – 72)

Table 1

Age(years)	Number
<30	2
30-50	13
>50	15

Sex ratio:

Male: Female= 17:13

Pre-operative variables

Number of patients with history of fever with chills = 8

Table 2 Association between fever with chills and bactibilia

History of fever with chills	Bactibilia		p value
	Present	Absent	
Present	8	0	0.010
Absent	10	12	

Number of patients who had pre-operative biliary intervention

ERCP and stenting = 11

Percutaneous Trans-hepatic Biliary Drainage (PTBD) = 1

Intra-operative variables

Number of patients who received blood transfusion: 8

Number of patients who developed persistent tachycardia: 4

Number of patients who developed persistent hypotension: 7

Intra-operative blood transfusion, persistent tachycardia or hypotension did not lead to greater incidence of post-operative septic complications.

Post-operative characteristics

Number of patients who were started on antibiotics in the immediate post-operative period: 14

(Indications for starting antibiotic in the immediate post-operative period):

Persistent, post-operative tachycardia: 7

Persistent high grade fever: 3

Persistent post-operative hypotension, requiring inotropes: 2

Persistently elevated serum lactates on arterial blood gas: 1

Reoperation in the immediate post-operative period due to bleeding: 1

Number of patients who received antibiotics later during the post-operative period: 9

Number of patients who developed septic complications

Wound infection: 2 (6.7%)

Bacteremia: 7 (23.3%)

Pulmonary infection: 4 (13.3%)

Infected intra-abdominal collections: 5 (16.7%)

Fungal septicemia: 1 (3.3%)

Death: 4 (13.3%)

Pancreatic anastomotic failure (PAF)

Number of patients with elevated drain fluid amylase levels: 7 (PAF)

Number of patients whose intra-abdominal fluid amylase levels were elevated

Fluid drained radiologically: 0

Fluid drained at re-laparotomy: 0

(Three patients underwent re-laparotomy for intra-abdominal collections, none of which showed elevated amylase levels.)

Number of patients who received only antibiotics, for infected intra-abdominal collection: 10 (These were mostly inter loop collections or collections too small to be drained. It was unclear as to whether these were truly related to PAF.)

Number of patients with copious wound discharge, secondary to intra-abdominal collection: 2 (Wound discharge amylase level was not estimated, and so it is unclear as to whether this was related to PAF.)

Table 3: Association between PAF and post-operative septic complications

Septic complication	Pancreatic anastomotic failure		p value
	Present	Absent	
Wound infection	0	2(8.7%)	1.000
Bacteremia	1(14.3%)	6(26.1%)	1.000
Pneumonia	1(14.3%)	3(13.0%)	1.000
Intra-abdominal collections	2(28.6%)	3(13.0%)	0.565

Post-operative morbidity grades

Table 4

Clavien grade	Number of patients	Percentage
1-2(minor)	22	36.65
3-4(major)	4	3.33
5(death)	4	13.33

Table 5 Association between post-operative morbidity and bile culture

Clavien grade	Bile culture		p value
	Positive	Negative	
1-2 (minor)	13(72.2%)	9(75%)	0.35
3-4 (major)	3(16.7%)	1(8.3%)	
5 (death)	2(11.1%)	2(16.7%)	

Table 6: Association between PAF and post-operative morbidity

Clavien grade	Pancreatic anastomotic failure		p value
	Present	Absent	
1-2 (minor)	5 (71.4%)	17 (73.9%)	1.000
3-4 (major)	2 (28.6%)	2 (87%)	
5 (death)	0	4 (17.4%)	

Biliary intervention

Table 7: Association between biliary intervention and bactibilia

Biliary intervention			
Yes		No	
Bile culture positive	Bile culture negative	Bile culture positive	Bile culture negative
9 (75%)	3 (25%)	9 (50%)	9 (50%)

p=0.62

Table 8: Association between biliary intervention and pancreatic anastomotic failure

Biliary intervention	Pancreatic anastomotic failure		p value
	Present	Absent	
Present	2 (16.7%)	10 (83.3%)	0.669
Absent	5 (27.8%)	13 (72.2%)	

Table 9: Association between pancreatic anastomotic failure and bactibilia

Pancreatic Anastomotic Failure(PAF)	Bactibilia		p value
	Present	Absent	
Present	4 (22.2%)	3 (25%)	1.000
Absent	14 (77.8)	9 (75%)	

Bacteriological profile of bile cultures

Table 10: Organisms isolated from bile cultures

Bacteria	Number	Percentage
E. coli	17	56.7
Enterococcus	13	43.3
Klebsiella	10	33.3
Aeromonas	1	3.3
NFGNB*	2	6.7
Morganella morgagni	1	3.3

*NFGNB = Non fermenting gram negative bacilli

Polymicrobial bile cultures (more than two organisms): 16

Bile cultures that grew only single organism: 2

Table 11: Sensitivity of biliary tract organisms to commonly used intra-operative antibiotic (Amikacin)

Bacteria	Sensitivity to Amikacin			
	Sensitive	Percentage	Resistant	Percentage
E. coli	16	94	1	6
Klebsiella	10	90	1	10
Aeromonas	1	100	0	0
NFGNB*	1	50	1	50
Morganella morgagni	1	100	0	0

*NFGNB = Non fermenting gram negative bacilli

Number of organisms sensitive to Amikacin: 28 (90.3%)

Number of organisms resistant to Amikacin: 3 (9.6%)

Table 12: Association of intra-operative variables with bile culture

Variable	Bile culture		
	Positive	Negative	p value
Intra-operative tachycardia	4 (100%)	0	0.130
Intra-operative hypotension	4 (57.1%)	3 (42.9%)	1.000

Table 13: Association between septic complications and positive bile culture

Septic complications	Bile culture		p value
	Positive	Negative	
Wound infection	2 (11.1%)	0	0.503
Intra-abdominal collection	4 (22.2%)	1 (8.3%)	0.622
Bacteremia	4 (22.2%)	3 (25%)	1.000
Pneumonia	2 (11.1%)	2 (16.7%)	1.000

Table 14: Association between intra-operative hypotension and sepsis

Intra-operative hypotension	Post-operative sepsis		p value
	Present	Absent	
Yes	5 (71.4%)	2 (29.6%)	1.000
No	14 (60.9%)	9 (39.1%)	

Table 15: Association between intra-operative tachycardia and sepsis

Intra-operative tachycardia	Post-operative sepsis		p value
	Present	Absent	0.153
Yes	4 (100%)	0	
No	15 (57.7%)	11 (42.3%)	

Table 16: Association between intra-operative blood transfusion and sepsis

Intra-operative blood transfusion	Post-operative sepsis		p value
	Present	Absent	1.000
Yes	5 (62.5%)	3 (37.5%)	
No	14 (63.6%)	8 (36.4%)	

DISCUSSION

Thirty consecutive patients who underwent pancreaticoduodenectomy were included in the study. The mean age of the study population was 48.97 years (range 24 – 72 years). There were 17 males and 13 females in the study population. Periampullary malignancy risk increases with increasing age, and has a slight male preponderance according to literature.

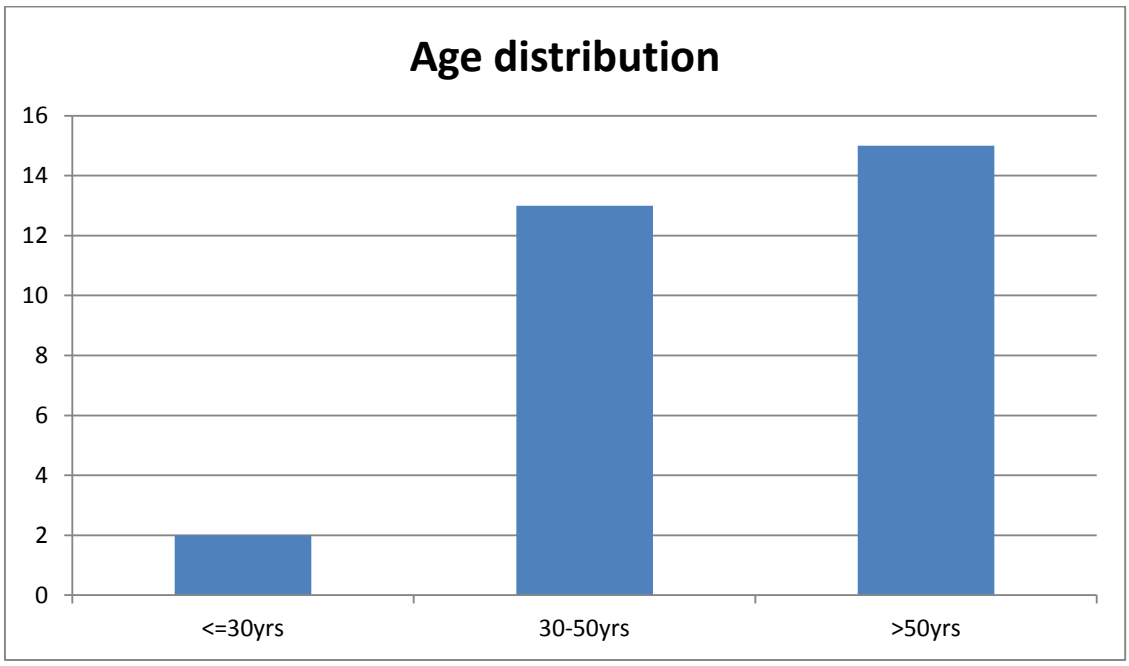


Figure18. Age distribution of study population

Of the 30 patients, 8 had history of fever with chills some time during the past, which was taken to mean an episode of cholangitis. All of these

patients had positive bile cultures, which was found to be statistically significant. Twelve patients (40%) had pre-operative biliary drainage procedures like biliary stenting and percutaneous trans-hepatic biliary drainage. (Figure 19)

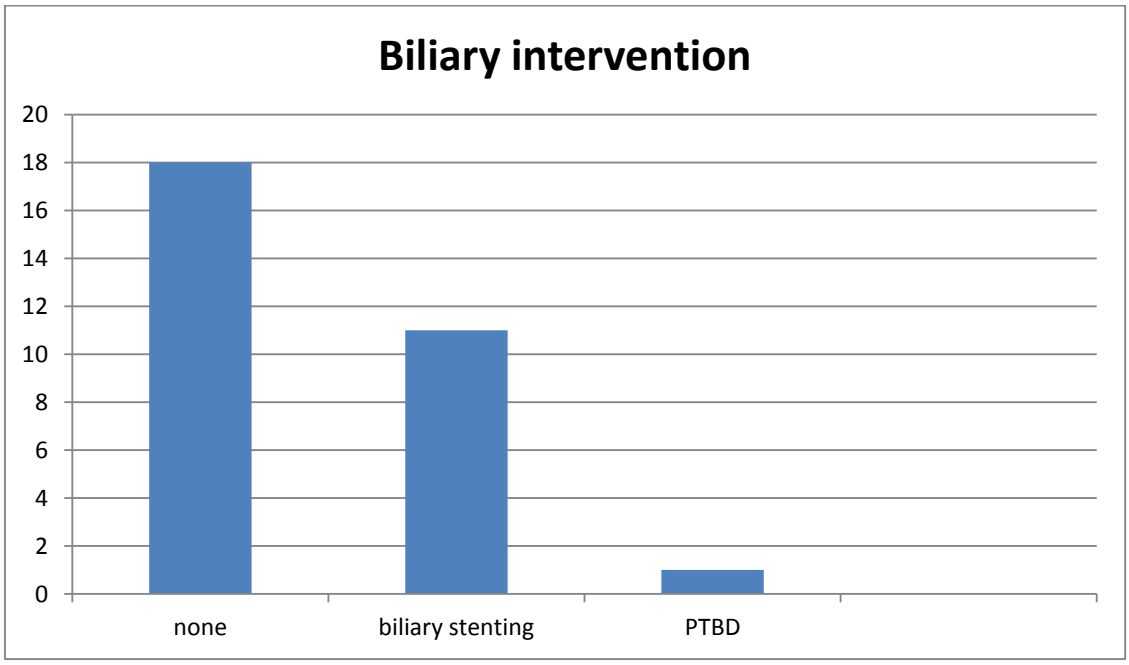


Figure 19 Distribution of biliary intervention in the study population

(PTBD = percutaneous trans-hepatic biliary drainage)

Intra-operative variables that were looked into included intra-operative blood transfusion, intra-operative tachycardia, and intra-operative

hypotension. Eight patients required intra-operative blood transfusion. None of these were predictors of having infected bile or increased risk of post-operative septic complications.

Eighteen (60%) of the study population had positive bile cultures. Prevalence of bactibilia in various international studies has been in the range of 44%. (17) Studies done in Indian population have reported prevalence of 46%. (16)

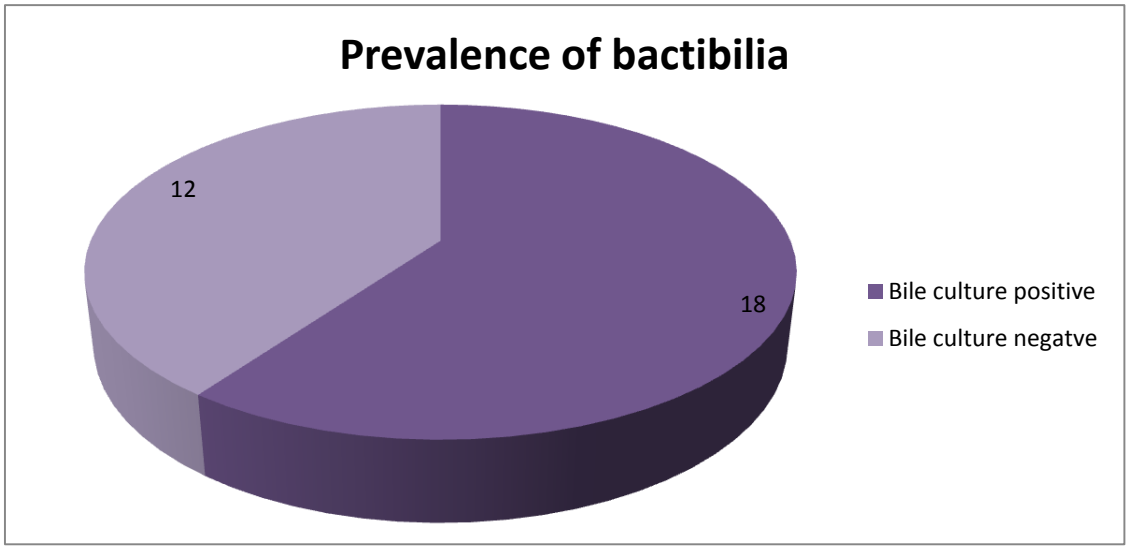


Figure 20 Distribution of positive bile cultures

The most common indication for pancreaticoduodenectomy in literature is adenocarcinoma of the pancreas. Of all the resected specimens, 40-60% are adenocarcinoma of the head of pancreas, 10-20% adenocarcinoma of

the ampulla of Vater, 10% distal cholangiocarcinoma and 10-20% adenocarcinoma of the duodenum. Ten to twenty percent of specimens reveal benign disease. Among the 30 patients who underwent pancreaticoduodenectomy in our study, the most common diagnosis was carcinoma of the ampulla of Vater, followed by carcinoma head of pancreas. Five patients had benign disease (Figure 21). In our practice carcinoma periampullary region is more than carcinoma head of pancreas because the former presents earlier as bile duct obstruction occurs earlier.

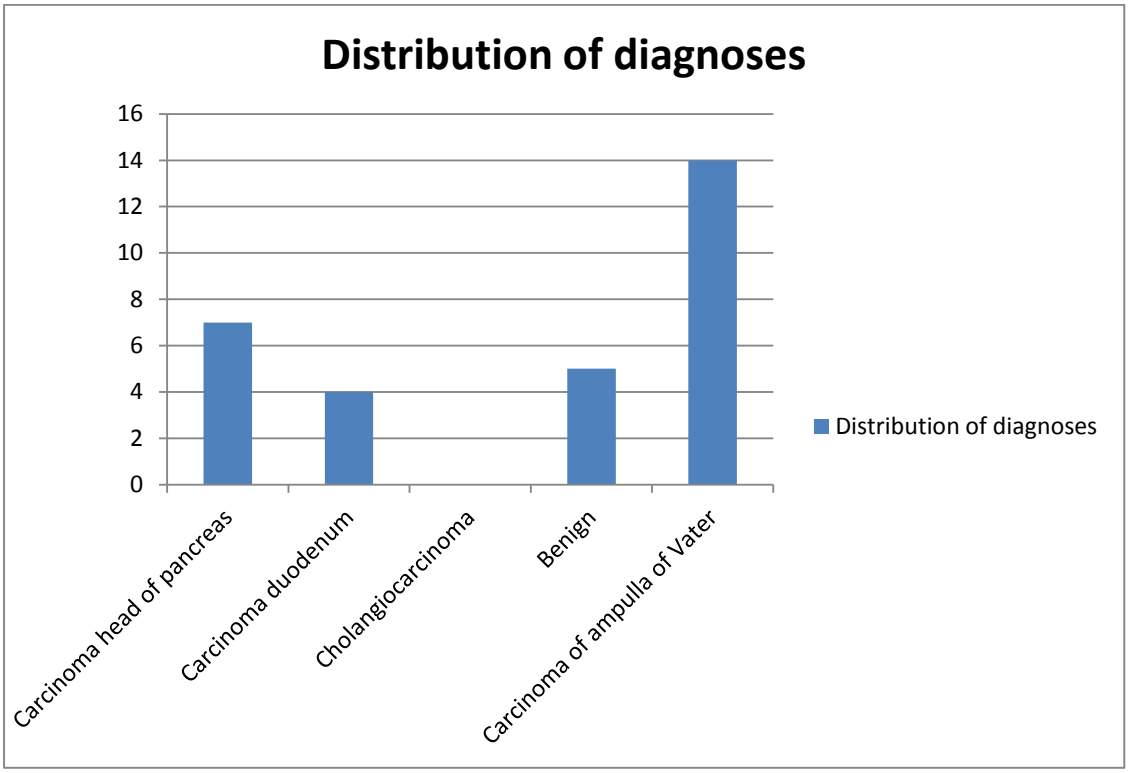


Figure 21 Distribution of diagnoses

Post-operative septic complications

Of the morbidities associated with pancreaticoduodenectomy, septic complications are commonest. Western studies have reported incidence of 17% (32), while Indian studies have shown septic complications to occur 9-32% (33) of the time. The commonest reported septic complications being wound infections and intra-abdominal infected collections.

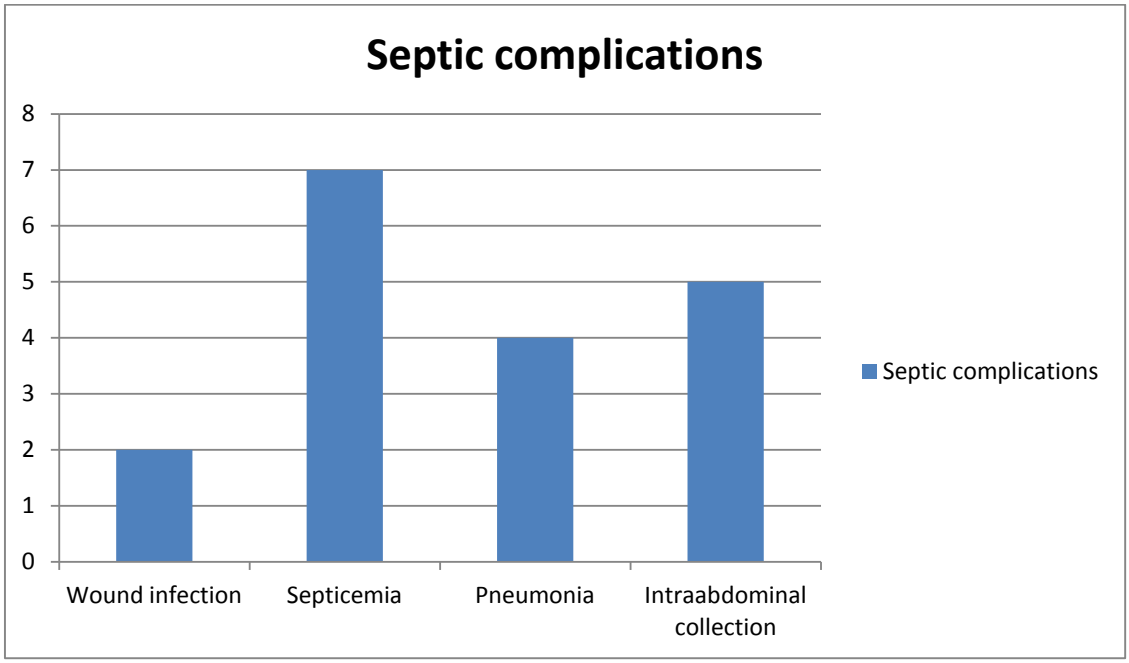


Figure 22 Distribution of septic complications

Of the septic post-operative complications, there were 7 patients (23.3%) who developed septicemia, which was by definition, a documented positive

blood culture. This was followed by pneumonia in 4 patients (13.3%). However these patients were on a ventilator at the time of diagnosis and likely to have had ventilator associated pneumonia. Five patients (16.7%) developed intra-abdominal infected collections, which were drained radiologically in 2 patients, while 3 underwent reoperation. Wound infection occurred in only 2 (6.7%) of the study population.

One patient developed fungal septicemia and 4 patients died of the septic complications.

Pancreatic anastomotic failure (PAF) is defined as drain fluid amylase levels in excess of three times the upper limit of serum amylase value. Seven patients (23%) developed pancreatic anastomotic failure. According to Western data, incidence of this complication is between 4-10% (25), while Indian data reports 26%. (33)

Post-operative morbidity was quantified by the Clavien Dindo system. Of the study population that developed complications post-operatively, thirteen patients required medical management, three required interventions, one patient developed multi-organ dysfunction but survived, and four patients died (Figure 23). The mortality rate in the study

population was thus 13%. Review of pancreaticoduodenectomy procedures done at Johns Hopkins hospital has revealed that grade I complications occurred in 10.0% patients, grade II in 30% patients, grade IIIa in 10.5% patients, and grade IIIb in 3.0%. Grade IVa and IVb complications were found in 2.5% and 0.5% of the patients, respectively. The grade V complication rate (mortality) was 2.0%. Most of the deaths were caused by multi-organ dysfunction caused by sepsis. Mortality rate of below 5% is acceptable in high volume centres. (34) Mortality rates in Indian centres range between 2 and 5%. (33)

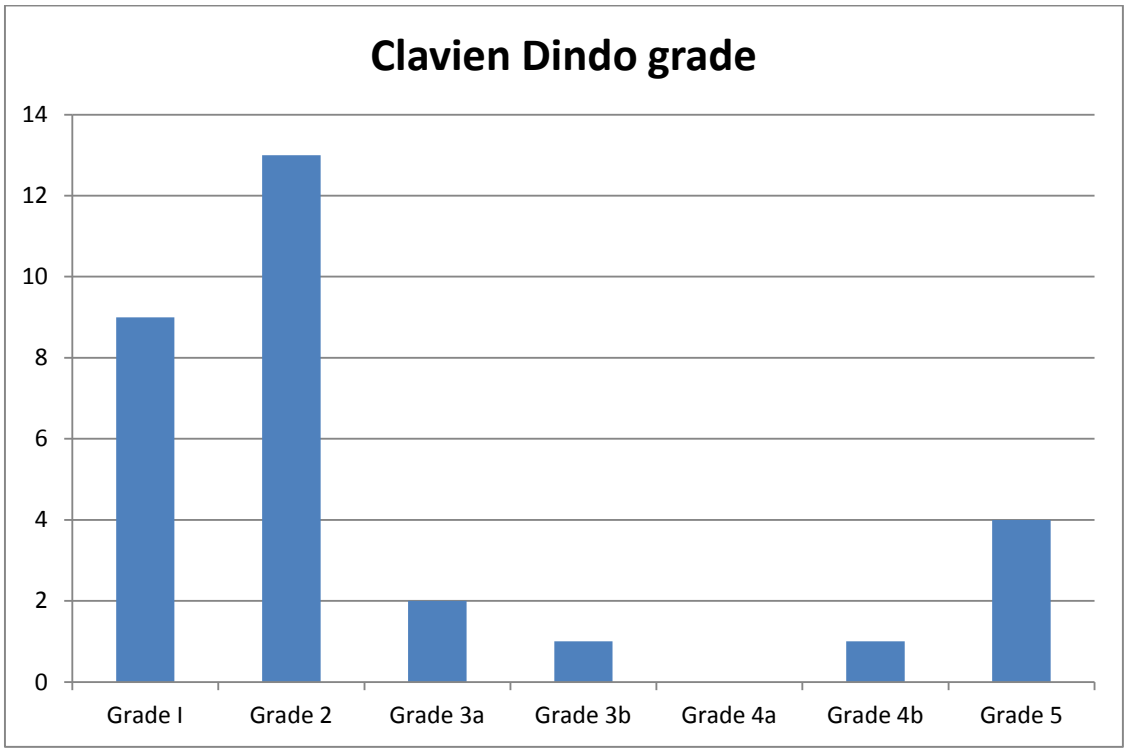


Figure 23 Distribution of complications

Biliary intervention and bactibilia

In the study population, of the 12 patients who had biliary intervention, 9 patients (75%) had positive bile cultures and of the 18 patients who did not have any biliary intervention, 9 patients (50%) had positive bile cultures. This was not statistically significant (p=0.712), (Figure 24). According to Howard TJ et al, pre-operative biliary stenting predisposes to infected bile. (26) This finding was also mirrored in a similar study carried out in India. (16)

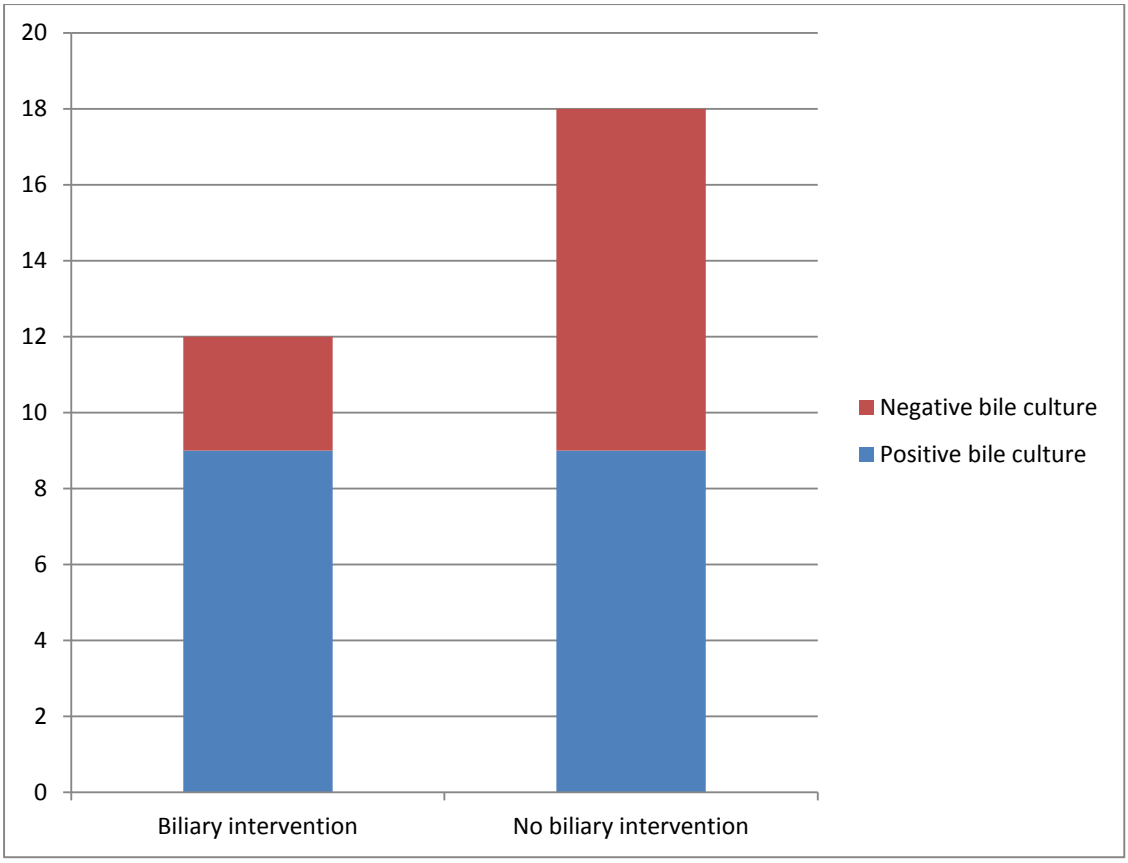


Figure 24 Comparison of biliary intervention and bactibilia

Biliary intervention and pancreatic anastomotic failure

Studies have shown that pre-operative biliary intervention predisposes to pancreatic anastomotic failure probably as a result of the inflammation caused by the intervention. (25) Of the 12 patients who underwent biliary drainage procedures, only 2 (16.7%) developed PAF post-operatively. This was not statistically significant. (Figure 25)

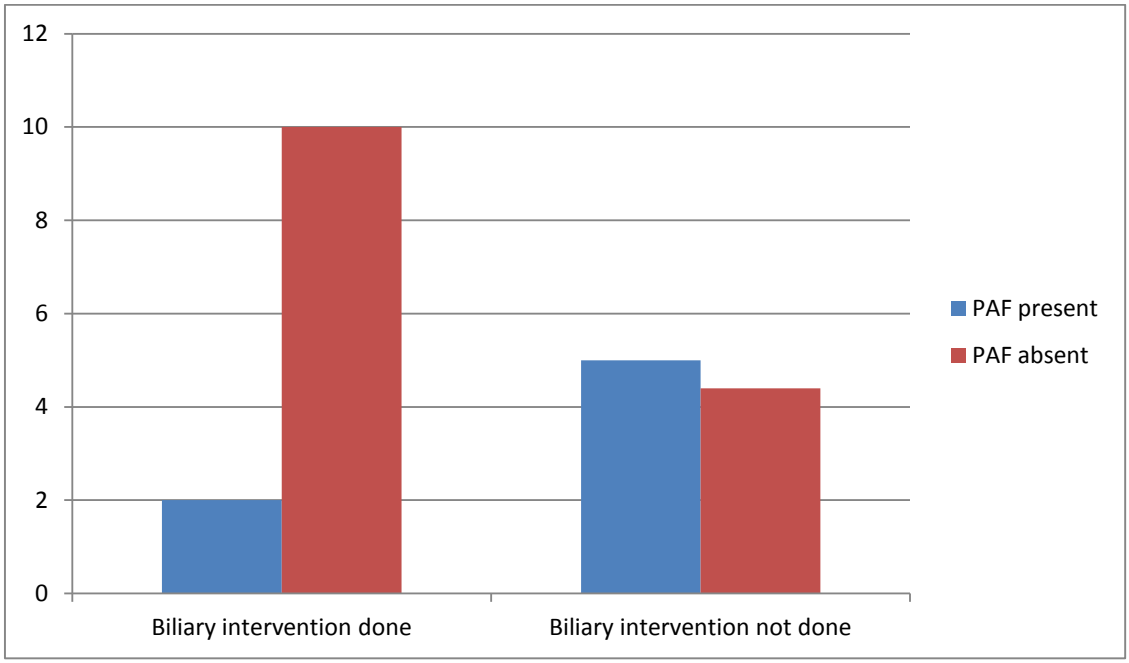


Figure 25 Comparison of biliary intervention and PAF

PAF is also thought to predispose to post-operative septic complications like wound infection and infected intra-abdominal collections. (25). Our study did not find evidence to support this notion (Figure 26).

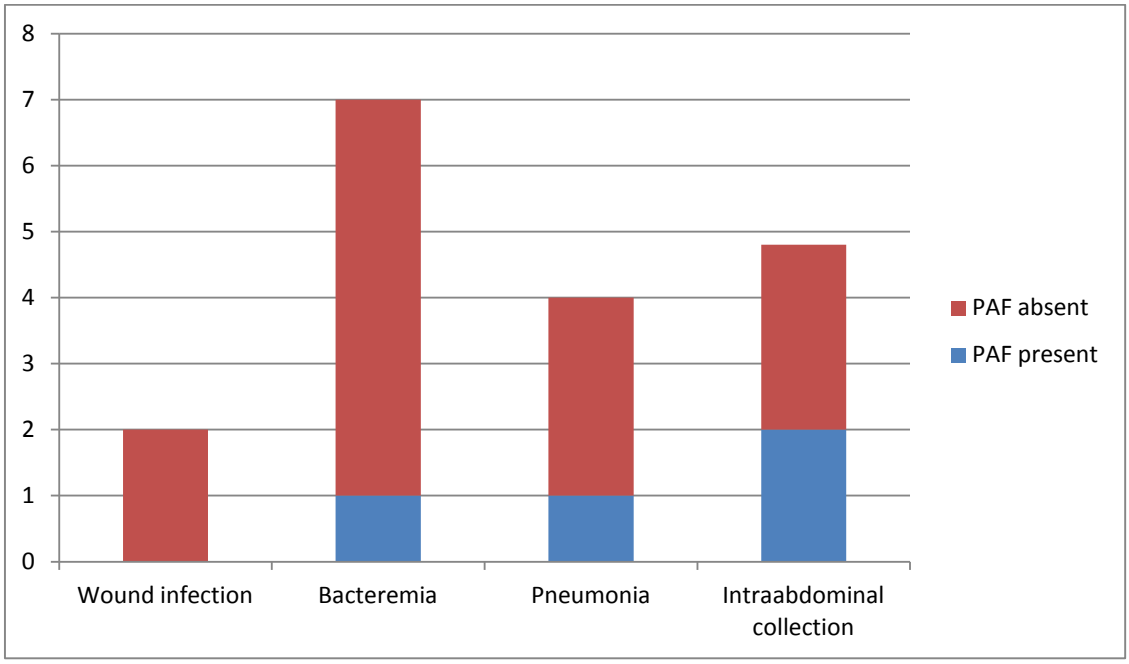


Figure 26 Comparison of PAF and septic complications

Most of the bile cultures grown from the patients were polymicrobial (50%). Most of the isolates grew *Escherichia coli* (56.6%), *Enterococci* (43.3%) and *Klebsiella* (33.3%). Bile cultures are known to grow common gram negative and gram positive commensal gut flora. Among them, the most commonly grown organisms are *E. coli* and *Enterococcus.*

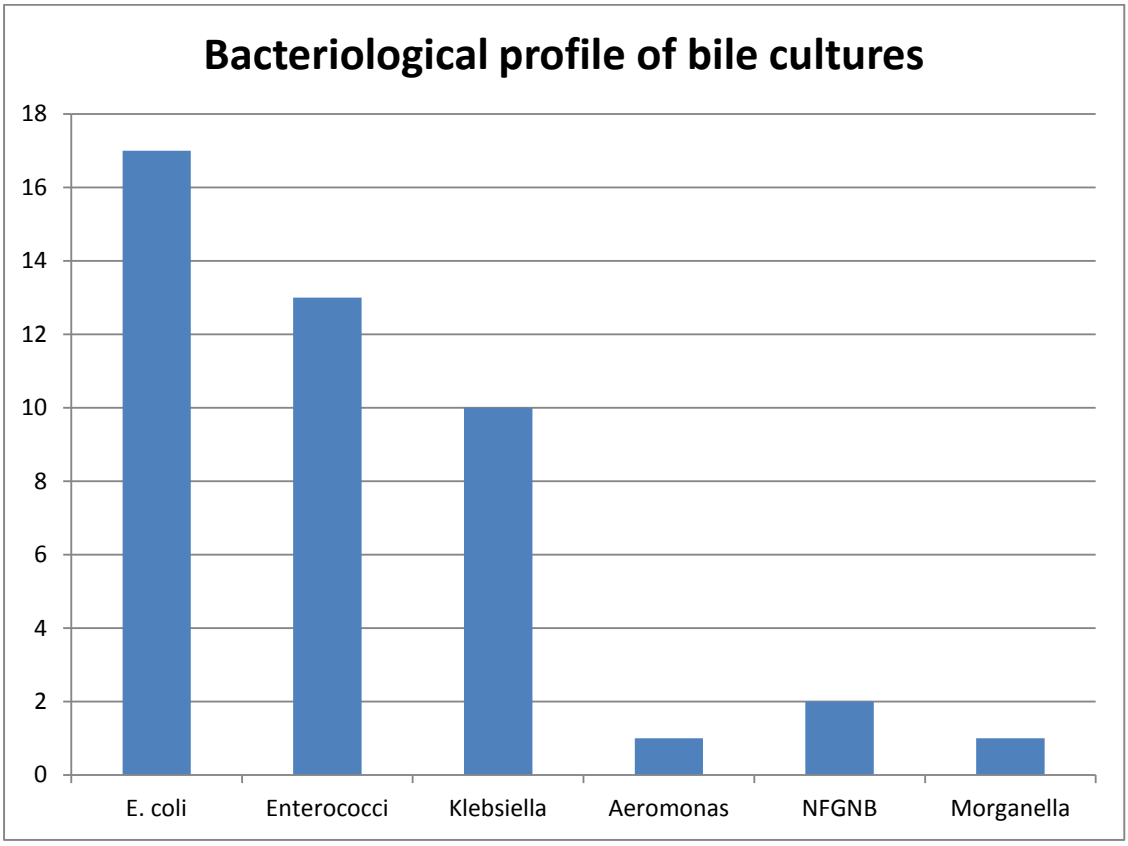


Figure 27 Bacteriological profile of bile cultures

(NFGNB = Non fermenting gram negative bacilli)

The sensitivity of these isolates to routinely used prophylactic antibiotic (Amikacin) was also looked into. Most of the organisms were found to be sensitive (Figure 28). Of the total organisms cultured, 28 were found to be sensitive to Amikacin, which is around 90%.

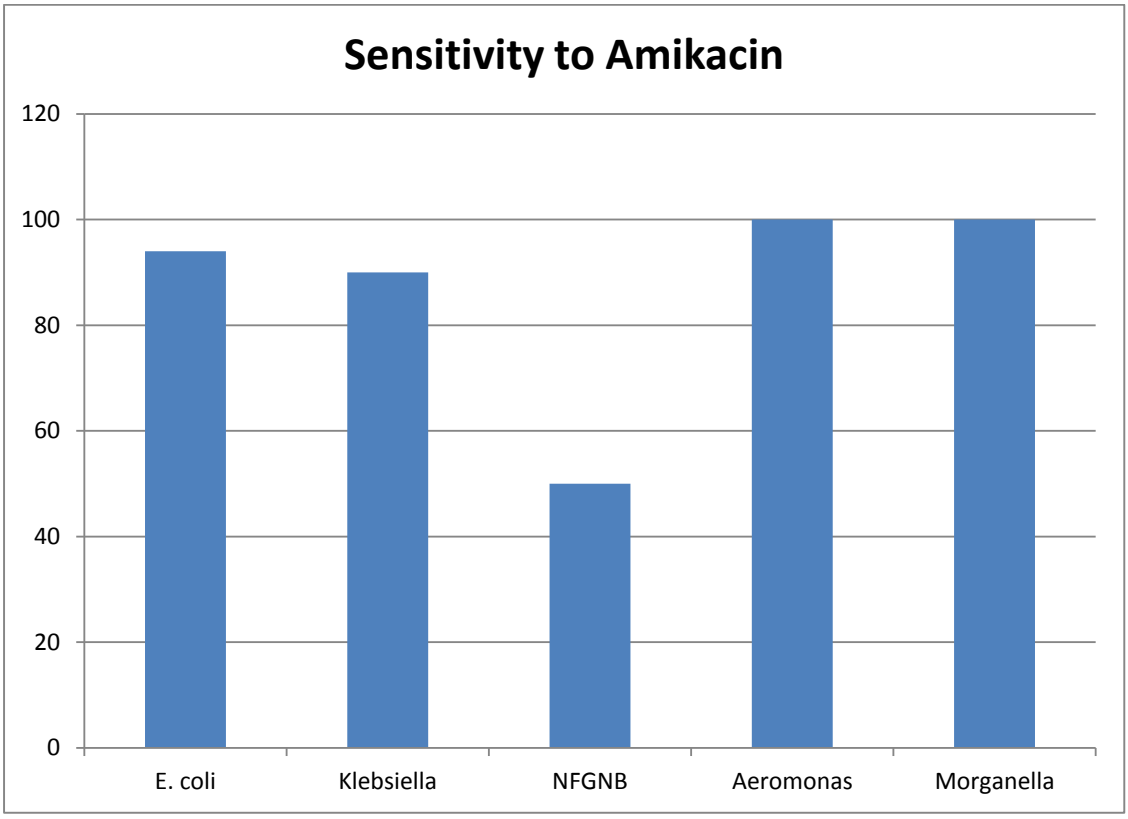


Figure 28 Sensitivity to Amikacin

(NFGNB = Non fermenting gram negative bacilli)

Comparison of post-operative morbidity with bile culture

Clavien grade of complication and its relation to bile culture was examined. (Figure 29) It was found that minor complications occur in greater numbers in both the bile culture positive and negative groups. There was no evidence to suggest that higher grade complications occurred more frequently in patients with positive bile cultures.

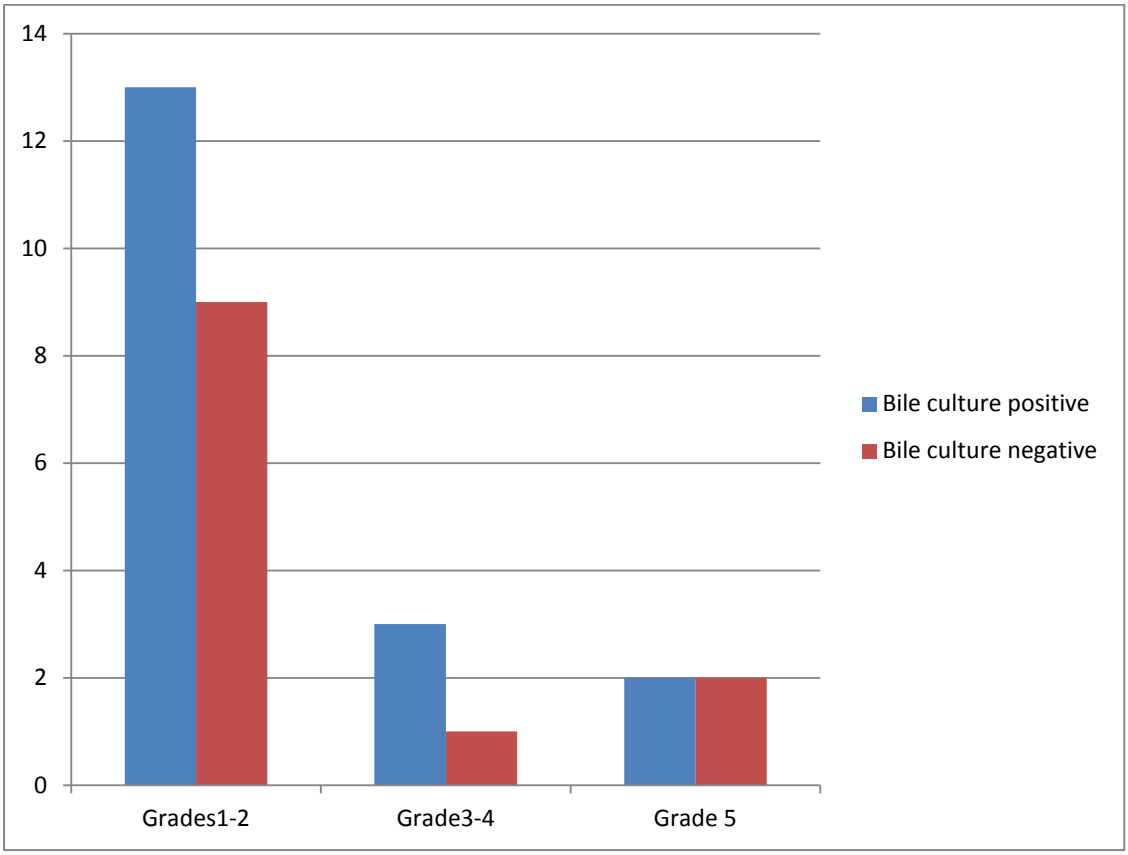


Figure 29 Clavien grade versus bile culture

CONCLUSIONS

The prevalence of bactibilia according to the study was 60%. Organisms commonly isolated from bile included *E. coli, Enterococci and Klebsiella*, which were found to be sensitive to the routinely used intra-operative antibiotic, Amikacin. This finding supports our antibiotic protocol and no change in policy is required.

The study was not able to demonstrate any statistically significant association between bactibilia and post-operative septic complications. Though the absolute numbers of patients with positive bile cultures following biliary stenting were higher, it did not translate into significant association on statistical analysis. Intra-operative tachycardia, hypotension or blood transfusion had no relation with post-operative complications. Post-operative complication most commonly encountered included septicemia and intra-abdominal infected collections.

Biliary intervention pre-operatively does not predispose to septic complications or increased risk of post-operative death in patients undergoing pancreaticoduodenectomy. It would be unnecessary to put these patients on higher grade antibiotics anticipating complications.

LIMITATIONS

1. The study was carried out at a tertiary center and so referral bias was inevitable.
2. Documentation of wound infection had a bias. Only major wound infections were documented.
3. Some patients were started on antibiotics in the immediate post-operative period based on the discretion of the operating surgeon and would have influenced cultures.
4. Patients who had undergone biliary intervention were given Amikacin on the second post-operative day, which would also have influenced cultures.

BIBLIOGRAPHY

1. Sung JY, Costerton JW, Shaffer EA. Defense system in the biliary tract against bacterial infection. Dig Dis Sci. 1992 May;37(5):689–96.

2. Csendes A, Burdiles P, Maluenda F, Diaz JC, Csendes P, Mitru N. Simultaneous bacteriologic assessment of bile from gallbladder and common bile duct in control subjects and patients with gallstones and common duct stones. Arch Surg. 1996 Apr;131(4):389–94.

3. Yeom DH, Oh HJ, Son YW, Kim TH. What are the risk factors for acute suppurative cholangitis caused by common bile duct stones? Gut Liver. 2010 Sep;4(3):363–7.

4. Navaneethan U, Jayanthi V, Mohan P. Pathogenesis of cholangitis in obstructive jaundice-revisited. Minerva Gastroenterol Dietol. 2011 Mar;57(1):97–104.

5. Vestergaard H, Kruse A, Rokkjaer M, Frøbert O, Thommesen P, Funch-Jensen P. Endoscopic manometry of the sphincter of Oddi and the pancreatic and biliary ducts in patients with chronic pancreatitis. Scand J Gastroenterol. 1994 Feb;29(2):188–92.

6. LH Blumgart. Blumgart:Surgery of the liver, biliary tract and pancreas. 4th ed.

7. J W Leung, J Y Sung, and J W Costerton. Bacteriological and electron microscopy examination of brown pigment stones. J Clin Microbiol. 1989 May;27(5):915–21.

8. Smith AL, Stewart L, Fine R, Pellegrini CA, Way LW. Gallstone disease. The clinical manifestations of infectious stones. Arch Surg. 1989 May;124(5):629–33.

9. Leung JW, Liu YL, Lau GC, Chan RC, Lai AC, Ling TK, Cheng AF. Bacteriological analyses of bile and brown pigment stones in patients with acute cholangitis. Gastrointest Endosc. 2001 Sep;54(3):340–5.

10. Rerknimitr R, Fogel EL, Kalayci C, Esber E, Lehman GA, Sherman S. Microbiology of bile in patients with cholangitis or cholestasis with and without plastic biliary endoprosthesis. Gastrointest Endosc. 2002 Dec;56(6):885–9.

11. Bae WK, Moon YS, Kim JH, Lee SH, Kim NH, Kim KA, Lee JS, Um TH, Cho CR. Microbiologic study of the bile culture and antimicrobial susceptibility in patients with biliary tract infection. Korean J Gastroenterol. 2008;51(4):248–54.

12. Englesbe MJ, Dawes LG. Resistant pathogens in biliary obstruction: importance of cultures to guide antibiotic therapy. HPB. 2005;7(2):144–8.

13. Strasberg SM, Harvey PR, Hofmann AF. Bile sampling, processing and analysis in clinical studies. Hepatology. 1990 Sep;12(3 Pt 2):176S–180S.

14. Christopher J.K. Bulstrode Norman S Williams,P. Ronan O'Connell, editor. Bailey and Love's Short Practice of Surgery. 25th ed.

15. Michael J Zinner, Stanley W Ashley. Maingot's Abdominal operations. 11th ed.

16. Sivaraj SM, Vimalraj V, Saravanaboopathy P, Rajendran S, Jeswanth S, Ravichandran P, et al. Is bactibilia a predictor of

poor outcome of pancreaticoduodenectomy? Hepatobiliary Pancreat Dis Int HBPD INT. 2010 Feb;9(1):65–8.

17. 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. J Am Coll Surg. 2006 Jan;202(1):93–9.

18. Sudo T, Murakami Y, Uemura K, Hayashidani Y, Hashimoto Y, Ohge H, et al. Specific antibiotic prophylaxis based on bile cultures is required to prevent post-operative infectious complications in pancreatoduodenectomy patients who have undergone pre-operative biliary drainage. World J Surg. 2007 Nov;31(11):2230–5.

19. Nomura T, Shirai Y, Hatakeyama K. Impact of bactibilia on the development of post-operative abdominal septic complications in patients with malignant biliary obstruction. Int Surg. 1999 Jul;84(3):204–8.

20. Povoski SP, Karpeh MS Jr, Conlon KC, Blumgart LH, Brennan MF. Pre-operative biliary drainage: impact on intra-operative bile cultures and infectious morbidity and mortality after pancreaticoduodenectomy. J Gastrointest Surg Off J Soc Surg Aliment Tract. 1999 Sep;3(5):496–505.

21. Gareth Morris-Stiff, Appou Tamijmarane, Yu-Meng Tan, Iestyn Shapey, Chandra Bhati, A David Mayer, John A C Buckels, Simon R Bramhall. Pre-operative stenting is associated with a higher prevalence of post-operative complications following pancreatoduodenectomy. Int J Surg Lond Engl. 2011;9(2):145–9.

22. Grizas S, Stakyte M, Kincius M, Barauskas G, Pundzius J. Etiology of bile infection and its association with post-

operative complications following pancreatoduodenectomy. Med Kaunas Lith. 2005;41(5):386–91.

23. Pokharel N, Rodrigues G, Shenoy G. Evaluation of septic complications in patients undergoing biliary surgery for gall stones in a tertiary care teaching hospital of South India. Kathmandu Univ Med J. 2007 Jul;5(3):371–3.

24. Augenstein VA, Reuter NP, Bower MR, McMasters KM, Scoggins CR, Martin RC. Bile cultures: a guide to infectious complications after pancreaticoduodenectomy. J Surg Oncol. 2010 Oct;102(5):478–81.

25. Sohn TA, Yeo CJ, Cameron JL, Pitt HA, Lillemoe KD. Do pre-operative biliary stents increase postpancreaticoduodenectomy complications? J Gastrointest Surg Off J Soc Surg Aliment Tract. 2000 May;4(3):258–67.

26. Howard TJ, Yu J, Greene RB, George V, Wairiuko GM, Moore SA, et al. Influence of bactibilia after pre-operative biliary stenting on post-operative infectious complications. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2006 Apr;10(4):523–31.

27. Miedema BW, Sarr MG, van Heerden JA, Nagorney DM, McIlrath DC, Ilstrup D. Complications following pancreaticoduodenectomy. Current management. Arch Surg. 1992 Aug;127(8):945–9.

28. Victor A. Ferraris,Erik Q. Ballert,Angela Mahan. The relationship between intra-operative blood transfusion and post-operative systemic inflammatory response syndrome. Am J Surg. 2013 Apr;205(4):457–65.

29. Bucová M, Mistrík M. [Transfusion-induced immunomodulation and infectious complications]. [Article in Czech]. Vnitr Lek. 2006 Nov;52(11):1085–92.

30. Biccard BM. Heart rate and outcome in patients with cardiovascular disease undergoing major noncardiac surgery. 2008 Jul;36(4):489–501.

31. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical compli... [Ann Surg. 2009] - PubMed - NCBI. Ann Surg. 2009 Aug;250(2):187–96.

32. Kotwall CA, Maxwell JG, Brinker CC, Koch GG, Covington DL. National estimates of mortality rates for radical pancreaticoduodenectomy in 25,000 patients. Ann Surg Oncol. 2002 Nov;9(9):847–54.

33. Parul J Shukla,1 Savio G Barreto,1 MMS Bedi,2 N Bheerappa,3 Adarsh Chaudhary,4 MD Gandhi,2 M Jacob,2 S Jesvanth,5 DG Kannan,5 Vinay K Kapoor,6 A Kumar,6 KK Maudar,7 Hariharan Ramesh,2 RA Sastry,3 Rajan Saxena,6 Ajit Sewkani,7 S Sharma,7 Shailesh V Shrikhande,1 A Singh,4 Rajneesh K Singh,6 R Surendran,5 Subodh Varshney,7 V Verma,3 and V Vimalraj5. Peri-operative outcomes for pancreatoduodenectomy in India: a multi-centric study. HPB. 2009 Dec;11(8):638–44.

34. Michelle L. DeOliveira,Jordan M. Winter,Markus Schafer,Steven C. Cunningham,John L. Cameron,Charles J. Yeo and Pierre-Alain Clavien,. Assessment of Complications After Pancreatic Surgery. Ann Surg. 2006 Dec;244(6):931–9.

ANNEXURES

Annexure 1: Proforma

Name :

Hospital no.:

Address:

Age: Sex:

Diagnosis:

Fever with chills:

Perioperative antibiotics:

Change /escalation of antibiotics in the immediate postoperative period:

Reason:

Intraoperative blood transfusion:

Bile culture:

Sensitivity to intraoperative antibiotics:

Intraoperative hypotension

Intraoperative persistent tachycardia

Pancreatic anastomotic failure:

Drain fluid amylase levels:

Reoperation for intraabdominal collection:

Fluid amylase level:

Drainage of intraabdominal collection under radiological guidance:

Antibiotics started for intraabdominal infected collections

Copious wound discharge, secondary to intraabdominal collection:

Postoperative complication:

COMPLICATION	YES/NO	CULTURE	SAME AS BILE CULTURE/NOT	SENSITIVITY
WOUND INFECTION				
IV LINE SEPSIS				
INTRAABDOMINAL ABSCESS				
BACTEREMIA				
PNEUMONIA				
UTI				

Claveins grade :

Duration of hospital stay:

ICU/HDU

Ward

Total

Extra information:

Annexure 2: Patient information sheet

IMPACT OF BACTIBILIA ON POST OPERATIVE SEPTIC COMPLICATIONS IN PATIENTS UNDERGOING PANCREATICODUODENECTOMY

You have the choice of participating in this study. In this study we will be studying the effect of having infected bile on the development of infective complications following Whipples operation. Bile is routinely sent for culture during the operation, to detect any bile infection. Following the operation, if you develop complications like wound infection, infection in the abdomen, blood, urine or lungs, samples of fluid from these will be sent for culture, to see if the germs that grew from your bile sample are the same as that grew from your infection

There is no risk to you during this study.

There is no additional cost involved.

No additional tissue will be taken from your body during the operation, for the purpose of this study.

All your personal details will be maintained in strict confidentiality.

We do this as part of our routine practice and this is the same protocol which we follow. We need your consent to analyse the data gathered from your investigations and try to formulate a policy, to be able to help patients undergoing the procedure in the future. As we will know if infected bile predisposes to infective complications, we would be able to plan antibiotic treatment for them before they develop infective complications.

Annexure 3: CONSENT FORM

Study title: Impact of bactibilia on the development of postoperative septic complications in patients undergoing pancreaticoduodenectomy

Patients name :

Age in years :

I, ..., son/daughter of .....

(Please tick boxes)

Declare that I have read the information sheet provided to me regarding this study and clarified any doubts that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or legal rights. [ ]

I understand that I will not receive any financial compensation for participation in this study. [ ]

I understand that my identity will not be revealed in any information released to third parties or published. [ ]

I voluntarily agree to take part in this study. [ ]

Name : .....

Signature : .....

Name of investigator : .....

Signature of investigator : .....

Name of witness :.....

Signature of witness : :.....

Relation to patient : ....

Date:...

id	h	age	sex	diagnosis	biliary inter	cholangitis	antibiotic c	antibiotic d
1	080552f	40	1	2	2	2	1	2
2	076421f	72	1	2	2	2	2	2
3	093928f	53	2	1	2	2	2	2
4	110570f	53	2	2	1	2	2	2
5	120828f	59	1	1	1	1	2	2
6	110762f	48	2	2	1	1	1	1
7	114259f	62	2	2	2	2	2	1
8	104444f	53	1	2	2	2	1	2
9	109677f	43	1	2	1	1	1	2
10	121414f	43	1	2	1	2	2	2
11	114371f	39	2	1	2	2	2	2
12	103776f	55	2	2	2	2	2	1
13	148219f	59	1	1	2	2	2	2
14	137860f	64	1	2	2	2	2	1
15	159699	33	2	4	2	2	2	2
16	173239f	40	2	2	2	2	2	2
17	143464f	59	2	2	2	1	1	2
18	183648f	29	2	2	2	2	2	2
19	182862f	64	1	2	1	2	2	1
20	075306f	37	1	2	1	2	1	2
21	199869f	48	2	1	1	2	1	2
22	231416f	24	2	4	2	2	1	1
23	261102f	42	1	4	2	2	2	1
24	249919f	54	1	2	2	2	2	2
25	310770f	61	1	1	1	1	1	1
26	3004331	40	2	4	2	2	1	2
27	288276f	45	1	4	2	2	1	2
28	272445f	43	1	1	1	1	1	2
29	299266f	54	1	2	1	1	1	1
30	184603f	53	1	2	1	1	1	2
31								

intraop hyp	intraop tac	intraop blo	bile culture	ecoli in bile	e coli sensi	klebsiella ir	klebsiella s	enterococc
1	1	1	1	1	1	1	1	2
2	2	2	2					
2	2	1	2					
2	2	1	1	1	2	1	1	2
2	2	2	1	1	2	1	1	1
2	2	2	1	1	1	1	3	1
2	2	1	1	1	1	2		1
2	2	2	2					
1	1	2	1	2		2		1
2	2	2	2					
2	2	2	2					
2	2	2	2					
1	2	2	2					
2	2	2	1	1	3	2		1
2	2	2	1	1	1	2		2
2	2	2	1	1	2	1	1	1
2	2	2	1	1	3	1	1	1
1	2	2	2					
2	2	2	2					
2	1	2	1	1	1	1	3	1
1	2	1	2					
2	2	2	2					
2	2	2	1	1	1	2		1
2	2	2	1	1	1	2		2
2	2	1	1	1	1	1	1	1
2	2	1	1	1	2	2		2
2	2	2	2					
1	2	1	1	1	1	1	1	1
2	2	2	1	1	2	2		1
1	1	2	1	1	3	1	3	1

enterococc	wound infe	w ecoli	we coli sen	wkleb	wkleb sens	wenter	wenter sen	iv line infec
	2							2
	2							2
	2							2
	2							2
1	2							2
1	2							2
1	1	1	3	1	3	2		2
	2							2
1	2							2
	2							2
	2							2
	2							2
	2							2
1	2							2
	2							2
1	2							2
1	2							2
	2							2
	2							2
1	2							2
	2							2
	2							2
1	2							2
	2							2
2	1	2		2		2		2
	2							2
	2							2
2	2							2
2	2							2
1	2							2

ivecoli	ivecoli sens	ivklebsiella	ivkleb sens	iventer	iventer sen	intraabd in	intraabd ec	iae coli sen
						2		
						2		
						2		
						2		
						2		
						1	1	3
						2		
						2		
						2		
						2		
						2		
						2		
						2		
						2		
						2		
						2		
						2		
						2		
						2		
						2		
						2		
						1	1	2
						2		
						1	1	1
						2		
						1	1	3
						2		
						2		
						2		
						1	1	1
						2		

iakleb	iakleb sens	iaenter	iaenter sen	bacteremia	bld ecoli	bld ecoli se	bld kleb	bld kleb se
				2				
				2				
				2				
				2				
				2				
1	3	1	1	2				
				1	1	1	2	
				1	1	1	1	1
				2				
				2				
				2				
				2				
				2				
				1	2		1	1
				2				
				2				
				2				
				2				
				1	2		1	2
				2				
2		1	2	2				
				1	1	1	2	
2		2		1	2		2	
				2				
1	3	1	3	1	1	1	2	
				2				
				2				
				2				
1	2	1	2	2				
				2				

bld enter	bld enter s	sputum cul	sp ecoli	specoli sen	sp klebsiell	sp klebsiell	sp enter	sp enter se
		2						
		2						
		2						
		2						
		2						
		2						
1	1	2						
2		2						
		2						
		2						
		2						
		2						
		1	2		2		2	
2		2						
		2						
		2						
		2						
		2						
2		1	2		2		2	
		2						
		2						
2		2						
2		2						
		2						
2		1	2		1	3	2	
		2						
		2						
		2						
		1	2		2		2	
		2						

urine cultu	ur ecoli	ur ecoli ser	ur klebsiell	ur kleb sen	ur enter	ur enter se	fungemia	duration of
2								14
2							2	16
2							2	10
2							2	32
2							2	20
2							2	17
2							2	35
2							2	17
2							2	11
2							2	14
2							2	17
2							2	15
2							2	24
2							2	21
2							2	11
2							2	16
2							2	15
2							2	17
2							2	19
2							2	13
2							1	25
2							2	21
2							2	26
2							2	25
2							2	22
2							2	12
2							2	14
2							2	16
2							2	32
2							2	26

do3duratio	death	claviens gra	Pancreatic anastomotic failure
1	2	2	2
2	2	1	1
1	2	1	1
2	2	1	2
3	2	1	2
1	2	3	2
2	1	7	2
4	2	2	2
2	2	2	2
2	2	2	2
2	2	2	2
1	2	2	2
19	1	7	2
2	2	2	2
2	2	1	2
2	2	1	2
4	2	2	1
3	2	2	2
11	2	6	2
6	2	2	2
9	1	7	2
8	2	2	2
3	2	3	1
3	2	1	2
10	1	7	2
2	2	2	2
7	2	2	1
4	2	1	2
7	2	4	1
5	2	1	1