Routine Antibiotic Irrigation in Patients Undergoing Pancreatoduodenectomy to Reduce Infection and Fistula Rates

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1.0 Background

Pancreatoduodenectomy, commonly referred to as a Whipple procedure, is a complex procedure performed for patients with both benign and malignant diseases of the periampullary region which consists of the head of the pancreas, the second portion of the duodenum near the ampulla of Vater, and the distal common bile duct. Although mortality from the procedure is reported to be less than 5% in high volume centers, morbidity rates are much higher with reports indicating rates around 40% [1, 2]. Two of the most common complications contributing to this high morbidity rate include infections and pancreatic fistulae. Studies have demonstrated that such complications have been associated with increased mortality rates in patients undergoing pancreatic surgery [3].

Many patients undergoing pancreatoduodenectomy already have a biliary stent in place draining their biliary system to prevent obstructive jaundice. While these stents allow for decompression of an obstructed or soon-to-be biliary tree, they are also quick to colonize with enteric flora of the gastrointestinal tract. Patients with preoperative stents have been shown to have higher wound infection and bacteremia rates [4]. Because pancreatoduodenectomy involves resection of the bile duct and construction of a biliary-enteric anastomosis, it is quite likely that contaminated bile is present in the surgical field. These bacteria sitting within the peritoneum are not appropriately treated by intravenous antibiotics and may contribute to local complications such as organ space infections, wound infections, and pancreatic fistulae.

2.0 Rationale and Specific Aims

Antibiotic irrigation during abdominal surgery via peritoneal lavage is used commonly in abdominal surgery when there are concerns about contamination. This technique offers the ability to decrease bacterial load, thereby potentially reducing intra-abdominal infections. While irrigation typically consists of normal saline, several antibiotics have been used with varying degrees of success. Recent literature in the field of colorectal surgery has demonstrated that the intraoperative use of antibiotic irrigation decreases wound complication rates to less than 5% compared to a rate of 14% among those receiving normal saline irrigation [5].

Hypothesis: The routine use of intraoperative antibiotic irrigation during pancreatoduodenectomy will decrease superficial and organ space infections.

Primary Specific Aim:

- Test the efficacy of routine antibiotic irrigation in reducing superficial and organ space infections among patients undergoing pancreatoduodenectomy.

Secondary Specific Aim:

- Test the efficacy of antibiotic irrigation in reducing pancreatic fistula rates.

3.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

1) At least 18 years of age and older.
2) Open pancreatoduodenectomy for any diagnosis.

Exclusion Criteria:

1) Pregnant
2) Prisoners
3) Patients undergoing concomitant colectomy
4) Antibiotic allergy to study medication
5) Serum creatitine > 2.0
6) Unable to provide informed consent

4.0 Enrollment/Randomization

All patients will be registered with the Surgery Research Office. Regulatory files will be maintained by Surgery Research team and applicable regulatory documents must be completed and on file prior to registration of any patients.

Screening and Informed Consent: Study personnel will identify the patients undergoing pre-operative evaluation at the surgical outpatient clinic (SOPA clinic). All eligible patients (fulfilling the inclusion criteria with no exclusion criteria) will be approached for informed consent.

Randomization: Once consented, eligible patients will be randomized in a 1:1 ratio to treatment with either antibiotic irrigation or placebo irrigation under a blocked randomization scheme. Randomization lists will be prepared by the Department of Biostatistics. When a subject is consented, the study coordinator will assign the patient a study subject number and inform the IDS pharmacist of the study number. The pharmacist will then use the randomization list to assign the randomized medication.

5.0 Treatment Plan

Study Medication: Randomized patients will receive the study drug or placebo intraoperatively during the reconstructive phase of the surgery. The study drug will consist of Polymyxin B (500,000 U) in 1 liter of 0.9% normal saline and the placebo will be 0.9% normal saline. In addition, all patients will receive one dose of parenteral antibiotics within 2 hours of the initial incision. This will consist of 2 grams of intravenous ceftriaxone and 1 gram of intravenous flagyl. For those patients who have allergic contradictions to this regimen, intravenous moxifloxacin (400mg) and clindamycin (600 mg) will be given.

Administration of Study Medication:

- The peritoneal irrigation solution will be manually lavaged over all intended peritoneal surface for a minimum of 60 seconds, but not to exceed 5 minutes. During the irrigation, the operating surgeon will "massage" the solution in the peritoneal surface for another minimum of 60 seconds, less than 5 minutes. The irrigation start and stop time will be recorded. Once this is completed, the residual solution will be cleaned up.

At the end of the reconstructive phase of surgery:

- One (1) Liter of either placebo or study medication will be gently irrigated directly at the pancreatojejunostomy anastomosis or at the pancreatogastrostomy anastomosis, if performed, upon its completion and then removed from the surgical field by suctioning.
- One (1) liter of either placebo or study medication will be gently irrigated at the site of the choledochojejunostomy or hepaticojejunostomy anastomosis at its completion and then removed from the surgical field by suctioning.

Administration of Parenteral Antibiotics:

Within 2 hours (before or after) of initial incision:

- One dose of parenteral antibiotics will be given

Dosing Schedule:

One (1) liter of study drug or placebo will be administered twice via peritoneal irrigation intra-operatively, once at the completion of the pancreatojejunal anastomosis or at the pancreatogastrostomy anastomosis and once at the completion of choledochojejunal or hepaticojejunal anastomosis.

Blinding:

The patient, treating surgeon, and research nurse coordinator will be blinded to the assigned treatment during the course of the study. Upon randomization, the investigational pharmacy will prepare two one liter bags of normal saline solution, either with the antibiotic or just normal saline. During the procedure, the solution will be provided and documentation of the treatment administered will be made as part of the investigational pharmacy documentation.

6.0 Study Calendar

	Baseline	Surgery	Follow up	
	(-30 days-Day 0)	Day 0	Day 30 (+/-14 days)	Day 90 (+/-14 days) [Telephone Visit]
REQUIRED ASSESSMENTS				
Medical history	x			
Height, Wt	x		x	
Physical examination	x		x	
Vital Signs	x		x	
AE and concomitant medication assessment	x	x	x	
Survival				x
TREATMENT				
Randomization	x*			
Polymyxin B/Placebo Irrigation		x		

x* randomization occurs after patient is registered to the study, prior to surgery

Toxicities to be monitored in this study:

Any evidence of allergic reaction to the antibiotic irrigation will be considered an adverse event.

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Definitions of Adverse Events

Adverse Event (AE)

An **adverse event** is defined as untoward medical occurrence associated with the use of a drug or procedure in humans, whether or not considered drug or procedure related. An adverse event can be **ANY** unfavorable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal (investigational) product or procedure, whether or not considered related to the medicinal (investigational) product or procedure (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). Examples of Adverse Events that will be recorded in this study are:

- Concomitant illness
- Physical injury
- Events possibly related to medication
- Significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions

- Drug interactions
- A laboratory or diagnostic test abnormality occurring shortly after the start of the study that results in the withdrawal of the patient from the study, requires medical treatment or further diagnostic work-up, or is considered by the study investigator to be clinically significant

Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0. Delayed gastric emptying will be graded using the International Study Group of Pancreatic Surgery (ISGPS) system.

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 28 days of last dose of study drug (even if it is not felt to be drug related)
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Hospitalizations that are not considered SAEs are:
  - Hospitalization planned prior to first administration of study drug
  - Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

Unexpected Adverse Event

An adverse event not mentioned in the package insert or the specificity or severity of which is not consistent with the package insert.

Determining Attribution to the Investigational Agent(s)

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational agent/intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

Adverse Event (AE) Reporting

Adverse events (AEs) will be reported to the principal investigator immediately and will be recorded from the time of first study drug administration until 30 days after surgery, regardless of whether or not the event(s) are considered related to trial procedures or medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

Reporting to the IRB:

1. Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- caused harm;
- were unexpected;
- were related or possibly related to the research intervention; AND
- required revision to the informed consent document.

If the serious adverse event does not meet all four (4) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it will be reported at the time of continuing review.

2. **Prompt** reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

Reporting to the Data Safety Monitoring Committee (DSMC):
Regardless of study sponsorship, the DSMC chair and/or coordinator will review all expedited SAE reports through OnCore®. Expedited reports are completed per IRB guidelines and may include the IRB Prompt Reporting form, non-compliance form. When follow-up information is received, a follow up report will also be created in OnCore. The DSMC chair and/or coordinator will review expedited SAE reports monthly, and report findings to the DSMC.

8.0 Study Withdrawal/Discontinuation

Subjects may be withdrawn from study participation at the discretion of the investigator or if the patient/surrogate or attending physician requests that the subject be withdrawn. The reason and date of every withdrawal will be recorded. The Informed Consent Document will notify participants that their participation is voluntary, and they can tell the study staff at any time if they decide to stop participating. In addition, if they choose to withdraw their authorization for study staff to access protected health information (PHI) in the medical record, they may do so by notifying study staff in writing. If a participant chooses to no longer participate but does not notify study staff that they withdraw authorization for access to PHI, their medical record may be accessed to obtain outcomes and safety data. Follow-up will be performed for all discontinuations due to an AE or other safety concern until resolution, until deemed chronic and stable, or as long as clinically appropriate.

Definitions:

Pancreatic fistulae will be defined by pre-existing definitions in the literature.

In general, a pancreatic fistula is considered to be leak from the pancreatic ductal system. More specifically, it is formally defined as an abnormal connection between pancreatic epithelium with another epithelial surface containing pancreatic fluid. In the context of pancreatic surgery where a pancreatojejunal anastomosis is created and a surgical drain is utilized, a fistula likely indicates a failure of proper healing of the anastomosis and may not be connected to another epithelial surface but instead a drain [7].

We will define a pancreatic fistula as output of at least 10mL/day of amylase-rich fluid (amylase content greater than 3 times the upper normal serum value) for greater than 5 days. Accordingly, drains placed near the pancreatojejunostomy will have daily outputs and daily amylase levels checked on the first five days following surgery.

Additionally, pancreatic fistulae are grading based on severity and will be classified as either grade A, grade B, or grade C as defined by the International Study Group on Pancreatic Fistula.

- Grade A pancreatic fistulae are the most common are have limited to no clinical impact. The patient appears clinical well, there no signs of infection or sepsis, there is typically no evidence of a fluid collection, drainage resolves and no specific treatment is indicated.
- In contrast grade B fistulae require a change in clinical management; patients are made NPO (nothing by mouth) and supported with enteral or parenteral nutrition. They require leaving pancreatic drains in place and will often necessitate a delay in discharge.
- In patients with a grade C fistula, major deviations in management are required. These patients may not be clinically stable and require aggressive interventions including care in the intensive care, nothing by mouth, supplemental nutrition, intravenous antibiotics and percutaneous drainage with a possible return trip to the operating room for repair, creation of a new

anastomosis between the pancreas and the gastrointestinal tract, or completion pancreatectomy [7].

Superficial and organ space infections are defined as follows from pre-exisiting definitions in the literature [6]:

Superficial infections will be defined as an infection which occurs within 30 days after surgery and involves either skin/subcutaneous tissue (superficial) or the fascial/muscle layer (deep) of the incision. Furthermore, the patient will need to meet at least one of the following criteria:
1. Purulent drainage from the incision but not from the organ/space component of the surgical site;
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;
3. At least one of the signs or symptoms of infection, including pain or tenderness, localized swelling, redness and heat and a superficial incision deliberately opened by a surgeon and either found to be culture-positive or not cultured (a culture-negative finding did not meet this criterion);
4. A deep incision spontaneously dehisced or deliberately opened by a surgeon and either found to be culture-positive or not cultured (a culture-negative finding did not meet this criterion) and at least one of the signs or symptoms of fever (>38 °C), localized pain or tenderness;
5. An abscess or other evidence of infection involving the deep incision found on direct examination, during reoperation, or by histopathologic or radiologic examination.

Organ space infections will be defined as infections that occur within 30 days after surgery that is related to the surgery and involves any part of the body excluding that skin, fascia, or muscle layers, and meets at least one of the following criteria:
1. Purulent drainage from a drain that was placed through a stab wound into the organ or space;
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ or space;
3. An abscess or other evidence of infection involving the organ or space found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Any intraperitoneal collection requiring percutaneous drainage

9.0 Statistical Considerations

The patients' characteristics will be summarized by treatment arms and compared using two-sample t-tests for continuous and Chi-square test for categorical variables as appropriate. Nonparametric tests will be used if there is a normal distribution assumption violation. All analysis will be performed using SAS 9.3 (Cary, NC)

Efficacy in reducing superficial and organ space infections: In the primary analysis, proportion of patients with infection will be tabled and calculated for each arms and compared using a Chi-square test. In the secondary analysis, we will also use a logistic regression model with infection as the outcome variable, treatment arm as the main predictor, and will adjust for disease process in order to further evaluate the efficacy.

Efficacy in reducing pancreatic fistula rates will be analyzed in a similar way to the primary outcome variable.

Toxicity data related to the treatment will be summarized by treatment arm.

Early Stopping Rule:
An interim analysis will occur after 82 patients have been treated. Overall complication rate and rate of major complication (e.g. Grade 3 through 5) will be analyzed for each treatment group at the interim analysis. If the placebo group infection rate is three (3) times the infection rate of the treatment group, the study will be stopped.

Sample Size and Statistical power: Historical data in hepatopancreatobiliary surgery show that the treated group will reduce primary outcome rate from 24% to 8%. The anticipated reduction in infectious complications was estimated based on historical outcome data for abdominal operations involving one or more gastrointestinal anastomoses. Using a two-sided Chi-square test, we will need 82 patients in each arm to detect such a difference with 80% power and 5% Type I error rate. With no attrition rate, we will need to recruit 164 patients totally. The power analysis was performed for the primary endpoint only.

10.0 Privacy/Confidentiality Issues

Patients will be consented in a private hospital room setting in order to protect confidentiality.

11.0 Follow-up and Record Retention

Information stored in the database will be stored for an indefinite period of time for future reference, including for use in subsequent data analyses. Throughout the study, all collected data will be entered directly in to the secure password-protected web-based database. In terms of study purposes, we will plan to follow for a 90 day period. The 90-day post operative visit will be a telephone visit.

As stated in the informed consent document, participants' consent to use or share PHI does not expire unless study staff has been explicitly notified of this decision in writing from the participant (even in the event that a subject withdraws from further participation).

11.0 DATA SAFETY MONITORING PLAN

DSMP for Moderate Risk Trials (Level 2)

Moderate Risk Trials
Investigators will conduct continuous review of data and patient safety. **Monthly review meetings** for Phase I/II and Phase II trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Monthly** meeting summaries will include review of data, the number of patients, significant toxicities as described in the protocol, and responses observed. Summaries will be submitted monthly and reviewed quarterly by the DSMC.

Study Auditing and Monitoring
All trials conducted at the IUSCC are subject to auditing and/or monitoring. Reports will be reviewed quarterly by the full DSMC (Reference Risk Table in full DSMC Charter).

Early Study Closure
At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation will be made in writing to the Data Safety Monitoring Committee. Alternatively, the DSMC may initiate suspension or early closure of the study based on its quarterly review of the investigator reports.

Reporting Guidelines
The DSMC has streamlined the reporting process by utilizing reports from OnCore. This has allowed direct view of reports within the Clinical Trials Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore monthly and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC quarterly.

Reporting Death:
Death will be reported per local IRB reporting guidelines. The DSMC will review all reported deaths monthly.

Study Accrual Oversight
Accrual data will be entered into the IU Simon Cancer Center OnCore system on a monthly basis. The Protocol Accrual Committee (PAC) reviews study accrual twice per year while the PAC coordinator reviews accrual quarterly.

Protocol Deviations
Protocol deviations are entered into OnCore monthly and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC quarterly.

12.0 References:

1. Yeo, C.J., et al., *Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes.* Ann Surg, 1997. **226**(3): p. 248-57; discussion 257-60.
2. Schmidt, C.M., et al., *Pancreaticoduodenectomy: a 20-year experience in 516 patients.* Arch Surg, 2004. **139**(7): p. 718-25; discussion 725-7.
3. Kelly, K.J., et al., *Risk stratification for distal pancreatectomy utilizing ACS-NSQIP: preoperative factors predict morbidity and mortality.* J Gastrointest Surg, 2011. **15**(2): p. 250-9, discussion 259-61.
4. Howard, T.J., et al., *Influence of bactibilia after preoperative biliary stenting on postoperative infectious complications.* J Gastrointest Surg, 2006. **10**(4): p. 523-31.
5. Ruiz-Tovar, J., et al., *Effect of peritoneal lavage with clindamycin-gentamicin solution on infections after elective colorectal cancer surgery.* J Am Coll Surg, 2012. **214**(2): p. 202-7.
6. Ceppa, E.P., et al., *Reducing surgical site infections in hepatopancreatobiliary surgery.* HPB (Oxford), 2013. **15**(5): p. 384-91.
7. Bassi, C., et al., *Postoperative pancreatic fistula: an international study group (ISGPF) definition.* Surgery, 2005. **138**(1): p. 8-13.

13.0 APPENDICES

13.1 APPENDIX I-TOXICITY CRITERIA

NOTE: the attached Appendix I contains reference to the DCT/NCI Common Toxicity Criteria, Version 4.0, used to grade toxicities in reporting an "ADR" (adverse drug reaction) as described in Section 15.0 of this protocol. Other toxicity criteria (i.e., related to specialized treatments such as immunotherapy or BRMs) may be used as needed.

13.2 APENDIX II-CTMC CHECK SHEET

Appendix I

NCI Common Toxicity Criteria

Version 4.0

Due to the size of the latest version of the Common Toxicity Criteria, copies of this appendix are not included with this protocol document.

An electronic copy is available on the CTEP web site,
http://ctep.cancer.gov/reporting/ctc.html

Appendix II
CTMC Check Sheet

Meeting Date:			
Team/Program: (include meeting sign in sheet)			
Protocol & Status (open/closed to accrual)			
PI:			
CRS:			
	Y	N	N/A
Weekly and Monthly meetings should include discussion on data, patient safety, dose levels, accrual numbers, significan toxicities, dose adjustments and responses observed, deviation summaries and SAE reports. (per IUSCC DSMP)			
Has patient safety data been discussed/reviewed? Have all SAE's and deviations been reported in Oncore for all IUSCC programs.			
Has all data been entered into Oncore per the *"Data Requirements for Cancer Center Reporting"* SOP?			
Deviation Log reviewed, discussed and signed by <u>ALL</u> team members including PI			
Has accrual been entered into Oncore for all IUSCC programs per the *"Data Requirements for Cancer Center Reporting"* SOP			

***Notes**		