CASE WESTERN RESERVE UNIVERSITY | CASE COMPREHENSIVE CANCER CENTER

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

STUDY NUMBER: CASE 2223

ClinicalTrials.gov NCT #: NCT05753735

Protocol Date: 2/5/2024

STUDY TITLE: eXtended antibiotic prophylaxis for intermediate- and high-risk glands after pancreatoduodenectomy to reduce clinically relevant PostOperative Pancreatic Fistula: A phase 2 randomized control trial (X-POPF)

PRINCIPAL INVESTIGATOR:

PRINCIPAL INVESTIGATOR: Lee M. Ocuin, MD
Division of Surgical Oncology
University Hospitals Cleveland Medical Center
Seidman Cancer Center
11100 Euclid Avenue
Cleveland, OH 44106
[redacted]

CO-INVESTIGATORS: Jordan M. Winter, MD
Division of Surgical Oncology
University Hospitals Cleveland Medical Center
Seidman Cancer Center
11100 Euclid Avenue
Cleveland, OH 44106

Jeffrey M. Hardacre, MD
Division of Surgical Oncology
University Hospitals Cleveland Medical Center
Seidman Cancer Center
11100 Euclid Avenue
Cleveland, OH 44106

John B. Ammori, MD
Division of Surgical Oncology
University Hospitals Cleveland Medical Center
Seidman Cancer Center
11100 Euclid Avenue
Cleveland, OH 44106

STATISTICIAN: Hao Feng
Case Western Reserve University School of Medicine
Dept of Population and Quantitative Health Sciences
[redacted]

STUDY COORDINATOR: Nikola Anusic, MD
Division of Surgical Oncology
University Hospitals Cleveland Medical Center
Seidman Cancer Center
[redacted]

SPONSOR: Case Comprehensive Cancer Center

SUPPORT/FUNDING: Internal Department Funding

SUPPLIED AGENT***(S):*** Not applicable

OTHER AGENT***(S):*** Piperacillin/Tazobactam, Amoxicillin/Clavulanic Acid

Title: eXtended antibiotic prophylaxis for intermediate- and high-risk glands after pancreatoduodenectomy to reduce clinically relevant PostOperative Pancreatic Fistula: A phase 2 randomized control trial (X-POPF)

Principal Investigator: Lee M. Ocuin

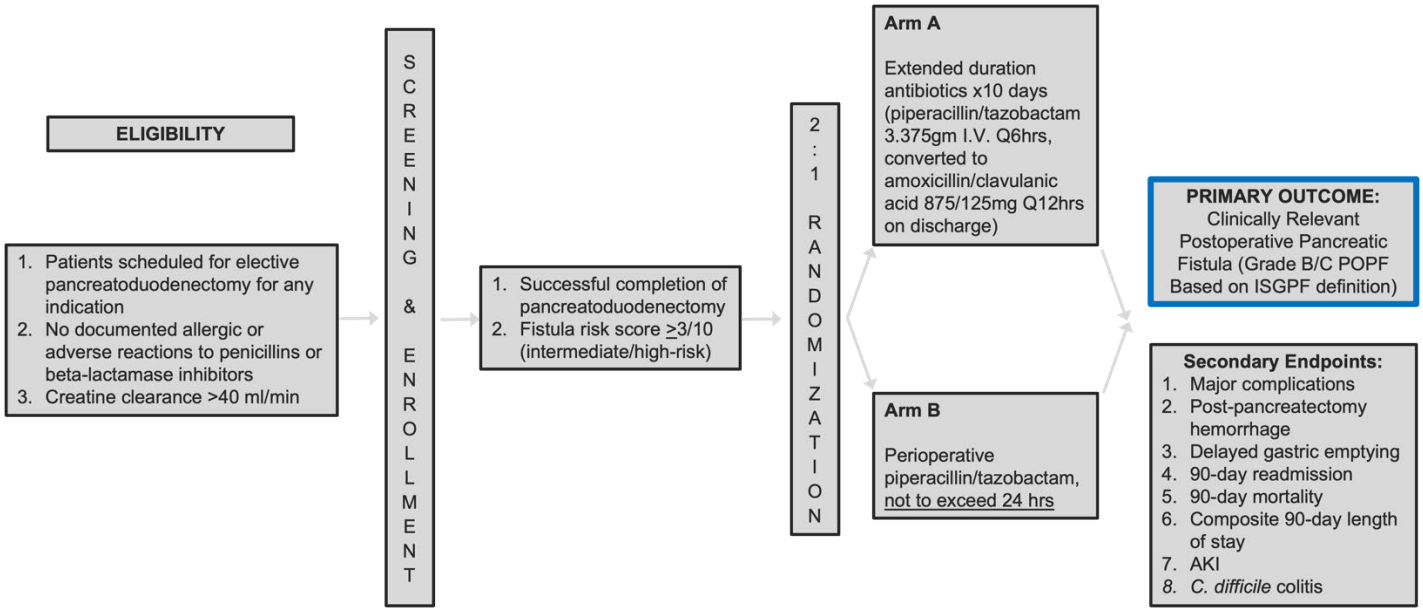
PRINCIPAL INVESTIGATOR SIGNATURE:

_____ Date: _____

SUMMARY OF CHANGES

Protocol Date	Section	Change
2/17/2023		Initial PRMC approval
2/23/2023	4.1	IRB pre-review clarifications: Age 18-90 years included in study
2/23/2023	3.1	Protocol clarification: patients with FRS ≥3 and soft gland.
2/23/2023	3.4	Follow-up clarified

STUDY SCHEMA



PROTOCOL SUMMARY

Protocol Number/Title	TBD
Study Phase	Phase 2 Randomized Clinical Trial
Brief Background/Rationale	This is a prospective, randomized, controlled, single center study. Up to 96 patients will be randomized after pancreaticoduodenectomy in 2:1 fashion to either Extended Antibiotic Prophylaxis or Standard Care.
Primary Objective	Primary Endpoint(s) Clinically relevant (Grade B/C) postoperative pancreatic fistula rate at 90 days.
Secondary Objective(s)	Secondary Endpoint(s) Major 90-day complications, 90-day mortality, 90-day composite length of stay, 90-day readmission, delayed gastric emptying, acute kidney injury, *C. difficile* colitis, postpancreatectomy hemorrhage
Sample Size	96 patients
Disease sites/Conditions	Pancreatectomy and Duodenectomy: A350, A360, A370, A700
Interventions	Piperacillin/Tazobactam 3.375 g IV every 6 hours while inpatient following surgery, not to exceed 10 days
	Amoxicillin/ Clavulanic acid 875/125 mg every 12 hours after discharge to complete 10 days total antibiotics

ABBREVIATIONS *Please update table with relevant abbreviations used in the protocol*

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
DCRU	Dahm's Clinical Research Unit
DSTC	Data Safety and Toxicity Committee
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation
UH	University Hospitals
CMC	Cleveland Medical Center
POPF	Postoperative Pancreatic Fistula
CS-POPF	Clinically Significant Postoperative Pancreatic Fistula
PD	Pancreaticoduodenectomy
I.V.	Intravenous
PO	By mouth (from Latin per os)
Q6H	Every 6 hours (from Latin quaque 6 hora)
BID	Twice a Day (from Latin bis in die)

TABLE OF CONTENTS

1.0 Introduction

1.1 Background of Study Disease

Pancreatoduodenectomy (PD) is a commonly performed surgical procedure utilized in the treatment of either localized malignancies or benign conditions that involve the pancreatic head, 2nd/3rd portions of the duodenum, ampulla of Vater, and distal biliary system. This procedure, also known as the Whipple procedure, was historically associated with high mortality and morbidity after being initially described in 1909 by Kausch and later in 1935 by Whipple. With improvements in surgical technique, suture, hemostasis, anesthesiology, and critical care, the PD is a routinely performed, safe operation with low mortality rates in appropriately selected patients in the current era.[1] In high-volume centers, surgical mortality has been further reduced by increased recognition and advanced treatment of complications when they occur, and resultant high salvage rate of patients who experience post-pancreatectomy complications.[2] However there has been little improvement in the rate of postoperative pancreatic fistula (POPF), which occurs in approximately 10-40% of patients, and is influenced by a number of factors, including surgeon experience, pancreatic gland texture, pancreatic duct size, and underlying diagnosis.[3] POPF is the leaking of enterically contaminated and amylase-rich fluid from the pancreatic-jejunal anastomosis created during PD.[4] This leak may be self-limited or lead to serious complications such as superficial and deep space surgical site infections, sepsis, and contribute to post-pancreatectomy hemorrhage or even death.

Pancreatic fistulae are defined and graded based upon the International Study Group of Pancreatic Fistula (ISGPF) into the categories of biochemical leak, grade B POPF, and grade C POPF, with grade C being the most severe.[5] Grades B and C POPF are also known as clinically relevant POPF (CR-POPF). **Table 1** summarizes the diagnosis and definitions of POPF.

Table 1. Definitions of biochemical leak and Grade B/C postoperative pancreatic fistula

Event	Biochemical leak	Grade B POPF	Grade C POPF
Increased amylase >3 times upper limit of normal serum value	Yes	Yes	Yes
Persistent drainage >3 weeks	No	Yes	Yes
Clinically relevant change in management	No	Yes	Yes
Percutaneous or endoscopic intervention	No	Yes	Yes
Angiographic intervention for POPF-related hemorrhage	No	Yes	Yes
Reoperation	No	No	Yes

Signs of infection related to POPF	No	Yes (no organ failure)	Yes (with organ failure)
POPF-related organ failure	No	No	Yes
POPF-related death	No	No	Yes

Given the prevalence and potential life-threatening consequences of CR-POPF, multiple mitigation strategies have been studied in both prospective and retrospective fashion. Studies have examined anastomotic techniques for pancreaticojejunostomy[6,7] and pharmacologic interventions with somatostatin analogues,[8,9] but no study with positive results has demonstrated reproducible efficacy, and overall results have been heterogenous.[10–14]

By definition, any leak from the pancreaticojejunostomy is infected, and antibiotics are a mainstay of treatment of CR-POPF. Therefore, the concept of antibiotic mitigation *prior to* development of a CR-POPF in patients at higher risk of developing CR-POPF is an attractive option.

The fistula risk score (FRS) is a prospectively validated 10-point score that assigns point values to several non-modifiable variables in patients undergoing pancreatoduodenectomy, with higher scores predictive of higher risk of any POPF and CR-POPF (**Table 2**).[15] Patients with negligible/low FRS (0-2) have a predicted ≤10% risk of CR-POPF, those with intermediate FRS (3-6) have a predicted 10-30% risk of CR-POPF, and those with high FRS (7-10) have a predicted 30-50% risk of CR-POPF (**Table 3**).[16]

Table 2. Fistula risk score for prediction of CR-POPF

Risk factor	**Parameter**	**Points**
Gland texture	Firm Soft	0 2
Pathology	Pancreatic adenocarcinoma/pancreatitis Other	0 1
Pancreatic duct diameter (mm)	≥5mm 4mm 3mm 2mm ≤1mm	0 1 2 3 4
Estimated blood loss (ml)	≤400 400-700 701-1000 >1000	0 1 2 3
TOTAL		

Table 3. Predicted rate of CR-POPF based on FRS score category

Negligible (FRS 0)	**Low (FRS 1-2)**	**Intermediate (FRS 3-6)**	**High (FRS 7-10)**
<5%	<10%	10-30%	30-50%

Shubert and colleagues from Mayo Clinic created a risk-based postoperative pathway, with extended antibiotic prophylaxis as a component in patients with intermediate or high FRS. The risk-based pathways were associated with decreased length of stay and overall cost savings, but no change in the overall rate of any POPF or CR-POPF. However, in patients with CR-POPF, the risk-based pathway was associated with having a lower CR-POPF grade.[17]

Table 4 summarizes the modified version of the antibiotic component of the risk-based pathway that has been adopted at University Hospitals Cleveland Medical Center for patients who undergo pancreatoduodenectomy by the four pancreatic surgeons within the Division of Surgical Oncology.

Table 4. Antibiotic mitigation protocol for patients who undergo pancreatoduodenectomy

FRS Category	Treatment
Negligible/low (FRS 0-2)	Standard perioperative antibiotics, discontinued within 24 hours.
Intermediate (FRS 3-6) or high (FRS 7-10)	Piperacillin/Tazobactam 3.375mg IV Q6hrs x10 days (converted to amoxicillin/clavulanic acid at discharge; total of 10 days of antibiotics).

Preliminary data

We have recently analyzed our initial results since the antibiotic mitigation protocol was adopted, and data are summarized in **Tables 5** and **6.** A total of 59 patients have undergone pancreatoduodenectomy since the pathway was introduced off-protocol. Patients who received extended antibiotic prophylaxis had smaller duct size (2mm vs. 3mm, p=0.04; **Table 5**). Median FRS and FRS categories were similar. One surgeon (LO) utilized the pathway exclusively, one surgeon (JH) adopted the pathway into routine practice, and two surgeons (JA and JW) did not utilize the pathway at any time.

Table 5. Clinical and demographic factors for patients with intermediate/high FRS treated with or without extended antibiotic prophylaxis.

Demographics	Antibiotics (n=18)	No Antibiotics (n=41)	p-value
Age (median, IQR)	64 (55, 73)	63 (55, 70)	0.86
Female (n, %)	11 (61.1%)	18 (43.9%)	0.22
Non-White	4 (22.2%)	7 (17.1%)	0.72
Pathology			--
Cyst/IPMN	1 (5.6%)	5 (12.2%)	
Cholangiocarcinoma	6 (33.3%)	6 (14.6%)	
Ampullary carcinoma	4 (22.2%)	11 (26.8%)	

Duodenal cancer **Neuroendocrine** **Other**	3 (16.6%) 2 (11.1%) 2 (11.1%)	3 (7.3%) 9 (22.0%) 7 (17.1%)	
Duct size (mm) (median, IQR)	2 (2, 4)	3 (3, 4)	**0.04**
Fistula risk score	6 (5, 7)	5 (4, 6)	0.39
FRS category (n, %) **Intermediate** **High**	 13 (72.2) 5 (27.8)	 33 (80.5) 8 (19.5)	0.48
Surgeon **JA** **JW** **JH** **LO**	 0 (0%) 0 (0%) 6 (33.3%) 12 (66.7%)	 8 (19.5%) 18 (43.9%) 15 (36.6%) 0 (0%)	

Patients who received extended antibiotic prophylaxis had lower rates of CR-POPF as compared to those who received standard perioperative antibiotic prophylaxis (11.1 vs. 36.6%, p=0.04; **Table 6**). Additionally, those who received extended antibiotic prophylaxis has shorter index length of stay (7 vs. 8 days, p=0.04), fewer superficial wound (5.6 vs. 35.0%, p=0.02) and deep space (16.7 vs. 43.9%, p=0.04) infections, and lower frequency of image-guided drain placement (5.6 vs. 14.6%, p=0.03). The composite 90-day length of stay was also shorter in those who received extended antibiotic prophylaxis (8 vs. 11 days), but this did not reach statistical significance. Importantly, there were no documented *C. difficile* colitis infections in patients who received extended antibiotics.

Table 6. Postoperative outcomes after pancreatoduodenectomy in patients with intermediate/high fistula risk scores, stratified by extended or standard perioperative antibiotics.

Outcomes	**Antibiotics (n=18)**	**No antibiotics (n=41)**	**p-value**
CR-POPF (n, %)	2 (11.1%)	15 (36.6%)	**0.04**
90-day Readmission	8 (44%)	14 (34.2)	0.45
Index LOS (median, IQR)	7 (6, 8)	8 (6, 14)	**0.04**
Composite 90 Day LOS	8 (6, 10)	11 (7, 17)	0.08
30 Day Mortality (n, %)	0 (0%)	2 (4.9)	0.34
90 Day Mortality	1 (5.6%)	3 (7.3%)	0.80
DGE	7 (38.9%)	6 (14.6%)	**0.04**
Post Pancreatectomy Hemorrhage	0 (0%)	3 (7.3%)	0.24
Superficial Wound Infection	1 (5.6%)	14 (35.0%)	**0.02**
Deep Space Infection	3 (16.7%)	18 (43.9%)	**0.04**
Image-guided drain placed	1 (5.6%)	13 (31.7%)	**0.03**
Return to OR	1 (5.6%)	6 (14.6%)	0.32
Bile Leak	0 (0%)	2 (4.9%)	0.34

1.2 Name and Description of Pharmacologic Agents

Piperacillin/Tazobactam is an FDA-approved broad spectrum antibiotic, delivered only by I.V. route. It is a combination of piperacillin sodium, a bactericidal agent that inhibits bacterial septum and cell wall synthesis, and tazobactam, a beta-lactamase inhibitor that stop bacteria from breaking down penicillins.

Amoxicillin/Clavulanic acid is an FDA-approved antibiotic that is orally dosed. It is a combination of amoxicillin, a bactericidal agent that inhibits bacterial cell wall synthesis, and clavulanic acid, a beta-lactamase inhibitor that serves to increase the activity of amoxicillin, particularly in gram-negative bacteria.

Both antibiotics are frequently used for intraabdominal infections given their extended gram-negative coverage. Adverse events are most commonly mild gastrointestinal symptoms and are fully detailed below.

1.3 Rationale

Our preliminary data suggest that extended broad-spectrum antibiotic prophylaxis may reduce the rate of CR-POPF in patients who undergo PD and have intermediate- or high FRS. CR-POPF drives many of the downstream postoperative outcomes following PD. The risks of administration of the proposed antibiotics are relatively low. Adverse drug reactions and the development of drug resistant bacterial strains are the two potential drawbacks of antibiotic exposure in this population. However, patients who undergo PD are all exposed to piperacillin/tazobactam in the perioperative setting, and patients who develop a CR-POPF will be exposed to a prolonged antibiotics course as part of the therapeutic management of CR-POPF, often exceeding the 10-day duration of prophylaxis in the treatment arm of this trial.

2.0 Objectives

2.1 Primary Objective

Our primary objective is to demonstrate that extended antibiotic prophylaxis in patients with intermediate/high FRS who undergo PD reduces the rate of CR-POPF in the intervention group, as defined by the ISGPF taskforce guidelines. **We hypothesize** that extended antibiotic prophylaxis will reduce the odds of CR-POPF by 79%, from 37% to 11% (OR=0.21).

2.2 Secondary Objective(s)

Our secondary objectives are to analyze other pertinent postpancreatectomy outcomes between treatment arms. These include 30- and 90-day postoperative mortality, 30- and 90-day readmission rates, index postoperative length of stay, composite 90-day length of stay, delayed gastric emptying, post-pancreatectomy hemorrhage, superficial

surgical site infections, deep surgical site infections, deep space infections/intra-abdominal abscess, and rate of image-guided drain placement.

3.0 Study Design

3.1 Study design and cohorts

This study will be a randomized, controlled, unblinded, double arm study with 2:1 randomization to the intervention group.

This study will enroll patients who are planned to undergo elective pancreatoduodenectomy at UH CMC for any indication. Patients will be consented for participation in trial at their preoperative clinic visit. During surgery, if patient has undergone a successful pancreatoduodenectomy, the fistula risk score will be calculated as described in **Table 2**. If the FRS is ≥3 and the patient has a soft gland, the subject will be randomized to intervention or control arms in 2:1 fashion.

3.2 Number of Subjects

A total of 96 subjects will be enrolled in this trial. More may need to be consented if they do not meet criteria for randomization intraoperatively (e.g., low/negligible FRS [FRS ≤2]) or if procedures are aborted based on intraoperative findings (e.g., non-resectability, metastases, need for total pancreatectomy, etc).

3.3 Replacement of Subjects

Patients will not be replaced after enrollment and randomization and are assigned to intervention vs control. Subjects who have been consented but are not eligible for randomization at time of surgery will be removed from trial and additional subjects consented.

3.4 Expected Duration of Treatment and Subject Participation

Patients who are enrolled in the study and who undergo successful pancreatoduodenectomy with fistula risk score ≥3 will be randomized to either standard care or intervention. The intervention group will receive a total of 10 days of antibiotics. While in the hospital, patients will receive piperacillin/tazobactam, 3.375 g I.V. Q6H. Upon discharge, patients will be converted to oral amoxicillin/clavulanic acid 875/125 mg PO BID to finish a 10-day total course of antibiotics. For example, if a patient is admitted 7 days, then they would receive PO antibiotics for the next 3 days outpatient to cover 10 days total.

After this course is completed there will be no intervention remaining for this study. Subjects will be followed for primary and secondary outcomes for up to 90 days postoperatively, with planned interval follow-ups at 2 weeks, 30 days, and 90 days postoperatively. Additional follow-ups will be as clinically indicated depending on patient's postoperative recovery.

The control group will be treated according to current standard perioperative antibiotic practice, and perioperative antibiotics will not exceed 24 hours postoperatively.

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

Subject's Name

_____

Medical Record #

_____

Research Nurse / Study Coordinator Signature:

_____

Date _____

Treating Physician [Print]

_____

Treating Physician Signature:

_____

Date _____

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

___ 4.1.1 Subject undergoing planned, elective pancreatoduodenectomy at UH CMC for any indication.

___ 4.1.2 Age 18-90 years
Pancreatoduodenectomy is rarely, if ever performed in the elective setting for the pediatric population at UH CMC. Therefore, this study will not include this small and different population of patients undergoing pancreatoduodenectomy.

___ 4.1.3 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

___ 4.1.4 Creatinine Clearance greater than 40 ml/min

4.2 Exclusion Criteria

___ 4.2.1 Concurrent participation in another clinical trial, where participation in the proposed clinical trial that prohibits participation in this clinical trial, or where subjects would be actively receiving another investigational agent during the 90-day evaluation period of this study.

___ 4.2.2 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Piperacillin, Tazobactam, Amoxicillin, Clavulanic Acid or other agents used in this study.

___ 4.2.3 Subjects who are found to have another active infection or presumed infection at time of surgery who will be treated per standard of care with antibiotics regardless of randomization status.

___ 4.2.4 Subjects who are found to have metastatic disease at time of planned pancreatoduodenectomy, if surgery is otherwise aborted, or if total pancreatectomy is performed due to interoperative considerations

___ 4.2. Any subject who, while not having history of adverse reaction to similar chemical or biologic composition to Piperacillin, Tazobactam, Amoxicillin, Clavulanic Acid or other agents used in this study, develops a suspected drug reaction to the standard perioperative dose of antibiotic, prior to randomization.

4.3 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

This trial may have a relatively large number of patients who are consented but not enrolled due to the intraoperative nature of the randomization and the unpredictable disease process.

All subjects will be registered through University Hospitals Cleveland Medical Center and will be provided a study number by contacting the study coordinator (Nikola Anusic) as listed on the cover page.

This trial will utilize merged block randomization with 2:1 allocation to the treatment arm (extended antibiotics).

6.0 Treatment Plan

6.1 Treatment Regimen Overview

6.1.1 **Standard perioperative antibiotics:** patients will receive piperacillin/tazobactam 3.375 g prior to surgical incision, with intraoperative re-dosing every 2 hours. At surgeon's discretion, antibiotics may be dosed every 6 hours following completion of surgery for up to, but not exceeding, 24 hours from completion of surgery.

6.1.2 **Extended antibiotic prophylaxis:** patients will receive piperacillin/tazobactam 3.375 g prior to surgical incision, with intraoperative re-dosing every 2 hours. Following completion of surgery, piperacillin/tazobactam, available from the UH CMC inpatient pharmacy, will be ordered 3.375 g Q6H and timed per protocol on the assigned hospital ward. Piperacillin/tazobactam will continue while the patient remains hospitalized for up to 10 days. If a patient meets discharge criteria prior to 10 days, they will continue amoxicillin/clavulanic acid 875/125 mg by mouth BID to complete 10 days of total antibiotic prophylaxis.

6.1.3 **Intraoperative drain placement:** patients in both treatment arms will have 2 operative drains placed (15 or 19 French) prior to abdominal closure. The drains will be placed posterior and anterior to the pancreaticojejunostomy. Drain exit site on the abdominal wall is at the discretion of the operating surgeon. Additional drains may be placed at the discretion of the operating surgeon if it is felt they are indicated (e.g., in Morrison's pouch, etc.). Drains will be placed to passive (gravity) drainage.

6.1.4 **Assessment for biochemical leak and postoperative pancreatic fistula:** drain amylase from operatively placed drains will be checked on postoperative days 1 and 4. By definition, biochemical leak or CR-POPF requires that at least one drain contains amylase levels 3 times the upper limit of normal serum amylase on postoperative day 3 or after.

6.1.5 **Operative drain removal:** at the discretion of the surgeon, operatively placed drains may be removed any time after testing of drain fluid for amylase levels is performed, and biochemical leak or CR-POPF has been ruled out, generally on or after postoperative day 4.

6.1.6 **Workup and management of suspected CR-POPF:** at the operating surgeon's discretion, workup and treatment of a suspected CR-POPF may begin on or after postoperative day 3. Workup includes standard labs (complete blood count, metabolic panels) and cross-sectional imaging (typically contrast-enhanced CT scan). If a CR-POPF is confirmed based on ISGPF definition (**Table 1**), antibiotics may be initiated in patients who were not randomized to extended prophylaxis. Initiation of antibiotics in patients randomized to the control arm will require consensus from the four pancreatic surgeons after group discussion. Other management (initiation of somatostatin analogues, image-guided drain placement, transfer to ICU, return to operating room, placement of existing operative drains to suction, etc.) will be determined by the operating surgeon.

6.1.7 **Workup for other post-pancreatectomy complications:** for non-POPF-related complications (e.g., early post-pancreatectomy hemorrhage, anastomotic concerns related to the hepaticojejunostomy or gastrojejunostomy, concerns related to operatively placed enteral feeding tubes, concerns related to synchronous procedures [e.g., partial colectomy]), workup and management may occur at any time at the discretion of the surgeon.

6.1.8 **Workup of diarrhea:** all patients with significant diarrhea following surgery will be tested for *C. difficile* colitis.

6.1.9 **Postoperative infections:** for patients with documented postoperative infections based on cultures of blood, urine, or drain fluid, antimicrobial sensitivities of organisms that grow will be documented.

6.2 Criteria for Removal from Study

Treatment will continue for a total of 10 days, while inpatient on IV Piperacillin Tazobactam as described above and to complete 10 days as outpatient on amoxicillin/clavulanic acid if patient is discharged prior to postoperative day 10.

• Subject decision to withdraw from treatment (partial consent) or from the study (full consent)

• Any severe adverse drug reaction

• The investigator considers it, for safety reasons, to be in the best interest of the subject. This would be most clinically relevant in the case of acute kidney injury thought to be due to piperacillin/tazobactam, and the patient appearing clinically well.

• Death

6.3 Duration of Follow-Up

Subjects will be followed for postoperative outcomes for 90 days after surgery or until death, whichever occurs first.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome of the event. Any serious adverse event that occurs after the study period and is possibly related to the study treatment or study participation will be recorded and reported immediately.

7.0 Dose Delays/Dose Modifications

Patients will be monitored while inpatient as part of their standard postoperative care. As part of this their creatinine clearance will be monitored. If it drops below 40 ml/min the

piperacillin/tazobactam dose will be adjusted per manufacturer's recommendations for renal function, in association with the inpatient unit's clinical pharmacist.

Amoxicillin/Clavulanic acid will also be renally dosed, with reduction per manufacturer's recommendations if creatine clearance is below 30 ml/min. However, it is possible that if renal impairment is felt to be due to the antibiotics they may be halted prior to dose adjustment. Amoxicillin/Clavulanic acid will be provided to patients by prescription, and the medication will be delivered to the patient's room prior to hospital discharge.

8.0 Adverse Events and Potential Risks

8.1 Piperacillin/Tazobactam

The most common adverse events associated with piperacillin/tazobactam are listed below with the percentages given in piperacillin/tazobactam monotherapy trials:

Gastrointestinal disorders
Diarrhea (11.3%)
Constipation (7.7%)
Nausea (6.9%)
Vomiting (3.3%)
Dyspepsia (3.3%)
Abdominal pain (1.3%)
General disorders and administration site conditions
Fever (2.4%)
Injection site reaction (≤1%)
Rigors (≤1%)
Immune system disorders
Anaphylaxis (≤1%)
Infections and infestations
Candidiasis (1.6%)
Pseudomembranous colitis (≤1%)
Metabolism and nutrition disorders
Hypoglycemia (≤1%)
Musculoskeletal and connective tissue disorders
Myalgia (≤1%)
Arthralgia (≤1%)
Nervous system disorders
Headache (7.7%)
Psychiatric disorders
Insomnia (6.6%)
Skin and subcutaneous tissue disorders
Rash (4.2%, including maculopapular, bullous, and urticarial)
Pruritus (3.1%)
Purpura (≤1%)
Vascular disorders
Phlebitis (1.3%)

Thrombophlebitis (≤1%)
Hypotension (≤1%)
Flushing (≤1%)
Respiratory, thoracic and mediastinal disorders
Epistaxis (≤1%)

For a comprehensive list of adverse events please refer to package insert, full information is available at: https://labeling.pfizer.com/showlabeling.aspx?format=PDF&id=1177

8.1.1 Amoxicillin/Clavulanic Acid

The most common adverse events associated with Amoxicillin/Clavulanic Acid use are listed below:

Gastrointestinal
Diarrhea/Loose Stools (9%)
Nausea (3%)
Vomiting (1%)
Dermatologic
Skin rashes and Urticaria (3%)
Genitourinary
Vaginitis (1%)

For a comprehensive list of adverse events please refer to package insert: www.accessdata.fda.gov/drugsatfda_docs/label/2011/050564s052,050720s025lbl.pdf

8.2 Definitions

8.2.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**

- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

8.2.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)

- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)**
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 6.0 will be utilized for AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.3 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.4 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur from surgery through 30 days after the final dose prophylactic antibiotic. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.4.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
    - Lee.ocuin@uhhospitals.org
        - Cell 4045805343
- The Lead Site Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.5 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

8.6 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.

9.1 Commercial Agent

9.1.1 Name of Agent Piperacillin/Tazobactam

Other Names: Zosyn

Product description: Piperacillin/tazobactam is an injectable antibacterial combination product consisting of the semisynthetic antibacterial piperacillin sodium and the beta-lactamase inhibitor tazobactam sodium for intravenous administration. It is supplied in a powder either in bulk vials or single dose vitals.

Solution preparation/Storage Requirments/Stability:

Per Inpatient Phamacy Standard Practice at UH CMC, below are manufacturer's recommendations:

Reconstitution of piperacillin/tazobactam for Injection for Adult Patients and Pediatric Patients Weighing Over 40 kg Pharmacy Bulk Vials Reconstituted pharmacy bulk vial solution must be transferred and further diluted for intravenous infusion. The pharmacy bulk vial is for use in a hospital pharmacy admixture service only under a laminar flow hood. After reconstitution, entry into the vial must be made with a sterile transfer set or other sterile dispensing device, and contents should be dispensed as aliquots into intravenous solution using aseptic technique. Use entire contents of pharmacy bulk vial promptly. Discard unused portion after 24 hours if stored at room temperature (20°C to 25°C [68°F to 77°F]), or after 48 hours if stored at refrigerated temperature (2°C to 8°C [36°F to 46°F]). Reconstitute the pharmacy bulk vial with exactly 152 mL of a compatible reconstitution diluent, listed below, to a concentration of 200 mg/mL of piperacillin and 25 mg/mL of tazobactam. Shake well until dissolved. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to and during administration whenever solution and container permit. 7 Single-Dose Vials Reconstitute piperacillin/tazobactam single-dose vials with a compatible reconstitution diluent from the list provided below. 2.25 g, 3.375 g, and 4.5 g piperacillin/tazobactam should be reconstituted with 10 mL, 15 mL, and 20 mL, respectively. Swirl until dissolved. After reconstitution, the single-dose vials will have a concentration of 202.5 mg/mL (180 mg/mL of piperacillin and 22.5 mg/mL of tazobactam). Compatible Reconstitution Diluents for Pharmacy Bulk Vials and Single-Dose Vials 0.9% sodium chloride for injection Sterile water for injection Dextrose 5% Bacteriostatic saline/parabens Bacteriostatic water/parabens Bacteriostatic saline/benzyl alcohol Bacteriostatic water/benzyl alcohol Dilution of the Reconstituted piperacillin/tazobactam Solution for Adult Patients and Pediatric Patients Weighing Over 40 kg Reconstituted piperacillin/tazobactam solutions for both pharmacy bulk vials and single-dose vials should be further diluted (recommended volume per dose of 50 mL to 150 mL) in a compatible intravenous solution listed below. Administer by infusion over a period of at least 30 minutes. During the infusion it is desirable to discontinue the primary infusion solution. Compatible Intravenous Solutions for Pharmacy Bulk Vials and Single-Dose Vials 0.9% sodium chloride for injection Sterile water for injection (Maximum recommended volume per dose of sterile water for injection is 50 mL) Dextran 6% in saline Dextrose 5% Lactated Ringer's Solution (compatible only with reformulated piperacillin/tazobactam containing EDTA and is compatible for co-administration via a Y-site) piperacillin/tazobactam should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

piperacillin/tazobactam is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH.

Route of administration:
Intravenous infusion over 30 minutes

9.1.2 Name of Agent Amoxicillin/Clavulanic Acid

Other Names: Augmentin

Product Description:
Amoxicillin/Clavulanic Acid is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. Amoxicillin/Clavulanic Acid 875-mg Tablets: Each scored white capsule-shaped tablet contains 875 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

Solution preparation/Storage Requirments/Stability:

This medication will be supplied and available in clinical pharmacies, and they will follow their protocols for storage and handling of medication.

Route of administration:
P.O.

10.0 STUDY PARAMETERS AND CALENDAR

10.1 Study Parameters

Patients will have all labs and imaging required by study done as part of the standard of care following pancreatoduodenectomy.

10.2 Calendar

	Pre-operative	Intra-operative	Postoperative Day 0-10	Postoperative Day 0-90
Informed consent	X			
Demographics	X			
Standard antibiotics (pre-incision, intraop redosing)		X		
Pancreatoduodenectomy		X		
Fistula risk score assessment		X		

Randomization		X		
Extended antibiotics			X	
Monitoring for CR-POPF			X	X
Monitoring of creatinine clearance	X		X	
Monitoring for any postoperative complications			X	X
Monitoring for any antibiotic-associated AEs			X	X
Two-week follow-up (assuming discharged)				X
One month follow-up				X
30-day baseline imaging (standard of care)				X
90-day follow-up				X
90-day imaging (standard of care if malignancy; otherwise only ordered if clinically indicated)				X

11.0 MEASUREMENT OF EFFECT

Clinical outcomes will be studied 90-days post operatively or until any complications have reached their conclusion. Standard clinic visits will occur at 2 weeks postoperatively (assuming the patient is discharged), 30 days postoperatively, and 90 days postoperatively. Assessment for complications will occur throughout index hospitalization and at follow-up visits. Labs and imaging will be obtained per standard of care.

12.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

The OnCore™ Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore™ is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore™. Access to data through OnCore™ is restricted by user accounts and assigned roles. Once logged into the OnCore™ system with a user ID and password, OnCore™ defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at [redacted].

OnCore™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore™ database. A calendar of events and required forms are available in OnCore™.

12.2 **Regulatory Considerations**

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

12.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

12.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

12.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

12.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable

regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study design

13.1.1 This will be a randomized controlled trial testing the efficacy of extended antibiotic prophylaxis with piperacillin/tazobactam in decreasing the rate of CR-POPF following PD in patients with intermediate- and high-risk FRS (FRS ≥3), as compared to standard perioperative administration of piperacillin/tazobactam, not to exceed 24 hours.

13.1.2 **Primary endpoint:** the rate of clinically relevant POPF within 90 days of surgery, defined as Grade B or Grade C POPF based on ISGPF consensus statement.

13.1.3 **Secondary endpoints:** major complications (Clavien-Dindo ≥3)[18], post-pancreatectomy hemorrhage, delayed gastric emptying, 30- and 90-day readmission rates, 30- and 90-day mortality rates, wound complications (superficial and deep), deep space infections, composite 90-day length of stay (index and any associated readmissions), rate of additional drain placement, unplanned return to OR, acute kidney injury, *C. difficile* colitis.

13.2 Sample size and power

13.2.1 **Hypothesis:** extended antibiotic prophylaxis will reduce the rate of CR-POPF from 37% to 11%, corresponding to an odds ratio of 0.21.

13.2.2 **Power:** the study will have 80% power with a 2-sided alpha level of 0.05.

13.2.3 **Sample size:** a total of **96 patients** are required to achieve 80% power with 2-sided alpha level of 0.05 to reject the null hypothesis of 37% CR-POPF rate in patients who are managed with standard perioperative antibiotics. **64 patients** will be randomized to extended antibiotic prophylaxis, and **32 patients** will be randomized to standard perioperative antibiotics.

13.3 Statistical methodology

13.3.1 Categorical outcomes will be analyzed by Pearson's chi-squared.

13.3.2 Continuous variables will be analyzed by the Student's t-test (normally distributed) or Wilcoxon rank-sum test (non-normally distributed).

13.3.3 Statistical significance is indicated by p-value of <0.05.

13.4 Accrual rate

13.4.1 Surgical volume: the Division of Surgical Oncology at UH CMC performs approximately 120-130 pancreatectomies annually, with approximately 90-100 pancreatoduodenectomies.

13.4.2 Accrual rate: we would anticipate an accrual rate of 4 patients per month and would expect to complete accrual by 36 months.

REFERENCES

1. Winter JM, Cameron JL, Campbell KA, et al. 1423 Pancreaticoduodenectomies for Pancreatic Cancer: A Single-Institution Experience. *Journal of Gastrointestinal Surgery*. 2006;10(9):1199-1211. doi:10.1016/j.gassur.2006.08.018

2. Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital Volume and Surgical Mortality in the United States. *New England Journal of Medicine*. 2002;346(15):1128-1137. doi:10.1056/NEJMsa012337

3. Xiang C, Chen Y, Liu X, Zheng Z, Zhang H, Tan C. Prevention and Treatment of Grade C Postoperative Pancreatic Fistula. *J Clin Med*. 2022;11(24). doi:10.3390/jcm11247516

4. Ciprani D, Bannone E, Marchegiani G, Nessi C, Salvia R, Bassi C. Progression from biochemical leak to pancreatic fistula after distal pancreatectomy. Don't cry over spilt amylase. *Pancreatology*. Published online 2022. doi:10.1016/j.pan.2022.06.257

5. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. 2017;161(3):584-591. doi:10.1016/j.surg.2016.11.014

6. Kang YH, Kang JS, Lee M, et al. Comparisons of short-term outcomes of anastomotic methods of duct-to-mucosa pancreaticojejunostomy: out-layer continuous suture *versus* modified Blumgart method. *Ann Surg Treat Res*. 2022;103(6):331. doi:10.4174/astr.2022.103.6.331

7. Halloran CM, Neoptolemos JP, Jackson R, et al. A Multicenter, Randomized, Double-Blinded, Clinical Trial Comparing Cattell-Warren and Blumgart Anastomoses Following Partial Pancreatoduodenectomy. *Annals of Surgery Open*. 2022;3(3):e198. doi:10.1097/as9.0000000000000198

8. Bootsma BT, Plat VD, van de Brug T, et al. Somatostatin analogues for the prevention of pancreatic fistula after open pancreatoduodenectomy: A nationwide analysis. *Pancreatology*. 2022;22(3):421-426. doi:10.1016/j.pan.2022.03.006

9. Pillarisetty VG, Abbasi A, Park JO, Sham JG. A phase II trial of lanreotide for the prevention of postoperative pancreatic fistula. *HPB*. 2022;24(11):2029-2034. doi:10.1016/j.hpb.2022.07.011

10. Russell TB, Aroori S. Procedure-specific morbidity of pancreatoduodenectomy: a systematic review of incidence and risk factors. *ANZ J Surg*. 2022;92(6):1347-1355. doi:10.1111/ans.17473

11. Pande R, Halle-Smith JM, Phelan L, et al. External validation of postoperative pancreatic fistula prediction scores in pancreatoduodenectomy: a systematic review and meta-analysis. *HPB*. 2022;24(3):287-298. doi:10.1016/j.hpb.2021.10.006

12. Kamarajah SK, Bundred JR, Lin A, et al. Systematic review and meta-analysis of factors associated with post-operative pancreatic fistula following pancreatoduodenectomy. *ANZ J Surg*. 2021;91(5):810-821. doi:10.1111/ans.16408

13. Zhao Z, Yin Z, Hang Z, Ji G, Feng Q, Zhao Q. A systemic review and an updated meta-analysis: Minimally invasive vs open pancreaticoduodenectomy. *Sci Rep*. 2017;7(1). doi:10.1038/s41598-017-02488-4

14. Dou CW, Liu ZK, Jia YL, et al. Systematic review and meta-analysis of prophylactic abdominal drainage after pancreatic resection. *World J Gastroenterol*. 2015;21(18):5719-5734. doi:10.3748/wjg.v21.i18.5719

15. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM. A Prospectively Validated Clinical Risk Score Accurately Predicts Pancreatic Fistula after Pancreatoduodenectomy. *J Am Coll Surg*. 2013;216(1):1-14. doi:10.1016/j.jamcollsurg.2012.09.002

16. Shubert CR, Wagie AE, Farnell MB, et al. Clinical Risk Score to Predict Pancreatic Fistula after Pancreatoduodenectomy: Independent External Validation for Open and Laparoscopic Approaches. *J Am Coll Surg*. 2015;221(3):689-698. doi:10.1016/j.jamcollsurg.2015.05.011

17. Shubert CR, Kendrick ML, Habermann EB, et al. Implementation of prospective, surgeon-driven, risk-based pathway for pancreatoduodenectomy results in improved clinical outcomes and first year cost savings of $1 million. *Surgery*. 2018;163(3):495-502. doi:10.1016/j.surg.2017.10.022

18. Breitenstein S, Deoliveira ML, Raptis DA, et al. Novel and simple preoperative score predicting complications after liver resection in noncirrhotic patients. In: *Annals of Surgery*. Vol 252. ; 2010:726-733. doi:10.1097/SLA.0b013e3181fb8c1a