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Association between biliary pathogens, surgical site infection, and pancreatic fistula: results of a randomized trial of perioperative antibiotic prophylaxis in patients undergoing pancreatoduodenectomy

Ryan J. Ellis, MD, MS[1,2,3], **Brian C. Brajcich, MD, MS**[2], **Kimberly A. Bertens, MD**[4], **Carlos H.F. Chan, MD, PhD**[5], **Carlos Fernandez-del Castillo, MD**[6], **Paul J. Karanicolas, MD, PhD**[7], **Shishir K. Maithel, MD**[8], **Bradley N. Reames, MD, MS**[9], **Sharon M. Weber, MD**[10], **Roberto J. Vidri, MD, MPH**[10], **Henry A. Pitt, MD**[11], **Vanessa M. Thompson, PhD**[2], **Mithat Gonen, PhD**[1], **Susan K. Seo, MD**[1], **Adam C. Yopp, MD**[12], **Clifford Y. Ko, MD, MPH, MSHS**[2,13,14], **Michael I. D'Angelica, MD**[1]

[1.]Memorial Sloan Kettering Cancer Center, New York, NY

[2.]American College of Surgeons, Chicago, IL

[3.]Indiana University Health, Indianapolis, IN

[4.]University of Ottawa, Ottawa, ON

[5.]University of Iowa Hospitals and Clinics, Iowa City, IA

[6.]Massachusetts General Hospital, Boston, MA

[7.]Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON

[8.]Emory University Hospital, Atlanta, GA

[9.]University of Nebraska Medical Center, Omaha, NE

[10.]University of Wisconsin School of Medicine and Public Health, Madison, WI

[11.]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

[12.]University of Texas Southwestern Medical Center, Dallas, TX

[13.]Department of Surgery, University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA

[14.]Department of Surgery, VA Greater Los Angeles Healthcare System, Los Angeles, CA

Abstract

Objective: Establish the association between bactibilia and postoperative complications when stratified by perioperative antibiotic prophylaxis.

Corresponding Author: Michael I. D'Angelica, MD, Hepatopancreatobiliary Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, dangelim@mskcc.org.

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Background: Patients undergoing pancreatoduodenectomy (PD) experience high rates of surgical site infection (SSI) and clinically relevant postoperative pancreatic fistula (CR-POPF). Contaminated bile is known to be associated with SSI, but the role of antibiotic prophylaxis in mitigation of infectious risks is ill-defined.

Methods: Intraoperative bile cultures (IOBC) were collected as an adjunct to a randomized phase 3 clinical trial comparing piperacillin-tazobactam with cefoxitin as perioperative prophylaxis in patients undergoing PD. After complication of IOBC data, associations between culture results, SSI, and CR-POPF were assessed using logistic regression stratified by the presence of a preoperative biliary stent.

Results: Of 778 participants in the clinical trial, IOBC were available for 247 participants. Overall, 68 (27.5%) grew no organisms, 37 (15.0%) grew one organism, and 142 (57.5%) were polymicrobial. Organisms resistant to cefoxitin but not piperacillin-tazobactam were present in 95 patients (45.2%). The presence of cefoxitin-resistant organisms, 92.6% of which contained either *Enterobacter* or *Enterococcus* species, was associated with development of SSI in participants treated with cefoxitin (53.5% vs 25.0%; OR 3.44, 95%CI 1.50-7.91; P=0.004) but not those treated with piperacillin-tazobactam (13.5% vs 27.0%; OR 0.42, 95%CI 0.14-1.29; P=0.128). Similarly, cefoxitin-resistant organisms were associated with CR-POPF in participants treated with cefoxitin (24.1% vs 5.8%; OR 3.45, 95%CI 1.22-9.74; P=0.017) but not those treated with piperacillin-tazobactam (5.4% vs 4.8%; OR 0.92, 95%CI 0.30-2.80; P=0.888).

Conclusion: Previously observed reductions in SSI and CR-POPF in patients that received piperacillin-tazobactam antibiotic prophylaxis are potentially mediated by biliary pathogens that are cefoxitin resistant, specifically *Enterobacter spp* and *Enterococcus spp*.

MINI ABSTRACT

In this analysis of intraoperative bile cultures from a randomized clinical trial comparing antibiotic prophylaxis regimens for pancreatoduodenectomy, patients were more likely to develop surgical site infection and clinically relevant postoperative pancreatic fistula if they harbored *Enterobacter* or *Enterococcus* species in biliary cultures and were treated with standard of care antibiotics. These results highlight the link between bactibilia, antibiotic prophylaxis, and surgical complications.

INTRODUCTION

Pancreatoduodenectomy (PD) is performed for both benign and malignant diseases of the periampullary region. While the last 40 years have seen improvements in postoperative mortality, morbidity remains high[1] with associated reductions in quality of life and possibly worse oncologic survival for patients that undergo PD for malignant indications.[2-4] The most common sources of severe morbidity are surgical site infection (SSI) and clinically-relevant postoperative pancreatic fistula (CR-POPF), which combined occur in more than a quarter of patients.[5]

While the etiology of postop SSI and CR-POPF is multifactorial, infection risk may be related to preoperative biliary instrumentation, which contaminates the normally sterile biliary tree and is associated with high SSI rates.[6-8] Multiple retrospective series have

attempted to identify associations between intraoperative bile culture (IOBC) results and postoperative complications with mixed results. A study from Maatman et al demonstrated no association between overall bactibilia and postoperative complications, but did identify an association between the presence of *Enterococcus* and *Enterobacter* and development of SSI.[9] Regardless of individual pathogen, biliary contamination and prolonged use of preoperative biliary stents are also associated with the presence of antibiotic-resistant bacteria on IOBC.[10,11] These observations have led some institutions to routinely obtain IOBCs to guide postoperative therapy in the event of SSI, but this practice has also been called into question given inconsistent correlations between IOBC and postoperative infection culture results.[12]

The notion that bactibilia and resistant organisms drive postoperative SSI led to multiple retrospective series[13,14] and recently a multicenter, phase III clinical trial comparing piperacillin-tazobactam with standard of care cefoxitin for use as routine antibiotic prophylaxis in patients undergoing PD.[15,16] This trial demonstrated significant reduction in both SSI and CR-POPF in patients administered piperacillin-tazobactam compared to standard of care cefoxitin which was particularly robust in patients with preoperative biliary stents.[16] Following the results of the randomized trial, we hypothesized that biliary pathogens that are inherently resistant to cefoxitin, specifically *Enterococcus* and *Enterobacter* species, would be associated with development of SSI and CR-POPF in patients treated with cefoxitin but not those given piperacillin-tazobactam. The objectives of the current study were to 1) describe the frequency of bactibilia in IOBC in patients undergoing PD in the randomized trial cohort and 2) define associations between specific biliary pathogens and development of SSI and CR-POPF in patients given cefoxitin vs those administered piperacillin-tazobactam.

METHODS

Trial Design and Participants

The trial was initiated by the American College of Surgeons (ACS) Division of Research and Optimal Patient Care in conjunction with the Americas Hepato-Pancreato-Biliary Association (AHPBA) Clinical Trials subcommittee. The trial was designed as a multicenter, open-label, phase 3 randomized trial and was conducted at 26 centers across the United States and Canada with ACS National Surgical Quality Improvement Program (ACS-NSQIP) as the primary data collection platform. Briefly, the ACS-NSQIP is a routinely audited, validated, prospective, multi-institutional outcomes and quality program that uses trained reviewers to collect data on >150 perioperative variables.[17] All hospitals participated in the ACS-NSQIP Pancreatectomy Procedure Targeted Program, which augments standard ACS-NSQIP data to include additional preoperative, intraoperative, and postoperative data pertinent to pancreatic surgery. Three additional trial-specific variables were collected in randomized participants: documentation of perioperative antibiotic administration to assess adherence to randomization, dosing violations, and adverse reactions.[18]

Adults aged ≥18 undergoing elective open PD for any indication were eligible for trial participation. Exclusion criteria included: minimally invasive (e.g., laparoscopic or robotic) PD, inability to receive trial antibiotics due to allergy or medical issues, active infection,

use of antibiotics within seven days of surgery for any indication, chronic glucocorticoid use, chronic dialysis or creatinine clearance ≤40 ml/min, or those pregnant or nursing. Participants were randomized 1:1 at the time of surgical scheduling to receive either piperacillin-tazobactam or cefoxitin. Randomization was performed centrally at Memorial Sloan Kettering Cancer Center (MSKCC), with randomization stratified by the presence or absence of preoperative biliary stent as reported by the operative site. Participants were removed and replaced post-randomization if they withdrew consent, were deemed ineligible, or did not undergo PD for any reason. All subsequent data collection was through standard ACS-NSQIP protocols.

Culture Result Analysis and Classification

Patients with IOBC collected were eligible for this subgroup analysis. Collection of IOBC was an optional but encouraged adjunct to the primary trial analysis and not collected directly by ACS-NSQIP. Following completion of the trial, participating sites provided results of IOBC, postoperative wound cultures, and postoperative blood cultures, when available. Once compiled, biliary cultures were further classified based on the number of bacterial species present (negative/sterile, single organism, multiple organisms). Among patients with available speciation and sensitivity data, cultures were classified based on the presence or absence of bacteria resistant to either cefoxitin, or, in cases where cefoxitin was not tested directly, other cephamycin type antibiotics (e.g., cefotetan). Organisms present in postoperative wound, abdominal, or blood cultures were compared with IOBC to assess concordance.

Intervention

Participants received their first dose of cefoxitin (2 gm intravenously) or piperacillin-tazobactam (3.375 or 4.5 gm intravenously as per local protocols) within 60 minutes of incision and additional doses during the operation every 2-4 hours until close of incision.[15] Perioperative antibiotic administration was required to end within 24 hours after close of incision. Participants who failed to receive the correct antibiotic, had inappropriate intraoperative redosing, or had antibiotics continued beyond 24 hours were marked as protocol violates in ACS-NSQIP but still included in the primary analysis.

Outcomes

The primary outcome was development of SSI within 30 days of surgery stratified by antibiotic prophylaxis regimen. SSI was defined according to standard ACS-NSQIP definitions as a composite of superficial, deep, and organ-space infections.[19] The secondary endpoint was development of CR-POPF, defined as clinically relevant Grade B and C fistulas according to the International Study Group in Pancreatic Surgery guidelines.[20,21]

Statistical Analysis

All analyses were performed on a modified intention-to-treat basis regardless of any observed antibiotic dosing violations, omitting those patients excluded post-randomization as described above. Data are reported as both absolute number and percentage unless noted otherwise. Missing data and changes in denominator for calculations are noted in table

footnotes. Comparisons between continuous variables were made using student's t-test and categorical variables were compared by chi square or Fisher's exact test, as appropriate. The association between biliary culture results and development of SSI and CR-POPF was assessed via logistic regression stratified by the presence or absence of biliary stent or by exact logistic regression stratified by biliary stent in comparisons with low event rates. All analyses were performed with SAS software, version 9.4 (Cary, NC).

RESULTS

Study Cohort

Between November 2017 and August 2021, 967 participants undergoing PD were randomized to receive either piperacillin-tazobactam (n=483) or cefoxitin (n=484) prophylaxis. Of those, 189 either withdrew consent or did not undergo PD, leaving 778 participants for the primary trial analysis (n=378 piperacillin-tazobactam; n=400 cefoxitin). Among those 778 patients, 247 (31.7%) at eight institutions had IOBC collected at the time of the index operation and were eligible for analysis. Of these 247 cases, 16 had IOBC results limited to "polymicrobial" without additional speciation, leaving 231 participants with speciated IOBC results. Of these, 210 had full sensitivity data available for analysis (Figure 1).

Of the 247 patients with IOBC collected, the cohort had a median age of 68.9 years (interquartile range [IQR] 60.6-75.5), 129 were male (52.2%), and 205 (83%) were American Society of Anesthesiologists (ASA) class 3 or 4. Most participants had an indwelling biliary stent at the time of the operation (n=164, 66.4%), 96 (38.9%) had received neoadjuvant therapy, and 173 (70.0%) underwent PD for a diagnosis of pancreatic adenocarcinoma. The correct antibiotic was administered in 243 (98.4%) participants. There were no significant differences between cefoxitin and piperacillin-tazobactam cohorts in measured clinical variables, though a higher proportion of patients in the cefoxitin cohort received the correct antibiotic (n=130, 100%) than the piperacillin-tazobactam cohort (n=113, 96.6%; P=0.049; Table 1).

Intraoperative Biliary Culture Results

Among all 247 patients with IOBC performed, 68 (27.5%) were sterile, 37 (15.0%) grew a single organism, and 142 (54.5%) were polymicrobial. Biliary stents were present in 66.4% of patients and were associated with higher rates of contaminated bile (92.7% vs 32.5%, P<0.001) compared to unstented patients. In the 231 patients with speciation data, the most commonly isolated species was *Enterococcus faecalis* (n=50, 21.6%), followed by *Klebsiella pneumoniae* (n=49, 21.2%), *Escherichia coli* (n=44, 19.0%), *Streptococcus anginosus* (n=44, 19.0%), *Klebsiella oxytoca* (n=39, 16.9%), and *Enterobacter cloacae* (n=38, 16.5%). No other individual species were found in more than 10% of IOBCs. In the 210 IOBC samples with antibiotic sensitivity data, the most common organisms resistant to cefoxitin were *Enterococcus faecalis* (n=50, 23.8%), *Enterobacter cloacae* (n=38, 18.1%), and *Enterococcus faecium* (n=21, 10.0%). Detailed IOBC results can be found in Table 2.

Biliary Culture Results and Postoperative Surgical Site Infection

Of the 247 cases, 77 (31.2%) developed an SSI, including 50 (38.5%) in the cefoxitin group and 27 (23.7%) in the piperacillin-tazobactam group. A lower rate of SSI was observed in patients with negative IOBC (22.1%) than in patients with either a single organism (n=14, 37.8%) or polymicrobial IOBC (n=48, 33.8%). Positive IOBC were significantly associated with SSI development in participants who received cefoxitin (negative IOBC 17.9%, single organism 52.2%, polymicrobial 41.8%; P=0.047) but not in those who received piperacillin-tazobactam (negative IOBC 25.0%, single organism 14.3%, polymicrobial 23.8%; P=0.717). No difference in SSI rate was observed for either the cefoxitin or piperacillin-tazobactam groups when stratifying SSI into superficial SSI and deep/organ space SSI (Table 3).

When analyzing specific organisms in the 231 patients with speciation data available (Figure 2, Table 3), *Enterobacter spp* (n=38, 16.4%) were associated with SSI development in participants treated with cefoxitin (55.2% vs 34.1% if no *Enterobacter spp*; OR 2.38, 95%CI 1.00-5.65; P=0.049) but not in those treated with piperacillin-tazobactam (11.1% vs 23.5% if no *Enterobacter spp*; OR 0.41, 95%CI 0.05-3.48; P=0.408). Similarly, the presence of *Enterococcus spp* (n=68, 29.4%) was associated with SSI in participants treated with cefoxitin (52.4% vs 32.1% if no *Enterococcus spp*; OR 2.33, 95%CI 1.06-5.15; P=0.035) but not in those treated with piperacillin-tazobactam (15.4% vs 24.7% if no *Enterococcus spp*; OR 0.55, 95%CI 0.17-1.84; P=0.332).

Among the 210 participants with sensitivity data for analysis, 95 (45.2%) grew organisms resistant to cefoxitin. Of note, the majority (88/95, 92.6%) grew either *Enterobacter spp* or *Enterococcus spp*. The presence of preoperative biliary stent was associated with the presence of cefoxitin-resistant organisms (61.7%% vs 19.5%, P<0.001). The presence of cefoxitin-resistant organisms on IOBC was associated with development of SSI in participants treated with cefoxitin (53.5% vs 25.0% if no resistant organisms; OR 3.44, 95%CI 1.50-7.91; P=0.004) but not those treated with piperacillin-tazobactam (13.5% vs 27.0% if no resistant organisms; OR 0.42, 95%CI 0.14-1.29; P=0.128).

Biliary Culture Results and Clinically Relevant Postoperative Pancreatic Fistula

The overall rate of CR-POPF in the cohort was 19.0% (n=27, 20.8% in cefoxitin group, n=20, 17.1% in piperacillin-tazobactam group). No difference in CR-POPF rate was found when comparing negative IOBC to positive IOBC in either the cefoxitin cohort (negative IOBC 7.1%, single organism 26.1%, polymicrobial 24.1%; P=0.188) or the piperacillin-tazobactam cohort (negative IOBC 20.0%, single organism 14.3%, polymicrobial 15.9%; P=0.832; Table 4).

When considering specific organisms (Figure 3, Table 4), *Enterobacter spp* were associated with CR-POPF development in participants treated with cefoxitin (41.4% vs 15.4% if no *Enterobacter spp*; OR 3.88, 95%CI 1.50-10.1; P=0.006) but not in those treated with piperacillin-tazobactam (11.1% vs 18.6% if no *Enterobacter spp*; OR 0.55, 95%CI 0.06-4.87; P=0.585). Similarly, the presence of *Enterococcus spp* was associated with CR-POPF in participants treated with cefoxitin (33.3% vs 15.4% if no *Enterococcus spp*; OR 2.57, 95%CI 1.11-6.82; P=0.029) but not in those treated with piperacillin-tazobactam

(15.4% vs 18.8% if no *Enterococcus spp*; OR 0.78, 95%CI 0.23-2.66; P=0.694). The presence of cefoxitin-resistant organisms on IOBC, 92.6% of which contained either *Enterobacter spp* or *Enterococcus spp*, was associated with development of CR-POPF in participants treated with cefoxitin (31.0% vs 11.5% if no resistant organisms; OR 3.45, 95%CI 1.22-9.74; P=0.020) but not those treated with piperacillin-tazobactam (16.2% vs 17.5% if no resistant organisms; OR 0.92, 95%CI 0.30-2.80; P=0.875).

Infectious Culture Results

Culture results were available for a limited number of patients who developed SSI with or without CR-POPF (n=24). Among those 24 patients with postoperative infection culture data, 18 (66.7%) grew organisms that were previously identified on IOBC. Of those 18 who grew identical bacteria, the most common isolates were *Enterococcus spp* (n=8, 44.4%) and *Enterobacter spp* (n=4, 22.2%). Conversely, 9 of 24 patients (37.5%) with postoperative culture data developed infections that contained at least one organism not present on IOBC.

DISCUSSION

In this subset analysis of a randomized clinical trial examining the association between bactibilia, perioperative antibiotics, and postoperative complications in patients undergoing PD, the rate of postoperative SSI and CR-POPF was associated with the presence of cefoxitin-resistant organisms in biliary cultures, most notably *Enterobacter spp* and *Enterococcus spp*. This association was highly dependent upon perioperative antibiotic prophylaxis, with *Enterobacter spp* and *Enterococcus spp* being associated with SSI and CR-POPF in patients who received cefoxitin as perioperative antibiotic prophylaxis but not in those who received piperacillin-tazobactam.

Postoperative morbidity following PD has remained high despite improved patient selection, technical advances in surgery, and improvements in rescue after postoperative complications.[1] With SSI and CR-POPF being the most common sources of morbidity, the randomized trial from which this cohort was derived represented a significant step towards meaningful reduction in the rate of these devastating postoperative complications.[16] However, the magnitude of the reduction in SSI observed with the use of piperacillin-tazobactam in the randomized trial (13.0% absolute risk reduction compared to cefoxitin), paired with the unexpected finding of lower rates of CR-POPF in patients treated with piperacillin-tazobactam, led to additional questions regarding the biology underlying these findings.

This study confirms that, as was hypothesized prior to initiation of the broader randomized controlled trial, the high rate of cefoxitin-resistant bacteria in the bile is the most likely mechanism for the observed reduction in SSI. The association between bactibilia and SSI, regardless of antibiotic sensitivity, has been known for decades.[7] Some discordance has existed in previously observed associations between SSI and bactibilia, with some studies identifying increased rates of superficial SSI only while others identified increased risk of both superficial and deep/organ space SSI.[22] In the present study, bactibilia in general was associated with SSI overall but not with either superficial or deep/organ space SSI individually. However, the presence of cefoxitin-resistant organisms was associated with

all types of SSI but only in patients treated with cefoxitin. These results imply that the long-recognized infectious risk of bactibilia, whether for superficial or deep/organ space SSI, can be effectively reduced with broader antibiotic prophylaxis specifically targeting common organisms that are intrinsically resistant to early cephalosporin antibiotics such as *Enterobacter* and *Enterococcus spp*.

These results also shed additional light on the interaction between perioperative antibiotic prophylaxis and the development of CR-POPF, which often leads to a cascade of downstream complications.[23] Improvements in CR-POPF have been elusive despite substantial research efforts.[20] The strong association between inadequate treatment of cefoxitin-resistant bacteria and CR-POPF development provides potentially novel insights into the mechanism underlying CR-POPF development. Previous research on intestinal anastomoses has implicated collagenase-producing bacteria such as *Enterococcus faecalis* in the formation of anastomotic leak.[24,25] It is possible that the use of piperacillin-tazobactam, which has activity against *Enterococcus spp*, may alter the microbial environment of the reconstruction and facilitate healing. Alternatively, the findings could demonstrate that the higher untreated bacterial load in the intestine leads to a more severe clinical phenotype and eventual CR-POPF in what might have been an asymptomatic and even undiagnosed biochemical leak with improved perioperative prophylaxis.[20] Future studies should attempt to more clearly delineate the exact interaction between the biliary microbiome, perioperative antibiotics, and healing of the pancreatojejunostomy.

Finally, while the total number of patients with postoperative culture data available was small, the results are instructive in the potential utility of IOBC to guide postoperative therapy. This strategy has been advocated in multiple previous studies, noting relatively high rates of concordance between IOBC and postoperative infections.[26] More recently, some studies have called this association into question given the relatively high likelihood of microbes that were not present on IOBC populating postoperative infections.[12] In the authors' opinion, the results of the present analysis yield credence to the concept of empirically treating based on IOBC results, as more than half of postoperative infections grew microbes present on IOBC. However, clinicians should approach these situations with an abundance of caution and attempt to sample and culture infectious fluids whenever clinically feasible, as microbes not present on IOBC are relatively common in postoperative infections and may dictate changes in antibiotic strategy.

This study has important limitations. First, the trial design and lack of a formal funding mechanism made it impossible to mandate routine IOBC collection at all sites. As such, this cohort is a non-random cross section of patients, either derived from institutions that do routine IOBC or perhaps due to patient-level factors intraoperatively (e.g., purulent bile). The cohort of this study does not accurately represent the true randomized cohort of the overall clinical trial. As a *post hoc* subgroup analysis, all findings within this study are associations only and hypothesis generating. Second, multiple levels of exclusions had to be applied to those patients who did have IOBC data available, including removal of samples without speciation or sensitivity analysis. Third, this study is fundamentally an analysis of multiple clinical trial subsets, which reduces the sample size of each comparison group to the point that adjusted multivariable analyses were not feasible. Third, the pragmatic

nature of the trial and ACS-NSQIP based data collection made several variables of interest for this study (e.g., extent of preoperative biliary instrumentation, duration and type of biliary stent, history of cholangitis) unavailable for analysis. Fourth, piperacillin-tazobactam resistance was not formally quantified in this cohort study due to inconsistent sensitivity testing (especially in *Enterobacter* and *Enterococcus* spp) and is likely dependent on local hospital resistance patterns. However, any bias introduced by this would be towards the null as the presence of bacteria resistant to piperacillin-tazobactam would likely increase the rate of adverse outcomes in the piperacillin-tazobactam cohort and blunt differences between the two antibiotic groups. Finally, transitioning towards routine broad-spectrum antimicrobial prophylaxis must be done within the parameters of antibiotic stewardship. It is possible that routine use of piperacillin-tazobactam could induce higher levels of piperacillin-tazobactam resistance. Additionally, cephamycin antibiotics such as cefoxitin may still be reasonably alternatives in patients with non-severe penicillin allergies as it is well tolerated and can be infused relatively rapidly prior to incision.

CONCLUSION

The previously observed reduction in postoperative SSI and CR-POPF in patients receiving piperacillin-tazobactam as antibiotic prophylaxis compared to cefoxitin may be mediated by the presence of certain biliary bacteria that are resistant to cefoxitin, notably *Enterobacter spp* and *Enterococcus spp*. While piperacillin-tazobactam or similar broad-spectrum penicillins should be standard of care prophylaxis for patients undergoing PD, alternative antibiotic regimens, when necessary, should be sure to target these resistant organisms. The mechanisms underlying these findings, especially the interaction between the microbiome and development of CR-POPF, should be further explored.

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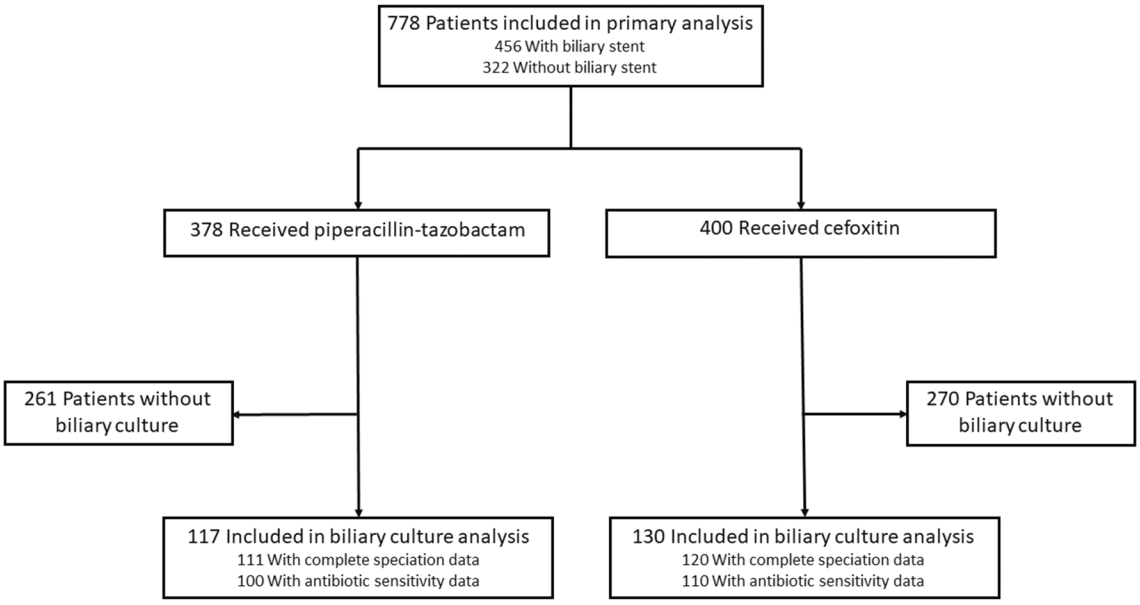

Figure 1. Development of Patient Cohort

Patient flow through overall randomized clinical trial and identification of subset of patients with intraoperative biliary cultures for analysis.

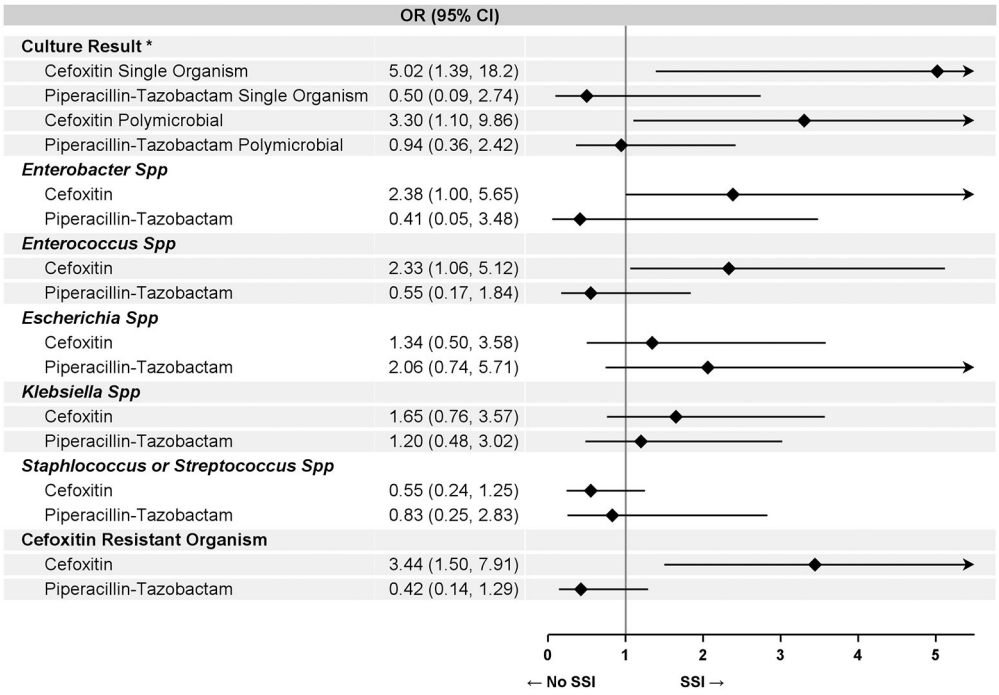

Figure 2. Association between IOBC results, antibiotic administered, and development of surgical site infection

Vertical line represents no association between the listed organisms and SSI. The diamond is subgroup-specific odds ratio and whiskers represent 95% confidence interval.

*Culture result uses sterile bile (no organisms) as reference group

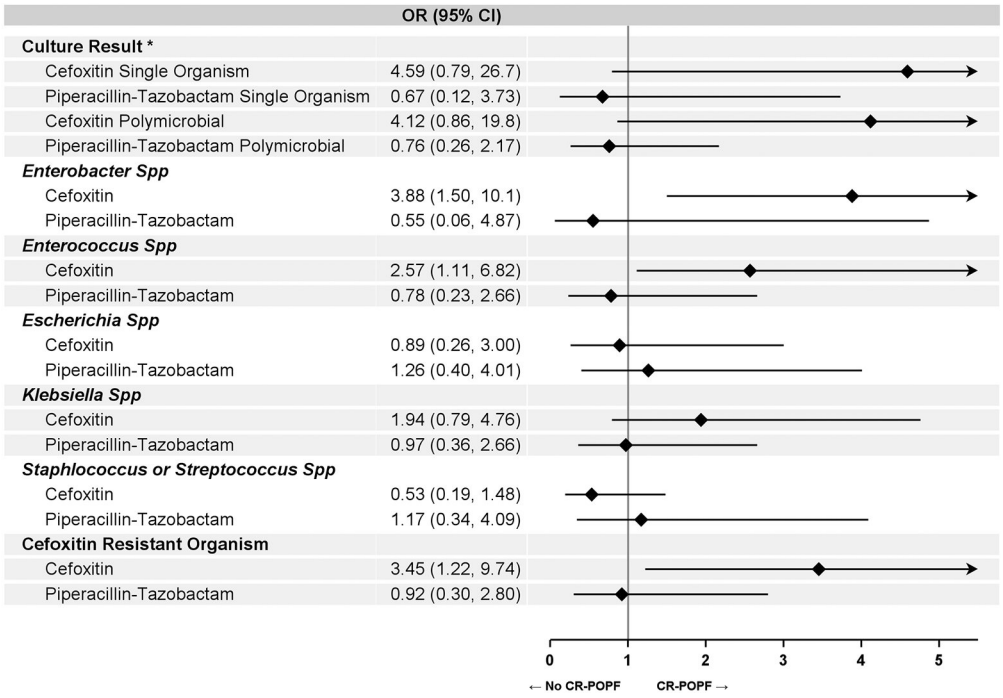

Figure 3. Association between IOBC results, antibiotic administered, and development of clinically relevant postoperative pancreatic fistula

Vertical line represents no association between the listed organisms and CR-POPF. The diamond is subgroup-specific odds ratio and whiskers represent 95% confidence interval. *Culture result uses sterile bile (no organisms) as reference group

Table 1:

Baseline Patient Characteristics

Participant Characteristic	Overall n=247 n (%)	Cefoxitin n=130 n (%)	Piperacillin-Tazobactam n=117 n (%)	P Value
Age, y (median, 25th-75th percentile)	68.9 (60.6-75.5)	69.5 (61.7-75.4)	67.9 (59.6-75.5)	0.379
Sex				0.295
Female	118 (47.8)	58 (44.6)	60 (51.3)	
Male	129 (52.2)	72 (55.4)	57 (48.7)	
Race				0.567
White	164 (66.4)	90 (69.2)	74 (63.3)	
Black or African American	8 (3.2)	5 (3.9)	3 (2.6)	
American Indian or Alaska Native	1 (0.5)	-	1 (0.8)	
Asian	5 (2.0)	3 (2.3)	2 (1.7)	
Unknown/Not Reported	69 (27.9)	32 (24.6)	37 (31.6)	
Diabetes				0.866
None	187 (75.7)	100 (76.9)	87 (74.4)	
Non-insulin dependent	33 (13.4)	16 (12.3)	17 (14.5)	
Insulin dependent	27 (10.9)	14 (10.8)	13 (11.1)	
Smoker	39 (15.8)	24 (18.5)	15 (12.8)	0.225
Chronic Obstructive Pulmonary Disease	7 (2.8)	4 (3.1)	3 (2.6)	0.808
Congestive Heart Failure	1 (0.4)	1 (0.8)	-	1.000
Hypertension	126 (51.0)	69 (53.1)	57 (48.7)	0.494
ASA Class				0.708
1-2	42 (17.0)	21 (16.2)	21 (18.0)	
3-4	205 (83.0)	109 (83.8)	96 (82.0)	
BMI, kg/m^2 (median, 25th-75th percentile) *				0.426
<18.5	8 (3.3)	2 (1.5)	6 (5.2)	
18.5 to < 25	94 (38.7)	49 (38.3)	45 (39.1)	
25 to < 30	77 (31.7)	43 (33.6)	34 (29.6)	
30+	64 (26.3)	34 (26.6)	30 (26.1)	
Preoperative Biliary Stent				0.496
Yes	164 (66.4)	89 (68.5)	75 (64.1)	
No	83 (33.6)	41 (31.5)	42 (35.9)	
Neoadjuvant Treatment‡	96 (38.9)	53 (40.8)	43 (36.8)	0.518
Pancreatic Duct Size				0.847
<3 mm	44 (17.8)	23 (17.7)	21 (18.0)	
3-6 3-6 mm	157 (63.6)	81 (62.3)	76 (65.0)	
>6 mm	37 (15.0)	20 (15.4)	17 (14.5)	
Unknown	9 (3.6)	6 (4.6)	3 (2.5)	
Pancreatic Gland Texture				0.082

Participant Characteristic	Overall n=247 n (%)	Cefoxitin n=130 n (%)	Piperacillin-Tazobactam n=117 n (%)	P Value
Soft	66 (26.7)	26 (20.0)	40 (34.2)	
Intermediate	75 (30.4)	45 (34.6)	30 (25.6)	
Hard	91 (36.8)	51 (39.2)	40 (34.2)	
Unknown	15 (6.1)	8 (6.2)	7 (6.0)	
OR Time, minutes (median, 25th-75th percentile)	351 (257-436)	356 (244-436)	344 (271-435)	0.672
Operative Drain Placed	179 (72.5)	88 (67.7)	91 (77.8)	0.076
Wound Protector Used	144 (58.3)	78 (60.0)	66 (56.4)	0.568
Perioperative Transfusions	35 (14.2)	15 (11.5)	20 (17.1)	0.211
Vascular Resection				0.557
Not performed	198 (80.2)	106 (81.5)	92 (78.6)	
Vein	44 (17.8)	22 (16.9)	22 (18.8)	
Artery	2 (0.8)	-	2 (1.7)	
Vein and artery	3 (1.2)	2 (1.6)	1 (0.9)	
Unknown	-	-	-	
Pathology				0.745
Pancreatic Adenocarcinoma	173 (70.0)	96 (73.9)	77 (65.8)	
Periampullary Cancer	31 (12.6)	15 (11.5)	16 (13.7)	
Pancreatic Cyst	19 (7.7)	8 (6.2)	11 (9.4)	
Neuroendocrine Tumor	8 (3.2)	3 (2.3)	5 (4.3)	
Other	5 (2.0)	3 (2.3)	2 (1.7)	
Unknown	11 (4.5)	5 (3.8)	6 (5.1)	
Correct Antibiotic Administered	243 (98.4)	130 (100)	113 (96.6)	0.049
Antibiotic Dosing Violations				
Given >60 minutes before incision	1 (0.4)	1 (0.8)	0 (0.0)	1.000
Late Intraoperative Redosing	26 (10.5)	16 (12.3)	10 (8.6)	0.336
Given >24 hours postoperatively	1 (0.4)	0 (0.0)	1 (0.9)	0.474

Data are n (%) unless noted

* n=243, missing BMI data: n=2 in piperacillin-tazobactam group, n=2 in cefoxitin group

≠ Includes neoadjuvant chemotherapy, neoadjuvant radiation therapy, or both

Table 2:

Intraoperative Bile Culture Results*

Organism	Prevalence n=231	Cefoxitin-Resistant** n=210
Citrobacter freundii	9 (3.9%)	3 (1.4%)
Enterobacter cloacae	38 (16.5%)	38 (18.1%)
Enterococcus casseliflavius	6 (2.6%)	6 (2.8%)
Enterococcus faecalis	50 (21.6%)	50 (23.8%)
Enterococcus faecium	21 (9.1%)	21 (10.0%)
Escherichia coli	44 (19.0%)	5 (5.0%)
Hafnia alvei	7 (3.0%)	0 (0.0%)
Klebsiella oxytoca	39 (16.9%)	6 (2.9%)
Klebsiella pneumonia	49 (21.2%)	0 (0.0%)
Klebsiella variicola	8 (3.5%)	0 (0.0%)
Proteus mirabilis	5 (2.2%)	1 (0.5%)
Pseudomonas aeruginosa	3 (1.3%)	3 (1.4%)
Staphylococcus aureus	6 (2.6%)	0 (0.0%)
Streptococcus anginosus	44 (19.0%)	0 (0.0%)
Streptococcus viridans	13 (5.6%)	0 (0.0%)
Anaerobic species	24 (10.4%)	--
Candida species	25 (10.8%)	--
Other^	48 (20.8%)	2 (1.0%)

*Prevalence calculated based on n=231 samples with speciation. Cefoxitin Resistant calculated among n=210 samples with full speciation.

**Defined as resistant to either cefoxitin or other cephamycin antibiotics (e.g., cefotetan) on sensitivity analysis.

^Consists of 26 additional bacterial species with frequency no higher than n=4. Both resistant organisms were Klebsiella aerogenes.

Table 3:

Association Between Bile Culture Result and Surgical Site Infection

		Any SSI				Superficial SSI				Deep or Organ Space SSI			
	Overall N=247	Cefoxitin n=130		Piperacillin-Tazobactam n=117		Cefoxitin n=130		Piperacillin-Tazobactam n=117		Cefoxitin n=130		Piperacillin-Tazobactam n=117	
	n (%)	n (%)	P Value	n (%)	P Value	n (%)	P Value	n (%)	P Value	n (%)	P Value	n (%)	P Value
All Patients	77 (31.2)	50 (38.5)		27 (23.1)		20 (15.4)		5 (4.3)		32 (24.6)		21 (18.0)	
Culture Result			0.047		0.717		0.178		0.787		0.257		0.476
Negative	15 (22.1)	5 (17.9)		10 (25.0)		1 (3.6)		2 (5.0)		4 (14.3)		9 (22.5)	
Single Organism	14 (37.8)	12 (52.2)		2 (14.3)		3 (13.0)		1 (7.1)		8 (34.8)		1 (7.1)	
Polymicrobial	48 (33.8)	33 (41.8)		15 (23.8)		16 (20.3)		2 (3.2)		20 (25.3)		11 (17.5)	
Enterobacter Spp			0.049		0.408		0.026		0.996		0.231		0.992
Yes (n=38)	17 (44.7)	16 (55.2)		1 (11.1)		8 (27.6)		0 (0.0)		10 (34.5)		0 (0.0)	
No (n=193)	55 (28.5)	31 (34.1)		24 (23.5)		9 (9.9)		5 (4.9)		21 (23.1)		19 (18.6)	
Enterococcus Spp			0.035		0.332		0.107		0.389		0.079		0.077
Yes (n=68)	26 (38.2)	22 (52.4)		4 (15.4)		9 (21.4)		2 (7.7)		15 (35.7)		1 (3.9)	
No (n=163)	26 (28.2)	25 (32.1)		21 (24.7)		8 (10.3)		3 (3.5)		16 (20.5)		18 (21.2)	
Escherichia Spp			0.563		0.164		0.424		0.929		0.926		0.256
Yes (n=44)	17 (38.6)	9 (45.0)		8 (33.3)		4 (20.0)		1 (4.2)		5 (25.0)		6 (25.0)	
No (n=187)	55 (29.4)	38 (38.0)		17 (19.5)		13 (13.0)		4 (4.6)		26 (26.0)		13 (14.9)	
Klebsiella Spp			0.202		0.694		0.062		0.366		0.560		0.879
Yes (n=90)	32 (35.6)	21 (46.7)		11 (24.4)		10 (22.2)		1 (2.2)		13 (28.9)		8 (17.8)	
No (n=141)	40 (28.4)	26 (34.7)		14 (21.2)		7 (9.3)		4 (6.1)		18 (24.0)		11 (16.7)	
Staph* or *Strep Spp			0.152		0.768		0.362		0.994		0.066		0.785
Yes (n=60)	16 (26.7)	12 (30.0)		4 (20.0)		4 (10.0)		0 (0.0)		6 (15.0)		3 (15.0)	
No (n=171)	56 (32.8)	35 (43.8)		21 (23.1)		13 (16.3)		5 (5.49)		23 (31.3)		16 (17.6)	
Cefoxitin Resistant			0.004		0.128		0.017		0.888		0.029		0.026
Yes (n=95)	36 (37.9)	31 (53.5)		5 (13.5)		14 (24.1)		2 (5.4)		20 (34.5)		1 (2.7)	
No (n=115)	30 (26.1)	13 (25.0)		17 (27.0)		3 (5.8)		3 (4.8)		8 (15.4)		15 (23.8)	

Table 4:

Association Between Bile Culture Result and Clinically Relevant Postoperative Pancreatic Fistula

	Overall N=247	Cefoxitin n=130		Piperacillin-Tazobactam n=117	
	n (%)	n (%)	P Value	n (%)	P Value
All Patients	47 (19.0)	27 (20.8)		20/117 (17.1)	
Culture Result			0.188		0.832
Negative (n=68)	10 (14.7)	2 (7.1)		8 (20.0)	
Single Organism (n=37)	8 (21.6)	6 (26.1)		2 (14.3)	
Polymicrobial (n=142)	29 (20.4)	19 (24.1)		10 (15.9)	
Enterobacter Spp			0.006		0.585
Yes (n=38)	13 (34.2)	12 (41.4)		1 (11.1)	
No (n=193)	33 (17.1)	14 (15.4)		19 (18.6)	
Enterococcus Spp			0.029		0.694
Yes (n=68)	18 (26.5)	14 (33.3)		4 (15.4)	
No (n=163)	28 (17.2)	12 (15.4)		16 (18.8)	
Escherichia Spp			0.845		0.689
Yes (n=44)	9 (20.5)	4 (20.0)		5 (20.8)	
No (n=187)	37 (19.8)	22 (22.0)		15 (17.2)	
Klebsiella Spp			0.148		0.957
Yes (n=90)	21 (23.3)	13 (28.9)		8 (17.8)	
No (n=141)	25 (17.7)	13 (17.3)		12 (18.2)	
Staph* or *Strep Spp			0.221		0.802
Yes (n=60)	10 (16.7)	6 (15.0)		4 (20.0)	
No (n=171)	36 (21.1)	20 (25.0)		16 (17.6)	
Cefoxitin Resistant			0.020		0.875
Yes (n=95)	24 (25.3)	18 (31.0)		6 (16.2)	
No (n=115)	17 (14.8)	6 (11.5)		11 (17.5)	