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Piperacillin-Tazobactam Compared With Cefoxitin as Antimicrobial Prophylaxis for Pancreatoduodenectomy
A Randomized Clinical Trial

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IMPORTANCE Despite improvements in perioperative mortality, the incidence of postoperative surgical site infection (SSI) remains high after pancreatoduodenectomy. The effect of broad-spectrum antimicrobial surgical prophylaxis in reducing SSI is poorly understood.

OBJECTIVE To define the effect of broad-spectrum perioperative antimicrobial prophylaxis on postoperative SSI incidence compared with standard care antibiotics.

DESIGN, SETTING, AND PARTICIPANTS Pragmatic, open-label, multicenter, randomized phase 3 clinical trial at 26 hospitals across the US and Canada. Participants were enrolled between November 2017 and August 2021, with follow-up through December 2021. Adults undergoing open pancreatoduodenectomy for any indication were eligible. Individuals were excluded if they had allergies to study medications, active infections, chronic steroid use, significant kidney dysfunction, or were pregnant or breastfeeding. Participants were block randomized in a 1:1 ratio and stratified by the presence of a preoperative biliary stent. Participants, investigators, and statisticians analyzing trial data were unblinded to treatment assignment.

INTERVENTION The intervention group received piperacillin-tazobactam (3.375 or 4 g intravenously) as perioperative antimicrobial prophylaxis, while the control group received cefoxitin (2 g intravenously; standard care).

MAIN OUTCOMES AND MEASURES The primary outcome was development of postoperative SSI within 30 days. Secondary end points included 30-day mortality, development of clinically relevant postoperative pancreatic fistula, and sepsis. All data were collected as part of the American College of Surgeons National Surgical Quality Improvement Program.

RESULTS The trial was terminated at an interim analysis on the basis of a predefined stopping rule. Of 778 participants (378 in the piperacillin-tazobactam group [median age, 66.8 y; 233 {61.6%} men] and 400 in the cefoxitin group [median age, 68.0 y; 223 {55.8%} men]), the percentage with SSI at 30 days was lower in the perioperative piperacillin-tazobactam vs cefoxitin group (19.8% vs 32.8%; absolute difference, −13.0% [95% CI, −19.1% to −6.9%]; $P < .001$). Participants treated with piperacillin-tazobactam, vs cefoxitin, had lower rates of postoperative sepsis (4.2% vs 7.5%; difference, −3.3% [95% CI, −6.6% to 0.0%]; $P = .02$) and clinically relevant postoperative pancreatic fistula (12.7% vs 19.0%; difference, −6.3% [95% CI, −11.4% to −1.2%]; $P = .03$). Mortality rates at 30 days were 1.3% (5/378) among participants treated with piperacillin-tazobactam and 2.5% (10/400) among those receiving cefoxitin (difference, −1.2% [95% CI, −3.1% to 0.7%]; $P = .32$).

CONCLUSIONS AND RELEVANCE In participants undergoing open pancreatoduodenectomy, use of piperacillin-tazobactam as perioperative prophylaxis reduced postoperative SSI, pancreatic fistula, and multiple downstream sequelae of SSI. The findings support the use of piperacillin-tazobactam as standard care for open pancreatoduodenectomy.

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Pancreatoduodenectomy is a common treatment for both benign and malignant diseases of the head of the pancreas and periampullary region. Although there have been major improvements in perioperative mortality after pancreatoduodenectomy, morbidity remains high.[1] This is of particular importance because perioperative complications negatively affect quality of life, limit receipt of adjuvant therapeutics, and have been associated with reduced overall survival.[2-4] The most common sources of severe perioperative morbidity are surgical site infection (SSI) and postoperative pancreatic fistula, which, combined, occur in more than 30% of patients.[5]

The underlying reasons for high rates of SSI after pancreatoduodenectomy are complex, and SSI rates have proven difficult to improve. For instance, postoperative intra-abdominal infections are often related to the development of pancreatic anastomotic leak and subsequent postoperative pancreatic fistula, but many abdominal infections develop in the absence of postoperative pancreatic fistula.[6] Infection risk may also be related to preoperative biliary instrumentation, which introduces bacteria into a normally sterile biliary tree and is associated with high SSI rates.[7-9] Biliary contamination is also associated with high rates of antibiotic-resistant bacteria and can lead to life-threatening infections after pancreatoduodenectomy.[10,11] Retrospective studies have shown that broader prophylactic perioperative antibiotic coverage is associated with reduced infection rates.[12,13] However, current guidelines recommend first- or second-generation cephalosporins as perioperative prophylaxis with limited coverage of resistant pathogens.[14]

Given the high rates of postoperative SSI potentially caused by antibiotic-resistant bacteria, it was hypothesized that the use of broad-spectrum antibiotics for prophylaxis would improve the rates of postoperative SSI after pancreatoduodenectomy compared with standard care antibiotics. To test this hypothesis, a pragmatic, registry-linked, randomized, open-label phase 3 clinical trial was initiated comparing piperacillin-tazobactam with standard care cefoxitin as perioperative antimicrobial prophylaxis for participants undergoing pancreatoduodenectomy. The simplicity of the clinical intervention proposed, paired with the limited time horizon of the outcome, made it possible to perform this trial in a pragmatic fashion utilizing a surgical registry for data collection. As the first registry-linked surgical clinical trial completed in North America, all data were abstracted routinely using the well-validated American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) data platform and without the aid of external funding.[15]

Key Points

Question Does use of perioperative broad-spectrum antibiotics reduce postoperative surgical site infection after open pancreatoduodenectomy?

Findings In this pragmatic, open-label, registry-linked randomized clinical trial including 778 participants from North America, the percentage of patients with 30-day postoperative surgical site infection was statistically significantly reduced with broad-spectrum piperacillin-tazobactam (19.8%) vs standard care cefoxitin (32.8%).

Meaning The findings support the use of piperacillin-tazobactam as perioperative antimicrobial prophylaxis for open pancreatoduodenectomy.

Methods

Ethical Statement

Institutional review board approval was obtained at the primary institution (Memorial Sloan Kettering Cancer Center [MSKCC]) and at each participating site. An independent data and safety monitoring board (DSMB) at MSKCC reviewed all trial data at prespecified intervals, ensured ethical conduct of the trial, and supervised interim analyses. All participants provided written informed consent.

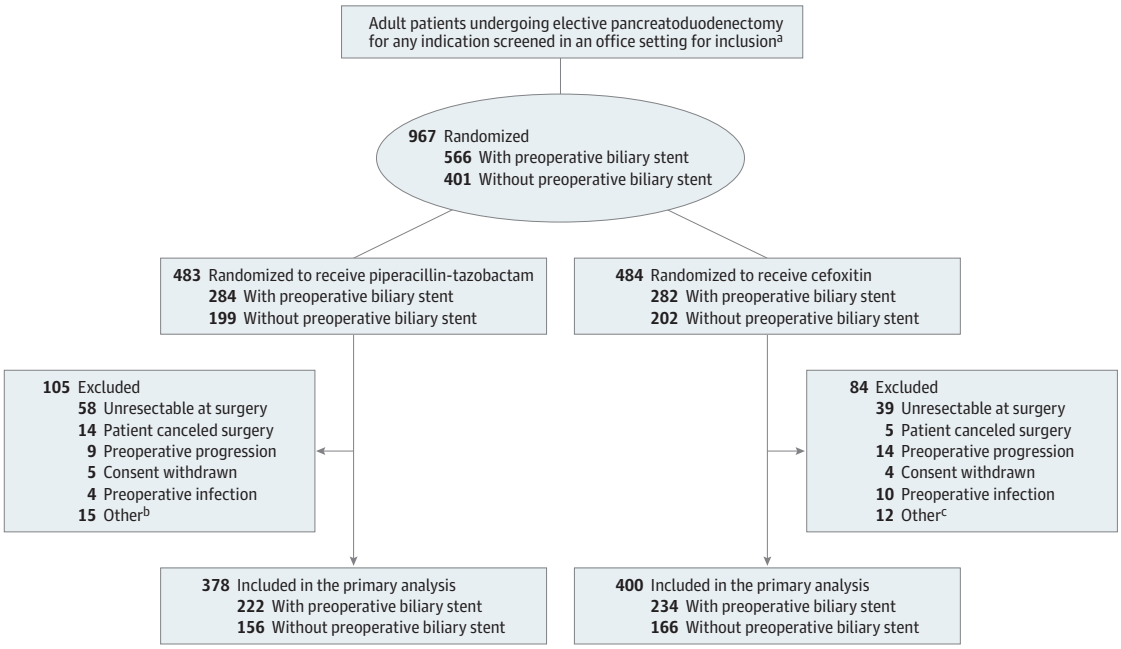
Trial Design and Setting

The trial was designed by the ACS Division of Research and Optimal Patient Care in conjunction with the Americas Hepato-Pancreato-Biliary Association clinical trials subcommittee. The trial was designed as a multicenter, open-label, phase 3 randomized trial and was conducted at 26 centers across the US and Canada. All hospitals participated in the ACS-NSQIP pancreatectomy Procedure Targeted Program, a surgical quality platform that was used to collect study outcome data. Details of the ACS-NSQIP have been described previously.[16] Briefly, the ACS-NSQIP is a routinely audited, validated, prospective, multi-institutional outcomes and quality program that uses trained reviewers to collect data on more than 150 perioperative variables.[17] Standard ACS-NSQIP data are augmented at hospitals participating in the pancreatectomy Procedure Targeted Program 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, dosing violations, and adverse reactions. The trial protocol has been previously described and is available in Supplement 1.[18]

Participants

Adults 18 years or older undergoing elective open pancreatoduodenectomy for any indication were eligible for the trial. Exclusion criteria included minimally invasive (eg, laparoscopic or robotic) pancreatoduodenectomy, inability to receive trial antibiotics due to allergy or medical issues, active infection, use of antibiotics within 7 days of surgical procedure for any indication, long-term glucocorticoid use, long-term dialysis or creatinine clearance less than or equal to 40 mL/min, and pregnancy or breastfeeding. Those eligible for the trial were identified at participating sites and confirmed by the primary site (**Figure 1**).

Figure 1. Participant Flow in a Study of Piperacillin-Tazobactam vs Cefoxitin as Antimicrobial Prophylaxis for Pancreatoduodenectomy



[a] Randomization stratified by the presence or absence of preoperative biliary stent. Data on screened patients were not collected due to the unfunded, pragmatic nature of the trial.

[b] Other reasons for exclusion in participants randomized to receive piperacillin-tazobactam included drug allergy (n = 2), preoperative steroid use (n = 3), operation changed to different resection (n = 8; 1 duodenal resection, 1 distal gastrectomy, 2 total pancreatectomy, 1 distal pancreatectomy, 1 Puestow procedure, 1 enucleation, 1 liver resection), and accrual closed (n = 2).

[c] Other reasons for exclusion in participants randomized to receive cefoxitin included kidney insufficiency (n = 1), operation changed to different resection (n = 9; 2 total pancreatectomy, 2 distal pancreatectomy, 2 minimally invasive resection, 1 enucleation, 1 central pancreatectomy, 1 liver resection), and accrual closed (n = 2).

Randomization

Participants were randomized in a 1:1 ratio at the time of surgical scheduling using randomly permuted block sizes of 2, 4, and 6 to receive either piperacillin-tazobactam or cefoxitin. Randomization was performed centrally at MSKCC, with randomization stratified by the presence or absence of preoperative biliary stent as reported by the operative site. Confirmation of randomization assignment was sent via email to the participating site study coordinator, principal investigator, and operating surgeon. The trial was performed open label and no blinding procedures were used. Participants were removed from and replaced in the trial after randomization if they withdrew consent, were deemed ineligible, or did not undergo pancreatoduodenectomy for any reason.

Intervention

Participants received their first dose of cefoxitin (2 g intravenously) or piperacillin-tazobactam (3.375 or 4.5 g intravenously per local protocols) within 60 minutes of incision and additional doses during the operation every 2 to 4 hours until close of incision.[14] Perioperative antibiotic administration was required to end within 24 hours after close of incision. Participants who did not 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 end point was development of SSI within 30 days of the surgical procedure. SSI was defined according to standard ACS-NSQIP interpretation of Centers for Disease Control and Prevention definitions as a composite of superficial, deep, and organ/space infections (Supplements 2-4). Superficial SSI includes purulent drainage from the incision, culture-positive fluid from the incision, deliberate opening of the incision by the surgeon, or development of erythema and swelling necessitating antibiotic treatment. Deep SSI is defined by similar criteria from the fascial/muscular layer and includes fascial dehiscence. Organ/space SSI is defined by postoperatively diagnosed intra-abdominal infections with or without percutaneous drainage or reoperation. Participants who died or were lost to follow-up within 30 days were considered events toward the primary end point. Secondary end points included postoperative outcomes often downstream of perioperative SSI, including 30-day mortality, sepsis, septic shock, percutaneous drain placement, pneumonia, postoperative reintubation, prolonged ventilation, venous thromboembolism events, kidney failure, urinary tract infections, stroke, myocardial infarction, cardiac arrest, *Clostridioides difficile* colitis, hospital readmission, reoperation, and length of hospital stay. Additional secondary end points specific to pancreatoduodenectomy included postoperative delayed gastric emptying and postoperative

pancreatic fistula, defined as clinically relevant grade B and C fistulas according to the International Study Group in Pancreatic Surgery guidelines.[19,20] A detailed description of end point definitions can be found in the Supplement 1.

Subgroup Analyses

Post hoc analyses were performed to explore differences in outcomes between clinically relevant subgroups. These subgroups included strata by participant sex, body mass index, presence or absence of biliary stent, receipt of neoadjuvant therapy, and surgical factors known to be associated with postoperative pancreatic fistula and SSI (eg, gland texture, pancreatic duct size, use of wound protectors, perioperative blood loss).

Statistical Analysis

Sample size calculations were based on an internal analysis of ACS-NSQIP pancreatoduodenectomy data that revealed an overall SSI rate of 20.4%. A 7% absolute reduction in SSI to 13% (an odds ratio [OR] of 0.6, or a 40% decrease in the odds of SSI) was deemed clinically meaningful and was used for power calculations. We calculated that inclusion of 890 participants (445 in each treatment group) would provide the trial with 80% power to detect this difference with a 2-sided significance level of 5%. This design included 1 planned interim analysis, halfway through accrual, using a 2-sided O'Brien-Fleming boundary. We anticipated approximately 10% of participants would be excluded after randomization due to unresectability, and thus anticipated enrolling approximately 979 participants to obtain 890 evaluable participants for analysis. Although this plan prevented a true intention-to-treat analysis, excluding these participants after randomization was felt to be appropriate because a participant is at risk for the primary end point only after undergoing resection. Outcome data were not available for participants who were randomized but subsequently excluded because they did not undergo pancreatectomy and were not abstracted via the ACS-NSQIP pancreatectomy Procedure Targeted Program.

The trial was monitored by MSKCC's independent DSMB that meets annually. Due to the timing of the annual meeting, the DSMB requested the first interim analysis before the initially planned analysis at 50% accrual (340 evaluable participants in May 2020). Following this interim analysis, the DSMB requested a second interim analysis at approximately two-thirds of target accrual (635 evaluable participants in May 2021). Due to this change in interim analysis plan, the efficacy stopping threshold was for the second interim analysis as inferred from the original boundary (set at .005) to be $P < .013$. This threshold was met at the time of the second interim analysis and the trial was terminated at the request of the DSMB.

All analyses were performed on a modified intention-to-treat basis regardless of any observed antibiotic dosing violations, omitting patients excluded after randomization as described above. Missing data were rare. We followed the same analysis plan for the primary and all secondary end points because all end points were binary. Results of each analysis are reported as ORs estimated from a logistic regression model in which the only independent variable was the randomized treatment group, stratified by presence of biliary stent as a stratum, and clustered by treatment site using a generalized estimating equations model with an exchangeable correlation structure. Analyses were also clustered by attending surgeon as a sensitivity analysis without change in inference and are available in eTable 1 in Supplement 5. All analyses were performed with SAS software, version 9.4 (SAS Institute).

Results

Participants

Between November 2017 and August 2021, a total of 967 participants undergoing open pancreatoduodenectomy were enrolled by 86 surgeons at 26 participating institutions. Of the 967 participants enrolled and randomized, 483 were assigned to receive piperacillin-tazobactam and 484 were assigned to receive cefoxitin. A total of 189 participants either withdrew consent or did not undergo pancreatoduodenectomy and were excluded, leaving 778 participants (378 in the piperacillin-tazobactam group and 400 in the cefoxitin group) included in the analyses, as shown in Figure 1.

The median (IQR) participant age was 67.3 (59.7-73.9) years, 456 (58.6%) were men, and 645 (82.9%) were considered American Society of Anesthesiologists Physical Classification System class III or IV. Preoperative biliary stents were present in 456 participants (58.6%), 273 (35.1%) received neoadjuvant chemotherapy and/or radiation, and 488 (62.7%) were undergoing resection for pancreatic adenocarcinoma. Participants received the correct antibiotic in 97.9% of cases (n = 762; 97.1% in piperacillin-tazobactam group and 98.8% in the cefoxitin group). Redosing violations were noted in 65 participants (17.2%) receiving piperacillin-tazobactam and 39 (9.7%) receiving cefoxitin, most commonly due to late intraoperative redosing (14.0% in the piperacillin-tazobactam group and 9.3% in the cefoxitin group). Additional baseline characteristics can be found in **Table 1** and detailed pathologic classification is available in eTable 2 in Supplement 5.

Primary Outcome

At the time of the second interim analysis and trial stoppage, participants who received piperacillin-tazobactam had statistically significantly fewer SSIs than those who received standard care cefoxitin (75 [19.8%] vs 131 [32.8%]; OR, 0.51 [95% CI, 0.38-0.68]; $P < .001$; **Table 2**). The difference between the groups was consistent when subdivided into superficial SSI (n = 51; 3.4% vs 9.5%; OR, 0.34 [95% CI, 0.20-0.58]) and organ/space SSI (n = 145; 14.3% vs 22.8%; OR, 0.57 [95% CI, 0.40-0.81]), but not deep incisional SSI (n = 2; 0.5% vs 0.5%; OR, 1.06 [95% CI, 0.13-8.59]).

Secondary Outcomes

The 30-day mortality rate was 1.3% (n = 5) in the piperacillin-tazobactam group and 2.5% (n = 10) in the cefoxitin group (OR, 0.52 [95% CI, 0.14-1.93]). Participants treated with

Table 1. Participant Characteristics in a Study of Piperacillin-Tazobactam vs Cefoxitin as Antimicrobial Prophylaxis for Pancreatoduodenectomy[a]

Participant characteristic	No. (%)	
	Piperacillin-tazobactam (n = 378)	Cefoxitin (n = 400)
Demographics		
Age, median (IQR), y	66.8 (59.6-73.8)	68.0 (59.8-73.9)
Sex		
Men	233 (61.6)	223 (55.8)
Women	145 (38.4)	177 (44.2)
Medical history[b]		
Diabetes		
Not insulin dependent	54 (14.3)	54 (13.5)
Insulin dependent	57 (15.1)	39 (9.8)
Current smoking	58 (15.3)	65 (16.3)
Chronic obstructive pulmonary disease	14 (3.7)	15 (3.8)
Congestive heart failure	1 (0.3)	2 (0.5)
Hypertension	205 (54.2)	213 (53.3)
American Society of Anesthesiologists class[c]		
I-II	63 (16.7)	70 (17.5)
III-IV	315 (83.3)	330 (82.5)
Body mass index, median (IQR)	26.2 (23.1-30.2) [n = 374]	26.5 (23.0-30.0) [n = 396]
<18.5	11 (2.9)	8 (2.0)
18.5 to <25	132 (35.3)	150 (37.9)
25 to <30	138 (36.9)	135 (34.1)
30 to <35	61 (16.3)	69 (17.4)
≥35	32 (8.6)	34 (8.6)
Preoperative therapies		
Preoperative biliary stent[d]	222 (58.7)	234 (58.5)
Neoadjuvant chemotherapy and/or radiation	143 (37.8)	130 (32.5)
Operative details		
Pancreatic duct size (intraoperative)		
<3 mm	77 (20.4)	98 (24.5)
3-6 mm	211 (55.8)	211 (52.8)
>6 mm	47 (12.4)	53 (13.2)
Unknown	43 (11.4)	38 (9.5)
Pancreatic gland texture (intraoperative)		
Soft	112 (29.6)	138 (34.5)
Intermediate	61 (16.1)	79 (19.7)
Hard	151 (40.0)	133 (33.3)
Unknown	54 (14.3)	50 (12.5)
Operating room time, median (IQR), min	356.5 (279.0-441.0)	359.5 (274.5-435.0)
Operative drain placed	306 (81.0)	333 (83.3)
Wound protector used[b]	163 (43.2%) [n = 377]	169 (42.6%) [n = 396]
Perioperative transfusions	65 (17.2)	56 (14.0)
Vascular resection		
Not performed	312 (82.5)	339 (84.7)
Vein	52 (13.8)	47 (11.8)
Artery	8 (2.1)	8 (2.0)
Vein and artery	5 (1.3)	6 (1.5)
Unknown	1 (0.3)	0
Pathology[e]		
Pancreatic adenocarcinoma	244 (64.6)	244 (61.0)
Periampullary cancer	43 (11.4)	53 (13.3)
Pancreatic cyst	45 (11.9)	36 (9.0)
Neuroendocrine tumor	17 (4.5)	28 (7.0)
Other	29 (7.7)	39 (9.7)
Correct antibiotic administered	367 (97.1)	395 (98.8)
Antibiotic dosing violations	65 (17.2)	39 (9.7)
Given >60 min before incision	9 (2.4)	1 (0.2)
Late intraoperative redosing	53 (14.0)	37 (9.3)
Given >24 h postoperatively	3 (0.8)	1 (0.2)

[a] Patients who were excluded after randomization were not abstracted and are not included. Percentages may not add to 100 due to rounding. Missing data were rare and denoted with revised n in any applicable row.

[b] Medical history items were yes/no based on physician documentation of the presence of preoperative comorbidities.

[c] Class I is defined as healthy; class II, mild systemic disease; class III, severe systemic disease; and class IV, severe systemic disease that is a constant threat to life.

[d] See eTable 3 in Supplement 2 for patient information stratified by preoperative biliary stent.

[e] Detailed pathologic diagnoses are available in eTable 2 in Supplement 2.

piperacillin-tazobactam vs cefoxitin were less likely to have postoperative sepsis (4.2% vs 7.5%; OR, 0.55 [95% CI, 0.32-0.92]), *C difficile* colitis (0.3% vs 3.5%; OR, 0.07 [95% CI, 0.01-0.63]), and postoperative pancreatic fistula (12.7% vs 19.0%; OR, 0.62 [95% CI, 0.40-0.96]). Additional secondary postoperative outcomes are provided in Table 2.

Subgroup Analysis

Use of piperacillin-tazobactam was associated with lower rates of SSI in most subgroups (**Figure 2**; eTable 3 and eTable 4 in Supplement 5). Use of piperacillin-tazobactam was also associated with lower rates of SSI across multiple variables known to be associated with the development of SSI and postoperative pancreatic fistula (eg, sex, body mass index, gland characteristics; Figure 2).

Discussion

In this trial of adults undergoing pancreatoduodenectomy, use of piperacillin-tazobactam for perioperative antimicrobial prophylaxis resulted in statistically and clinically significantly less frequent SSIs vs use of standard care cefoxitin. In addition, use of piperacillin-tazobactam resulted in reduced rates of many SSI-related morbidities, including postoperative sepsis, postoperative pancreatic fistula, and *C difficile* colitis.

Postoperative morbidity after pancreatoduodenectomy has remained stubbornly high despite advances in surgical care.[1] The results of this trial are noteworthy because SSI is the most

Table 2. Efficacy Outcomes by Postoperative Day 30 Among Participants in the Primary Analysis

Outcome	No. (%)		Absolute difference (95% CI), %	Odds ratio (95% CI)[a]	*P* value
	Piperacillin-tazobactam (n = 378)	Cefoxitin (n = 400)			
Primary outcome					
Any SSI[b]	75 (19.8)	131 (32.8)	−13.0 (−19.1 to −6.9)	0.51 (0.38 to 0.68)	<.001
Superficial SSI	13 (3.4)	38 (9.5)	−6.1 (−9.5 to −2.7)	0.34 (0.20 to 0.58)	<.001
Deep incisional SSI	2 (0.5)	2 (0.5)	0.0 (−1.0 to 1.0)	1.06 (0.13 to 8.59)	.96
Organ/space SSI	54 (14.3)	91 (22.8)	−8.5 (−13.9 to −3.1)	0.57 (0.40 to 0.81)	.003
Secondary outcomes					
Pancreatectomy-specific complications					
Delayed gastric emptying	61 (16.1)	72 (18.0)	−1.9 (−7.2 to 3.4)	0.88 (0.62 to 1.24)	.45
Pancreatic fistula[c]	48 (12.7)	76 (19.0)	−6.3 (−11.4 to −1.2)	0.62 (0.40 to 0.96)	.03
Infectious complications					
Percutaneous drain placement	46 (12.2)	70 (17.5)	−5.3 (−10.3 to −0.3)	0.65 (0.42 to 1.02)	.06
Sepsis	16 (4.2)	30 (7.5)	−3.3 (−6.6 to 0.0)	0.55 (0.32 to 0.92)	.02
Urinary tract infection	11 (2.9)	16 (4.0)	−1.1 (−3.7 to 1.5)	0.72 (0.28 to 1.84)	.49
Pneumonia	10 (2.7)	15 (3.8)	−1.1 (−3.6 to 1.4)	0.70 (0.29 to 1.66)	.41
Clostridioides difficile colitis	1 (0.3)	14 (3.5)	−3.2 (−5.1 to −1.3)	0.07 (0.01 to 0.63)	.02
Noninfectious complications					
Myocardial infarction	11 (2.9)	9 (2.3)	0.6 (−1.6 to 2.8)	1.30 (0.56 to 3.02)	.53
Pulmonary embolism	9 (2.4)	4 (1.0)	1.4 (−0.4 to 3.2)	2.42 (0.76 to 7.64)	.13
Acute kidney failure or progressive kidney insufficiency	7 (1.9)	11 (2.8)	−0.9 (−3.0 to 1.2)	0.67 (0.21 to 2.13)	.47
Venous thrombosis requiring therapy	7 (1.9)	9 (2.3)	−0.4 (−2.4 to 1.6)	0.82 (0.33 to 2.07)	.67
Unplanned intubation	6 (1.6)	11 (2.8)	−1.2 (−3.3 to 0.9)	0.57 (0.14 to 2.28)	.42
Ventilator >48 h	5 (1.3)	10 (2.5)	−1.2 (−3.1 to 0.7)	0.52 (0.18 to 1.52)	.23
Stroke (ischemic or hemorrhagic)	2 (0.5)	2 (0.5)	0.0 (−1.0 to 1.0)	1.06 (0.14 to 8.13)	.96
Cardiac arrest	1 (0.3)	6 (1.5)	−1.2 (−2.5 to 0.1)	0.17 (0.02 to 1.66)	.13
Antibiotic drug reaction (rash)	0	1 (0.2)	−0.2 (−0.6 to 0.2)		
Hospitalization outcomes					
Unplanned readmission	64 (16.9)	73 (18.3)	−1.4 (−6.8 to 4.0)	0.91 (0.57 to 1.47)	.70
Unplanned return to the operating room	11 (2.9)	20 (5.0)	−2.1 (−4.8 to 0.6)	0.57 (0.30 to 1.09)	.09
Death	5 (1.3)	10 (2.5)	−1.2 (−3.1 to 0.7)	0.52 (0.14 to 1.93)	.32
Length of stay, median (IQR), d	7 (5-10)	7 (5-11)			.11

[a] Odds ratios were estimated from a logistic regression model in which the only independent variable was the randomized treatment group, stratified by presence of biliary stent as a stratum, and clustered by treatment site using a generalized estimating equations model with an exchangeable correlation structure.

[b] The primary outcome of any surgical site infection (SSI) includes any superficial, deep, or organ/space infection. Superficial SSI defined as incisional infections within the skin skin or subcutaneous tissues; deep SSI, within fascial or muscular layers; and organ space SSI, within abdominal cavity with or without drainage or reoperation. Twenty-six cases were identified as failures toward the primary outcome due to death or loss to follow-up (10 in the piperacillin-tazobactam group and 16 in the cefoxitin group) and included in the numerator for calculations. Some patients may have developed more than 1 type of SSI but were counted only once toward the primary end point.

[c] Defined as clinically relevant postoperative pancreatic fistulas based on International Study Group in Pancreatic Surgery consensus guidelines.[19]

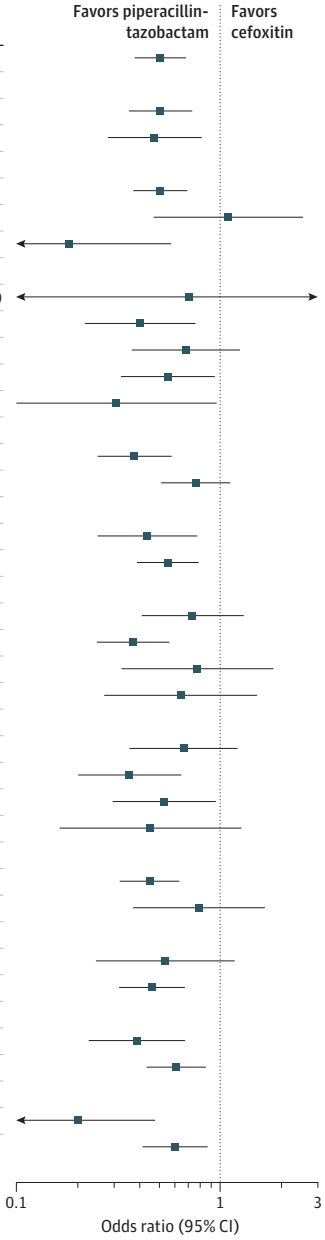
common driver of this morbidity, both directly and through downstream events such as ileus, *C difficile* infection, deconditioning due to prolonged hospitalization, readmission, and increased cost.[21,22] The observed effect on SSI was significant in both superficial and organ/space subgroups of SSI, indicating that the change in prophylaxis strategy can prevent both superficial and life-threatening intra-abdominal infections. The effect of piperacillin-tazobactam observed in the trial was evident on stratified analyses of multiple subgroups, providing support for making broad-spectrum antibiotic prophylaxis standard care in all patients undergoing pancreatoduodenectomy. It should be noted that the observed effect of piperacillin-tazobactam was nonsignificant based on CIs for some subgroups (eg, participants without biliary stents). Results of these post hoc analyses should be interpreted with caution, but may identify subgroups that benefit more or less from broad-spectrum prophylaxis.

The clinically significant reduction in SSI translated to improvements in multiple downstream outcomes, including reductions in *C difficile* colitis and postoperative sepsis. These results are intuitive, because those experiencing postoperative SSI will be at higher risk for sepsis and undoubtedly receive additional antibiotics, thereby increasing their risk for *C difficile* colitis. Reduced rates of severe infectious complications are likely related to the clinically relevant absolute reduction in rates of reoperation, percutaneous drain placement, and 30-day postoperative mortality observed in participants treated with piperacillin-tazobactam. This constellation of findings highlights the importance of avoiding initial postoperative complications, rather than relying on rescue strategies, to truly optimize outcomes.

Use of piperacillin-tazobactam also resulted in a significant reduction in postoperative pancreatic fistula compared with cefoxitin. Postoperative pancreatic fistula often leads to

Figure 2. Risk of Surgical Site Infection for Participant Subgroups

Characteristic	No. of patients with SSI/total No. (%)		Absolute difference (95% CI), %	Odds ratio (95% CI)
	Piperacillin-tazobactam	Cefoxitin		
Overall	75/378 (19.8)	131/400 (32.8)	-13.0 (-19.1 to -6.9)	0.51 (0.38 to 0.68)
Sex				
Men	51/233 (21.9)	79/223 (35.4)	-13.5 (-8.4 to 8.1)	0.51 (0.36 to 0.73)
Women	24/145 (16.6)	52/177 (29.4)	-12.8 (-9.2 to 8.9)	0.48 (0.28 to 0.81)
Diabetes				
None	52/267 (19.5)	99/307 (32.3)	-12.8 (-7.2 to 6.9)	0.51 (0.37 to 0.69)
Not insulin dependent	16/54 (29.6)	15/54 (27.8)	1.8 (-17.0 to 17.1)	1.09 (0.47 to 2.55)
Insulin dependent	7/57 (12.3)	17/39 (43.6)	-31.3 (-18.1 to 17.4)	0.18 (0.06 to 0.58)
Body mass index				
<18.5	1/11 (9.1)	1/8 (12.5)	-3.4 (-31.9 to 25.1)	0.70 (0.02 to 23.55)
18.5 to <25	19/132 (14.4)	44/150 (29.3)	-14.9 (-24.3 to -5.5)	0.41 (0.22 to 0.76)
25 to <30	29/138 (21.0)	38/135 (28.2)	-7.2 (-17.4 to 3.0)	0.68 (0.37 to 1.25)
30 to <35	16/61 (26.2)	27/69 (39.1)	-12.9 (-28.8 to 3.0)	0.55 (0.33 to 0.94)
≥35	9/32 (28.1)	19/34 (55.9)	-27.8 (-50.6 to -5.0)	0.31 (0.10 to 0.96)
Stent				
Present	39/222 (17.6)	84/234 (35.9)	-18.3 (-8.1 to 7.7)	0.38 (0.25 to 0.58)
Absent	36/156 (23.1)	47/166 (28.3)	-5.2 (-9.6 to 9.5)	0.76 (0.51 to 1.12)
Neoadjuvant therapy				
Yes	22/143 (15.4)	38/130 (29.2)	-13.8 (-9.9 to 9.7)	0.44 (0.25 to 0. 77)
No	53/235 (22.6)	93/270 (34.4)	-11.8 (-7.9 to 7.7)	0.55 (0.39 to 0.79)
Duct size				
<3 mm	23/77 (30.0)	36/98 (36. 7)	-6.7 (-14.1 to 13.9)	0.73 (0.41 to 1.30)
3-6 mm	33/211 (15.6)	70/211 (33.2)	-17.6 (-8.2 to 7.8)	0.37 (0.25 to 0.56)
>6 mm	11/47 (23.4)	15/53 (28.3)	-4.9 (-17.2 to 17.1)	0.77 (0.33 to 1.83)
Unknown	8/43 (18.6)	10/38 (26.3)	-7.7 (-18.3 to 18.1)	0.64 (0.27 to 1.52)
Gland texture				
Soft	32/112 (28.6)	52/138 (37.7)	-9.1 (-11.7 to 11.5)	0.66 (0.36 to 1.22)
Intermediate	11/61 (18.0)	30/79 (38.0)	-20.0 (-14.6 to 14.2)	0.36 (0.20 to 0.64)
Hard	21/151 (13.9)	31/133 (23.3)	-9.4 (-9.2 to 9.0)	0.53 (0.30 to 0.95)
Unknown	11/54 (20.4)	18/50 (36.0)	-15.6 (-17.3 to 16.9)	0.45 (0.16 to 1.27)
Operative drain placement				
Yes	55/306 (18.0)	109/333 (32.7)	-14.7 (-6.8 to 6.5)	0.45 (0.32 to 0.63)
No	20/72 (27.8)	22/67 (32.8)	-5.0 (-15.3 to 15.2)	0. 79 (0.37 to 1.66)
Drain removed by postoperative day 3				
Yes	9/77 (11.7)	14/71 (19.7)	-8.0 (-11.8 to 11.6)	0.54 (0.25 to 1.18)
No	46/224 (20.5)	92/257 (35.8)	-15.3 (-8.0 to 7.7)	0.46 (0.32 to 0.67)
Wound protector used				
Yes	27/163 (16.6)	57/169 (33.7)	-17.1 (-9.3 to 9.0)	0.39 (0.23 to 0.67)
No	48/214 (22.4)	73/227 (32.2)	-9.8 (-8.4 to 8.2)	0.61 (0.44 to 0.85)
Perioperative transfusion				
Yes	9/65 (13.9)	25/56 (44.6)	-30.7 (-15.8 to 15.2)	0.20 (0.08 to 0.48)
No	66/313 (21.1)	106/344 (30.8)	-9.7 (-6.7 to 6.6)	0.60 (0.41 to 0.87)



The dotted vertical line represents no association, squares are subgroup-specific odds ratios, and whiskers represent 95% CIs.

a cascade of downstream complications, resulting in perioperative mortality of up to 35%.[21] Improvements in this complication have been elusive despite substantial research efforts.[19] The mechanism underlying the observed reduction in postoperative pancreatic fistula in the current trial is unclear, but one potential mechanism relates to the microbiome. Previous research on intestinal anastomoses has implicated collagenase-producing bacteria, such as *Enterococcus faecalis*, in the formation of anastomotic leak.[23,24] It is possible that the use of piperacillin-tazobactam, which has activity against *Enterococcus* species, while cefoxitin does not, may alter the microbial environment of the reconstruction and facilitate healing. Alternatively, the reduced rate could simply be due to lower clinical severity of biochemical pancreatic leaks with the use of broad-spectrum antibiotic therapy, effectively turning clinically relevant fistulas into near-asymptomatic biochemical leaks and reducing the likelihood of detection.[19]

Another notable aspect of the trial was the linkage of a clinical registry for data collection, the first surgical trial of its kind in North America. Previous trials using registries have been completed largely in medical specialties,[25,26] with

advantages being demonstrated in participant accrual and cost.[27] Due to these strengths, significant interest in registry-linked clinical trials has emerged. This mechanism is particularly enticing in surgery, which has traditionally struggled to perform large prospective randomized trials.[27] Using this novel mechanism and leveraging collaboration between multiple professional societies, a large, conclusive randomized clinical trial was conducted. The backbone of this study design was the robust and well-validated ACS-NSQIP, which is built on structured review of clinical events by trained clinical reviewers using rigorous definitions.[17,28] Data in ACS-NSQIP are abstracted in a manner similar to traditional clinical trial variables, with a trained reviewer performing detailed encounter assessments and asking participating clinicians for input in the event that unclear diagnoses are encountered. These data have been shown to have excellent interrater reliability and have compared favorably to more traditional prospective institutional data.[15] Despite a lack of formal funding, the pragmatic trial design and registry-linked data collection led to 97.9% of participants receiving the correct treatment regimen and undoubtedly practice-changing results. This trial should be considered proof of concept that registry trials can be executed successfully in surgery and should facilitate future randomized trials.

It is important to interpret these results in the context of concerns regarding antimicrobial stewardship. First, it should be noted that these results apply only to pancreatoduodenectomy and do not imply that broad-spectrum prophylaxis should be used in other major operations. Pancreatoduodenectomy is unique in its surgical complexity, extent of preoperative biliary manipulation, high baseline incidence of SSI, and volume of observational data implicating bacteria resistant to early-generation cephalosporins, such as *Enterococcus* species, in SSI development.[12] Second, although these results should change the standard of care for perioperative prophylaxis, future investigations aimed at maximizing antimicrobial stewardship should be considered. For example, early data have implied that rectal swabs may predict the presence of resistant enteric bacteria, and further development of this technique may allow for more targeted use of broad-spectrum prophylaxis.[29]

Limitations

This study has limitations. First, there was a high rate of unresectability and disease progression leading to a higher than anticipated rate of postrandomization exclusion. This rate is similar to those observed in previous pancreatectomy trials[30] and may reflect increasingly aggressive operative approaches, especially in locally advanced and borderline-resectable tumors. It is unlikely that there would be any association between unresectability and perioperative antibiotic, and thus the number of postrandomization exclusions is unlikely to affect the results of the trial. Second, the trial design and lack of formal funding precluded routine collection of intraoperative or postoperative culture data, which could have provided more concrete evidence for a causal link between the intervention and outcome. This was by design based on the overwhelming historical culture data identifying high rates of antibiotic-resistant bacteria in the biliary system during pancreatoduodenectomy and associated postoperative infections.[12,13] Third, a slightly higher number of protocol violations was observed in patients receiving piperacillin-tazobactam. This issue was most commonly due to intraoperative misdosing of the drug, which may have been related to the relatively short intraoperative redosing interval of the antibiotic compared with standard dosing. However, this difference was clinically insignificant and would likely result in patients in the piperacillin-tazobactam group receiving less treatment; thus, any bias would be toward the null. Fourth, the pragmatic design of the trial, paired with the registry-based data collection, necessitated that blinding did not occur and that many variables were outside the control of the trial. The authors agree with previous statements that omission of blinding is unlikely to significantly bias results, and submit that the risk of bias in data collection in this trial is uniquely low because the trained ACS-NSQIP clinical reviewers have no part in the trial or interest in the outcome of the study.[31,32] The pragmatic design also necessitated that some traditional clinical trial variables were not collected (eg, patients screened for eligibility) and that many variables were not strictly controlled, such as local dosing practices of piperacillin-tazobactam (3.375g vs 4.5g), extent of preoperative/intraoperative biliary manipulation, and nuances in perioperative care. However, robust clinical findings in pragmatic studies likely have superior external validity compared with traditional, tightly controlled trials.[33]

Conclusions

Perioperative use of piperacillin-tazobactam as antimicrobial prophylaxis reduced the risk of postoperative SSI, pancreatic fistula, and multiple downstream sequelae of surgical infection compared with standard care in participants undergoing pancreatoduodenectomy. This reduction was seen regardless of the presence of a preoperative biliary stent and supports the use of piperacillin-tazobactam as standard care for open pancreatoduodenectomy.

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