Discordance Between Perioperative Antibiotic Prophylaxis and Wound Infection Cultures in Patients Undergoing Pancreaticoduodenectomy

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IMPORTANCE Wound infections after pancreaticoduodenectomy (PD) are common. The standard antibiotic prophylaxis given to prevent the infections is often a cephalosporin. However, this decision is rarely guided by microbiology data pertinent to PD, particularly in patients with biliary stents.

OBJECTIVE To analyze the microbiology of post-PD wound infection cultures and the effectiveness of institution-based perioperative antibiotic protocols.

DESIGN, SETTING, AND PARTICIPANTS The pancreatic resection databases of 3 institutions (designated as institutions A, B, or C) were queried on patients undergoing PD from June 1, 2008, to June 1, 2013, and a total of 1623 patients were identified. Perioperative variables as well as microbiology data for intraoperative bile and postoperative wound cultures were analyzed from June 1, 2008, to June 1, 2013.

INTERVENTIONS Perioperative antibiotic administration.

MAIN OUTCOMES AND MEASURES Wound infection microbiology analysis and resistance patterns.

RESULTS Of the 1623 patients who underwent PD, 133 with wound infections (8.2%) were identified. The wound infection rate did not differ significantly across the 3 institutions. The predominant perioperative antibiotics used at institutions A, B, and C were cefoxitin sodium, cefazolin sodium with metronidazole, and ampicillin sodium–sulbactam sodium, respectively. Of the 133 wound infections, 89 (67.1%) were deep-tissue infection, occurring at a median of 8 (range, 1-57) days after PD. A total of 53 (40.0%) of the wound infections required home visiting nurse services on discharge, and 73 (29.1%) of all PD readmissions were attributed to wound infection. Preoperative biliary stenting was the strongest predictor of postoperative wound infection (odds ratio, 2.5; 95% CI, 1.58-3.88; \( P = .03 \)). There was marked institutional variation in the type of microorganisms cultured from both the intraoperative bile and wound infection cultures (Streptococcus pneumoniae, 114 cultures [47.9%] in institution A vs 3 [4.5%] in institution B; \( P = .001 \) and wound infection cultures (predominant microorganism in institution A: Enterococcus faecalis, 18 cultures [51.4%]; institution B: Staphylococcus aureus, 8 [43.9%]; and institution C: Escherichia coli, 17 [36.2%], \( P = .001 \)). Similarly, antibiotic resistance patterns varied (resistance pattern in institution A: cefoxitin, 29 cultures [53.1%]; institution B: ampicillin-sulbactam, 9 [69.2%]; and institution C: penicillin, 32 [72.7%], \( P < .001 \)). Microorganisms isolated in intraoperative bile cultures were similar to those identified in wound cultures in patients with post-PD wound infections.

CONCLUSIONS AND RELEVANCE The findings of this large-scale, multi-institutional study indicate that intraoperative bile cultures should be routinely obtained in patients who underwent preoperative endoscopic retrograde cholangiopancreatography since the isolated microorganisms closely correlate with those identified on postoperative wound cultures. Institution-specific internal reviews should amend current protocols for antibiotic prophylaxis to reduce the incidence of wound infections following PD.

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Wound infection after surgery is associated with a prolonged hospital length of stay and increased cost of treatment, imposing a significant economic burden on health care. Kirkland et al demonstrated that postoperative wound infection directly contributed to an additional 12 days of hospitalization and direct costs of $5038 per complication. A more contemporary study of the National Inpatient Sample database revealed that postoperative wound infection contributed to a total of 406,730 additional days of hospitalization and more than $900 million in excess cost annually. Furthermore, there were 91,613 readmissions as a result of postoperative wound infection, accounting for 521,933 additional hospitalization days and costing an additional $700 million.

Pancreatectoduodenectomy (PD) is no exception when it comes to the incidence and clinical burden of postoperative wound infection. In fact, postoperative wound infection is more common after PD secondary to the extensive physiologic alterations (fluid shifts, blood loss, and systemic vasodilation) and multiple enteric anastomoses associated with the procedure. Even at high-volume tertiary referral centers, the incidence of post-PD wound infection is estimated to be approximately 10% to 17%, which is similar or slightly higher than wound infection rates after colon resection. In a cost analysis of infectious complications after PD, the extra cost incurred was $15,336 per complication, with wound infection being the most common postoperative infectious complication. More important, postoperative wound infection also delays postoperative adjuvant chemotherapy, which is indicated in most patients undergoing PD for pancreatic cancer.

In an effort to overcome the clinical and financial burden imposed by postoperative wound infections, multiple measures, such as perioperative warming of patients and timing of preincisional antibiotic administration, have been investigated and proven to be effective. The Surgical Care Improvement Project (SCIP), an independent nonprofit organization that accredits and certifies health care organizations in the United States, was established in 2006 and provided guidelines to reduce wound infections. Adherence to SCIP measures has been endorsed by multiple stakeholders as a valid measure of publicly reported surgical quality. However, recent studies have shown that adherence to SCIP measures did not result in measurable improvement in postoperative wound infections at the patient or hospital level. In addition, the perioperative antibiotic choices as recommended by the SCIP for “colon/abdominal” surgery may not be appropriate for the PD operation, which involves both intraoperative biliary and enteric contamination. The aim of this multiinstitutional study was to analyze the results of intraoperative bile and postoperative wound cultures in patients with wound infections after PD and compare them with the findings obtained in patients who received perioperatively administered antibiotics to better understand post-PD wound infections and explore alternative initiatives aiming to improve post-PD wound infection rates beyond the SCIP measures.

Methods

We queried the pancreatic surgery databases for Massachusetts General Hospital, University of Pennsylvania, and University of Verona for patients who developed a wound infection after PD over a 5-year period (June 1, 2008, to June 1, 2013). The 3 institutions were randomly designated A, B, and C to maintain anonymity. Bile cultures were performed intraoperatively with a sterile cotton swab at the time of bile duct transection. Microbiology data for intraoperative bile cultures were accrued for the 2 institutions that performed them. In patients who developed postoperative wound infection after PD, wound infection culture microbiology data (microorganisms and antibiotic susceptibilities) were also accrued. Intraoperative bile cultures and postoperative wound infection microbiology data were compared to determine the predictive value of bile cultures. The American College of Surgeons National Surgical Quality Improvement Program and research patient data registry databases at Massachusetts General Hospital were linked to the clinical database at that hospital by means of medical record numbers to supplement perioperative data. Wound infection-specific complications and grading were identified and entered into the databases by the institution-specific designated individuals (Z.V.F., M.T.M., and G.M.).

This study was approved by the institutional review boards of the Massachusetts General Hospital, University of Pennsylvania, and University of Verona and was compliant with the Health Insurance Portability and Accountability Act. The need for informed consent was waived.

Definitions

Postoperative wound infection was defined according to the standardized American College of Surgeons National Surgical Quality Improvement Program criteria, and both superficial and deep wound infections were included irrespective of time from surgery (includes wound infections that develop >30 days after surgery). Superficial wound infection was defined as wound infections that did not require removal of staples, incision, or drainage (superficial cellulitis). Deep wound infections were those that required incision and drainage of pus for resolution of the infection. Organ-space infections were not included in the analysis because they have different risk profiles and should be analyzed separately. The American Society of Anesthesiology score and age-adjusted Charlson comorbidity index score were used to quantify the comorbidity burden of the study cohort. Major vessel resection was defined as the need for resection or reconstruction of the superior mesenteric artery, superior mesenteric vein, portal vein, or hepatic artery.

Statistical Analysis

Data are presented as mean (SD), median (interquartile range [IQR]), odds ratio (OR) (95% CI), or number (percentage). Categorical variables were compared using the Fisher exact test or χ² test. Nonparametric continuous variables were analyzed using the Wilcoxon rank sum test, whereas parametric
Results

Demographics
A total of 1623 patients who underwent PD at the 3 institutions were identified. Several differences existed across the hospitals. There were more males at institution C (329 [58.5%] vs 282 [49.0%] and 231 [47.5%] in institutions A and B, respectively; \( P = .001 \)), and use of corticosteroids was less frequent at institution B (4 [0.8%] vs 9 [3.2%] and 20 [3.6%] at institutions A and C, respectively; \( P = .01 \)). The proportion of patients with diabetes mellitus was similar between institutions (134 [23.3%] vs 122 [25.2%] vs 122 [21.7%] for institutions A, B, and C, respectively; \( P = .42 \)). The proportion of patients with American Society of Anesthesiology scoring between anesthesiologists. Perioperative factors were discrepant between all 3 institutions as well; institution B had the shortest surgery duration (median [IQR], 277 [244.5-336] minutes vs 328 [279-400] minutes and 380 [335-435] minutes for institution A and C, respectively; \( P < .001 \)) and the lowest rate of major vessel resection (2.7% vs 11.0% and 8.5% for institutions A and C, respectively; \( P < .001 \)). Estimated blood loss and the need for transfusion were the lowest at institution A (350 [150]; \( P < .001 \)).

Preoperative Biliary Stenting
There was no significant difference in preoperative bilirubin levels between institutions, with the overall cohort having a median (IQR) bilirubin level of 0.7 (3.7) mg/dL (to convert to micromoles per liter, multiply by 17.104). Preoperative biliary stenting was performed more frequently at institution A (371 patients [64.6%] vs 192 [39.5%] and 273 [48.6%] for institutions B and C, respectively; \( P < .001 \)). Institutions A and B administered periprocedural antibiotics in all patients undergoing endoscopic retrograde cholangiopancreatography, whereas institution C did so in only 160 patients [28.6%] (\( P < .001 \)).

Intraoperative Bile Culture Analysis
Intraoperative bile culture data were available only for institutions A and C. There was a median (IQR) of 3 (2-4) different species of microorganisms found in intraoperative bile cultures, which was no different between institutions. Intraoperative bacteriobilia was associated with preoperative biliary stenting (98.8% vs 10.5% in patients who did not undergo preoperative biliary stenting; \( P < .001 \)). Bacteriobilia was also associated with higher rates of postoperative wound infection (12.4% vs 5.3% in patients without bacteriobilia; \( P = .05 \)).

The predominant microorganisms grown from the intraoperative bile cultures at institution A were Enterococcus faecalis (140 cultures [58.8%]), Streptococcus pneumoniae (114 [47.9%]), and Klebsiella pneumoniae (107 [44.8%]). Conversely, the predominant microorganisms found in intraoperative bile cultures at institution C were E. faecalis (30 cultures [44.8%]), K pneumoniae (16 [23.9%]), Enterobacter cloacae (13 [19.4%]), and Escherichia coli (13 [19.4%]); S pneumoniae was present in only 3 (4.5%) of the intraoperative cultures. There was a statistically significant difference in the proportion of E. faecalis, S pneumoniae, K pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa grown in the intraoperative bile cultures between both institutions (Figure 1). Notably, the overall incidence of Candida albicans in intraoperative bile culture was...
12.8% (39 cultures); there was no significant difference between the institutions.

**Postoperative Wound Infection and Microbiology Analysis**

The overall wound infection rate was 8.2% and was not significantly different across institutions ($P = .52$). Of the 133 wound infections, 67% were deep-tissue infection and occurred a median of 8 days (range, 1-57) after PD. Up to 67% of wound infections required home visiting nurse services after discharge, and almost 30% of the infections required readmission. When analyzed by institution, 31 patients (73.8%) with postoperative wound infections at institution A were discharged with visiting nurse assistance (VNA), which was significantly more so than institution B (2 patients [7.5%]) ($P < .001$) (VNA services not provided at hospital C). Conversely, only 8.7% of patients with postoperative wound infections at institution A required readmission compared with 46.1% and 58.3% at institutions B and C, respectively (Table 1) ($P < .001$). Logistic regression analysis identified preoperative biliary stenting as the strongest predictor (reported as OR [95% CI]) of postoperative wound infection (2.5 [1.58-3.88]; $P < .001$), followed by body mass index (1.5 [1.33-1.71]; $P = .001$) and Charlson comorbidity index (1.2 [1.06-1.39]; $P = .05$).

Most postoperative wound infections were polymicrobial, with a median (IQR) of 3 (2-4) different species cultured. There was marked variation in the type of microorganisms cultured from the wound infection. The predominant microorganisms cultured from postoperative wound infections at institution A were *E faecalis* (18 cultures [51.4%]) and *E cloacae* (16 [45.7%]). Conversely, the most common microorganisms at institution B were *S aureus* (8 cultures [43.9%]) and *K pneumoniae* (4 [21.4%]), and at institution C, *E faecalis* and *E coli* (17 [36.2%] for both). The overall incidence of *C albicans* in postoperative wound infection cultures was 11.5%, and there was no significant difference between institutions. Significant differences in the predominance of microorganisms are highlighted in Figure 2.

The predominant (>95%) perioperative antibiotics used at institutions A, B, and C were cefoxitin sodium, cefazolin sodium–metronidazole, and ampicillin sodium–sulbactam sodium, respectively. Most microorganisms grown from wound cultures at institution A were resistant to ampicillin (55.6%) and cefoxitin (53.1%). Institution B grew microorganisms that were predominantly resistant to ampicillin (69.2%) and cefazolin (42.9%). However, institution C’s microorganisms had a different profile, with most showing resistance...
toward penicillin (72.7%) and cefoxitin (65.9%). Institution C also had a disproportionately higher resistance rate to cefazolin and methicillin (Table 2).

**Discussion**

Postoperative wound infection poses a significant clinical and economic burden in the field of surgery, often leading to extended length of stay, the need for VNA services, readmissions, and increased costs. Multiple studies have reported the incidence of wound infection to be as high as 12% to 17% following PD. Even at high-volume referral centers, the incidence of wound infection exceeds 10%. A recent study analyzed the burden of infection for pancreatic resections, reporting a mean cost of $15,336 across all Clavien grades from infectious complications (as high as $80,490 for Clavien grade 4 [life-threatening complication, with resulting organ dysfunction]), with wound infection being the most common infectious complication. More important, postoperative wound infection has been shown to delay adjuvant chemotherapy in patients with pancreatic cancer and double the risk of chemotherapy omission. However, to our knowledge, the microbiology pattern and efficacy of perioperative antibiotic administration on postoperative wound infections in pancreatic surgery have not been studied in detail. Although the implementation of SCIP measures has undoubtedly led to a drop in the incidence of surgical wound infection during the early years of their adoption, contemporary analyses have shown that wound infection remains a significant burden despite improved SCIP adherence and that initiatives outside of SCIP need to be explored to address this issue.

In this study, we report (as OR [95% CI]) a very strong association of preoperative biliary stenting with bacteriobilia (725.3 [155.6-3380.5]; P < .001), which in turn is strongly associated with postoperative wound infection (2.5 [0.583-11.05]; P = .05). Not surprisingly, preoperative biliary stenting was found to be the strongest independent predictor of postoperative wound infection (2.5 [1.58-3.88]; P < .001). In previous studies, the clinical effect of bacteriobilia found on intraoperative bile culture has demonstrated an association with not just postoperative wound infection but also with organ space infection and sepsis. Despite that finding, intraoperative sampling of bile during PD is not common practice, limiting adequately powered, reproducible analysis that can be generalizable. Our data reveal that bacteriobilia, in line with the literature, is often polymicrobial. However, to our knowledge, our study is the first to demonstrate heterogeneity in both the practice of intraoperative bile culturing and microorganisms grown between different institutions, suggesting the need for institution-specific internal review.

The overall wound infection rate of 8.2% in our study was similar between all 3 institutions and marginally lower than the post-PD wound infection rate reported in the literature. Wound infections have been one of the most common reasons for readmission after PD, often occurring as a late complication. Our analysis demonstrates that 29.1% of post-PD wound infections required a readmission. Although institution A more frequently used VNA services for patients with wound infections on discharge (73.8% vs 75.8% for institution B; P < .001), the proportion of wound infections requiring readmission was proportionately lower (8.7% vs 46.1% and 58.3% for institutions B and C, respectively; P < .001). Although it was not within the scope of the study to perform a cost analysis, one can hypothesize that the liberal use of VNA services represents a potential avenue for decreasing length of stay, cost, the patient’s distress, and hospital outcome measures associated with readmissions.

When analyzing wound culture microorganisms, there was marked variation in the microorganisms grown, with equal variation in the antibiotic resistance pattern. More important, none of the 3 institutions analyzed was using effective perioperative antibiotics based on their cultured microorganisms. Institution A mainly administered cefoxitin for perioperative coverage, but the cultures predominantly grew Enterococcus and Enterobacter. There are strains of E faecalis that are cephalosporin resistant, and cefoxitin is largely ineffective in covering Enterobacter. Institution B used cefazolin and metronidazole but had the largest proportion of cultures growing S aureus and K pneumoniae, which were resistant to cefazolin. Finally, institution C used ampicillin-sulbactam; however, more than 60% of their strains of...
E faecalis and E coli are resistant to that agent. In addition, institution C had the highest incidence of C albicans identified in their wound cultures (15%).

Are these findings truly a call for institution-specific internal review for educated selection of antibiotic therapy, or are the findings a reflection of bacterial resistance development as a result of institution-specific perioperative antibiotic coverage? To answer this, we compared intraoperative bile cultures with wound cultures based on institution and found a marked similarity in microorganisms grown from the cultures in institutions A and C (Figure 3). This similarity argues against our findings that bacterial resistance develops in response to institution-specific perioperative antibiotic choice. Conversely, the similarity highlights the importance of obtaining intraoperative bile cultures given their ability to predict the microbial species grown in postoperative wound cultures and guide antibiotic selection in patients with postoperative wound infection. In an early study when patients routinely had indwelling biliary tubes after pancreaticoduodenectomy, Pitt et al29 studied intraoperative bile cultures and compared them with those obtained on postoperative days 4 to 7 in 111 patients; the results indicated a significant alteration in the types of microorganisms isolated. However, the patients in that study were receiving more than 5 days of postoperative antibiotics and, because the biliary drains were external, the cultures might have been confounded by contamination. Our study represents a large cohort with a subanalysis of more than 250 patients showing that the initial intraoperative bile culture determines the microbiology of postoperative wound infection and that subsequent alteration in microorganisms or resistance patterns as a result of perioperative antibiotic therapy, even if present, should hold no bearing.

Our data also suggest that the antibiotic regimen recommended by the SCIP for colon/abdominal surgery, which consists primarily of cephalosporins and ampicillin-sulbactam, should be reconsidered for PD given the extensive biliary and enteric intraoperative contamination associated with this surgery and the different infectious risk profile. A UCLA (University of California, Los Angeles) group of investigators recently analyzed wound cultures in 34 patients whose cultures mainly grew cefoxitin-resistant E faecalis and E cloacae (similar to institution A in the present study) and tailored their antibiotic therapy by switching to piperacillin-tazobactam, which reduced their wound infection rates from 32.4% to 6.6%.15 Similar to our findings, most of the microorganisms isolated were also resistant to ampicillin-sulbactam (ie, the other SCIP-approved regimen).
A French group has investigated the duration of antibiotic coverage after PD. Sourrouille et al\textsuperscript{37} performed an exploratory study in which a 5-day course of bile-antibiogram-based antibiotics were administered to high-risk patients (those undergoing preoperative endoscopic procedures) and found reduced rates of urinary tract infections, pulmonary infections, and septicemia but no significant difference in the incidence of wound infection and intra-abdominal abscess compared with the rate in low-risk patients (those who did not undergo endoscopic procedures). The investigators concluded that the postoperative short course of extended antibiotics reduces the overall infectious rate after PD. Although our study was not designed to evaluate an extended course of antibiotics, the significant risk of \textit{C difficile} infection associated with piperacillin-tazobactam\textsuperscript{38,39} seems to be excessive when only 12.4% of patients with bacteriobilia developed wound infection compared with those without bacteriobilia (5.3%). Instead of indicating a need for prolonged antibiotic treatment, these data on bile culture microorganisms should guide physicians on informed antibiotics administration in the setting of wound infection without culture data or when culture data are pending.

One of the limitations of this study is its retrospective design and consequent difference in patient demographics between the 3 institutions. However, our study focused on the microbiology analysis of intraoperative bile cultures, perioperative antibiotic regimens, and postoperative wound cultures; demographic factors have minimal implications on the final analysis of these variables. In addition, given that institution-specific research assistants were tasked with data collection, information bias may play a confounding role in the capture of wound infection-specific complications between institutions. Among the strengths of this analysis are the granularity and reliability of the data accrued from individual institutions. It has been proven that large administrative data sets (eg, National Surgical Quality Improvement Program and Centers for Disease Control and Prevention’s National Healthcare Safety Network) report incongruent data when analyzing wound infection rates.\textsuperscript{40-44} In the present study, data used for analysis were personally accrual by coauthors (Z.V.F., M.T.M., and G.M.) at their respective institutions and reviewed for accuracy.

Conclusions

Our analysis of data from a large-scale study analyzing post-PD wound infections identified significant interinstitutional variability in intraoperative bile and wound cultures as well as antibiotic resistance patterns. None of the 3 institutions analyzed was using effective antibiotic prophylaxis. We propose that intraoperative bile cultures should be routinely obtained during PD to predict microorganisms isolated in wound cultures and allow for tailored antibiotic therapy in the setting of pending or unavailable wound culture data, especially if there has been preoperative biliary manipulation. The SCIP performance measures and antibiotic regimens recommended for PD should be reevaluated, and institution-specific internal reviews should guide trials before amending current protocols for antibiotic prophylaxis to reduce the incidence of wound infections following PD. Based on the reported microbiology data, our institutions are collaborating on a randomized, double-blind clinical trial evaluating the efficacy of standard-of-care perioperative SCIP regimens vs more aggressive therapy (piperacillin-sulbactam) in our attempt to reduce the incidence of post-PD wound infections.

REFERENCES

Antibiotic Prophylaxis and Postsurgery Wound Infection Cultures


