Antimicrobial Stewardship Reduces Surgical Site Infection Rate, as well as Number and Severity of Pancreatic Fistulae after Pancreatoduodenectomy

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Abstract

Background: Surgical site infections (SSIs) remain a major source of morbidity after pancreatoduodenectomy (PD). We noted a higher than anticipated incidence of SSI in our patients undergoing PD, and after an internal audit and detailed analysis of the microflora of SSIs, as well as a multidisciplinary discussion, the local prophylactic antibiotic policy was changed based on sensitivities to the bacteria isolated from post-operative infections. The hypothesis was that a targeted change in antibiotic prophylaxis would reduce the rate of SSIs. The aim of the current study was to analyze the results of a change in prescribing policy on SSI rates, and in addition, on the occurrence and severity of post-operative pancreatic fistulae (POPF) because this complication is often linked to the presence of an organ/space SSI.

Methods: After implementing a change of prophylaxis policy from cefalexin to ceftriaxone and metronidazole, and educating staff and residents, a prospectively maintained departmental database was used to identify consecutive patients undergoing PD pre- and post-institution of policy change. Incidence data relating to SSIs and POPF were obtained from the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) data set and the details of culture results and organism sensitivity extracted from the electronic medical record, as were details on the severity of fistulae, and verified by the senior author.

Results: The pre- and post-implementation cohorts consisted of 111 and 216 patients, respectively, and were matched in terms of all demographic features. After the change in the antibiotic prophylaxis policy, there was a reduction in the overall SSI rate (26.4% vs. 14.8%; $p=0.01$) and the organ/space SSI rate (OS-SSI; 15.3% vs. 8.6%; $p=0.03$). There were also reductions in the POPF rate (38.2% vs. 19%; $p=0.002$) and in the clinically relevant POPF (CR-POPF; 23.4% vs. 6.0%; $p=0.001$). The rate of *Clostridium difficile* infections also decreased (8.1% vs. 1.9%; $p=0.006$) as did the median length of hospital stay (7 vs. 6 days; $p=0.003$). After excluding patients with a penicillin allergy ($n=24$) from the post-implementation cohort, cases compliant (158/192) and non-compliant (34/192) to the new antibiotic policy were compared. The overall SSI (26.4% vs. 10.7%; $p=0.025$), OS-SSI (17.6% vs. 5.1%; $p=0.021$), overall POPF (32.4 vs. 14.6; $p=0.023$), CR-POPF (10.8% vs. 5.5%; $p=0.047$) and *Clostridium difficile* (8.8% vs. 1.3%; $p=0.040$) were all lower in the compliant patient cohort.

Conclusions: A change in antibiotic prophylaxis prior to PD based on the local microflora, resulted in reductions in SSI, POPF, and *Clostridium difficile* rates.

Keywords: pancreatic resection; risk factors; surgical site infection

THE MORTALITY OF PANCREATIC SURGERY, and in particular pancreatoduodenectomy (PD) has decreased drastically and is now 2% or less in high-volume centers [1]. However, the morbidity of pancreatectomy remains high with published rates of 33%–51% for PD even in high-

volume institutions [2,3]. Evaluation of the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) data revealed a morbidity rate of 28% for PD that excluded pancreas-specific complications (H. Pitt, personal communication, March 18, 2018). In the

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Presented at the 38th Annual Meeting of the Surgical Infection Society, Westlake Village, California, April 2018.

NSQIP database, surgical site infections (SSIs) were the most common cause of morbidity, accounting for 21% of the post-operative complications with two-thirds being organ/space and one-third superficial SSIs (H. Pitt, personal communication, March 18, 2018). Such high rates for SSI are also reported in the recent literature: 17%–28% for PD [4,5] and so it is certain that this is a genuine problem.

Currently, 152 hospitals are collecting procedure-targeted pancreatectomy data for ACS-NSQIP and 89 of these are part of the HPB Collaborative, with their data contributing 84% of the PD volume (H. Pitt, personal communication, March 18, 2018). Overall it is anticipated that the NSQIP targeted pancreatectomy data represents 60%–70% of the entire U.S. PD volume (H. Pitt, personal communication, March 18, 2018).

In one such publication, we noted our institutional SSI to be an outlier, with the incidence of superficial (13.9% vs. 7.2%), deep (4.1% vs. 2.2%), and organ/space SSI (15.6% vs. 10.8%) being greater than those of our fellow collaborative members (Fig. 1A). As an institution, we at that time followed Surgical Care Improvement Project (SCIP) guidelines [6], namely, prophylactic antibiotic agents received within one hour prior to incision; prophylactic antibiotic selection for surgical patients; and prophylactic antibiotic agents discontinued within 24 hours after surgery. In addition, we had previously implemented a policy on glove change prior to closure, and the use of designated closure kits [7].

As a result, an internal audit was conducted examining all SSIs observed in our PD population during a one-year period. We hypothesized that with a number of measures in place, our high incidence of SSI may have been caused by choice of antibiotic that although meeting SCIP criteria, was inappropriate to our patient population. The local antibiogram was examined and sensitivities of all organisms causing SSIs in this population were determined. As a result, the prophylactic antibiotic policy for PDs was changed from cefazolin to ceftriaxone and metronidazole. A subsequent audit demonstrated a marked reduction in SSI rates, with an improvement in rank in HPB Collaborative (Fig. 1B).

The relation between organ/space SSI and post-operative pancreatic fistulae (POPF) is a contentious one. A 2012 single center analysis of 408 patients undergoing PD identified POPF as the most important risk factor for organ/space SSI with an odds ratio of 7.56 [8]. The relation between pancre-

atic fistula and organ/space was evaluated in two further recent studies. In a 2014 multivariable analysis, Namsashim et al. [9] identified pancreatic fistula as the only risk factor for the development of an SSI. However, in the same year Parikh et al. [10], evaluating 250 of their patients looking for a link between organ/space infections and grade B/C fistulas and found the sensitivity (55%) and specificity (45%) for a relation between fistula and organ space/infection, and deemed it unlikely the two factors were linked. The aim of the current study was to determine whether the change in prescribing policy, in addition to reducing the SSI rates as shown in our previous study, also influenced the occurrence and severity of POPF.

Patients and Methods

A prospectively maintained Institutional Review Board approved departmental database was queried to identify all consecutive patients who had undergone PD between January 2014 and December 2017. Our institution adapted a new antibiotic policy in May 2015 and so patients were grouped as either “Pre” (before May 2015) or “Post” (after May 2015) implementation of the new regimen. No other changes in personnel, operative technique, or clinical management occurred during the duration of the study.

Basic demographic data as well as details of culture results and organism sensitivity were extracted from the electronic medical record (EMR), as were details on the severity of fistulae, these being validated by the senior author. The use of pre-operative biliary drainage was also noted.

Definitions of SSI and POPF were based on those included in the ACS-NSQIP operations manual [11]. The institutional ACS-NSQIP data set was accessed to obtain data relating to the incidence of SSIs and POPF. All patients had drain amylase assessed on post-operative day one and this was used as an indicator for the likelihood of developing a POPF, however, clinical decisions as to drain removal were based on assessment of day three drain and fluid amylase. All drains were removed on post-operative day three unless a POPF was present.

Data from the NSQIP data set and the EMR were used to predict the likelihood of developing a POPF using a validated and open access fistula risk score hosted by the Pancreas Club using the data points: gland texture, pancreatic duct size,

FIG. 1. Results from the 2014 (A) and 2015 (B) ACS-NSQIP HPB Collaborative reports indicating an initially high rate of SSI within our institution (indicated in blue) that improved within 6 months after changing the prophylactic antibiotic policy.

TABLE 1. DEMOGRAPHIC FEATURES OF THE PRE- AND POST-MODIFICATION ANTIBIOTIC GROUPS

Factor	Pre (n=111)	Post (n=216)	Significance (p)
Gender, M/F	66/45	118/98	0.40
Age, mean $\pm$ SD	63.1 $\pm$ 12.9	64.2 $\pm$ 12.0	0.23
BMI, mean $\pm$ SD	28.1 $\pm$ 5.9	28.1 $\pm$ 6.2	0.70
Minimally invasive, n (%)	12 (10.8)	26 (12.0)	0.88
Pre-operative stent, n (%)	64 (57.7)	104 (48.1)	0.10
Operative time (min), mean $\pm$ SD	411 $\pm$ 95	400 $\pm$ 104	0.82
Fistula risk score, mean $\pm$ SD	2.96 $\pm$ SD 2.3	3.30 $\pm$ SD 2.0	0.07

SD=standard deviation; BMI=body mass index.

pathology, and intra-operative blood loss [12]. The antibiotic prophylaxis policy in the pre-change group consisted of a single dose of 1–2 g cefazolin (Ancef®; GSK, Brentford, England) within one hour of incision. After an internal audit of the organisms present in SSIs after PD, and after evaluation of the local antibiogram, the protocol was amended to 1–2 g ceftriaxone (Rocephin®; Roche, Berne, Switzerland) and 500 mg metronidazole (Flagyl®; Pfizer, New York, NY). In the cefazolin-treated patients, a second dose of antibiotic agents was administered in cases exceeding six hours. Surgical residents were educated on the importance of compliance prior to introducing the change in policy. Prior to the change in antibiotic prophylaxis, as an institution the SCIP guidelines were followed and a glove change was compulsory as was the use of a designated closure kit [6,7]. In all cases without documentation of a penicillin allergy, the use of antibiotic agents other than ceftriaxone or metronidazole after the beginning of May 2015 was regarded as non-compliance.

Continuous values were described by means and standard deviations or medians and interquartile ranges. Categorical values were described by counts and percentages. Comparisons of infection types between levels of categorical variables were made using the Pearson χ^2 test.

All analyses were on a complete-case basis and were done using Statistical Package for the Social Sciences software (version 25, SPSS; IBM, Armonk, NY). All testing was two-sided and used a 5% significance level.

Results

A total of 327 patients were identified, of whom 111 and 216 were classified as belonging to the pre- and post-implementation groups, respectively. The demographic features of the groups are summarized in Table 1. The cohorts were comparable in terms of gender ratios with a male predominance in both at 59.5% versus 54.6% ($p=0.40$), and in relation to age distributions with mean age at 63.1 ± 12.9 versus 64.2 ± 12.0 years ($p=0.23$), respectively. The mean body mass of the two groups was identical at 28.1 kg/m^2 .

The proportion of laparoscopic/robotic PDs in each group was similar (10.8% vs. 12.0%; $p=0.88$) as was the percentage of patients undergoing pre-operative biliary stenting (57.7% vs. 48.1%; $p=0.10$). The mean duration of the operation was also comparable in the two cohorts at 411 ± 95 versus 400 ± 104 ($p=0.82$). Furthermore, assessment of the distribution of fistula scores (FRS) for the pre- and post-intervention groups revealed no statistical difference between the mean FRS of the two groups (3.0 ± 2.3 vs. 3.3 ± 2.0 ; $p=0.07$).

After the change in the antibiotic prophylaxis policy, analysis of the NSQIP data revealed that the overall SSI rate decreased from 26.4% versus 14.8% ($p=0.01$) and on further analysis in relation to SSI location, the organ/space SSI rate was lower at 15.3% versus 8.6% ($p=0.03$). The rates of superficial and deep SSI were also reduced but not substantially (Table 2).

TABLE 2. Peri-Operative Outcomes in the Pre- and Post-Modification Antibiotic Groups

Factor	Pre (n=111)	Post (n=216)	Significance (p)
SSI, n (%)	29 (26.4)	32 (14.8)	0.01
Superficial	8 (7.2)	10 (4.1)	0.443
Deep	3 (2.7)	1 (0.4)	0.115
Organ/space	18 (15.3)	21 (8.6%)	0.03
POPF, n (%)	42 (38.2)	41 (19)	0.0002
A	15 (13.5)	29 (11.8)	>0.999
B	23 (20.7)	12 (4.9)	<0.001
C	3 (2.7)	0 (0)	0.015
CR-POPF	26 (23.4)	13 (6.0)	0.001
<i>Clostridium difficile</i> , n (%)	9 (8.1)	4 (1.9)	0.006
Fistula risk score mean $\pm$ SD	2.96 $\pm$ SD 2.3	3.30 $\pm$ SD 2.0	0.07
Length of stay (d) median (IQR)	7 (6–11)	6 (5–9)	0.003

SSI=surgical site infection; POPF=post-operative pancreatic fistulae; CR-POPF=clinically relevant post-operative pancreatic fistulae; SD=standard deviation; IQR=interquartile range.

TABLE 3. COMPARISON OF PERI-OPERATIVE OUTCOMES IN COMPLIANT AND NON-COMPLIANT PATIENTS IN THE POST-MODIFICATION ANTIBIOTIC GROUP

Factor	Non-compliant (n=34)	Compliant (n=158)	Significance (p)
SSI, n (%)	9 (26.4)	17 (10.7)	0.025
Organ/space SSI, n (%)	6 (17.6)	8 (5.1)	0.021
POPF, n (%)	11 (32.4)	23 (14.6)	0.023
CR-POPF, n (%)	4 (10.8)	4 (5.5)	0.047
<i>Clostridium</i> <i>difficile</i> , n (%)	3 (8.8)	2 (1.3)	0.040

Factor	Non-compliant (n=34)	Compliant (n=158)	Significance (p)
SSI, n (%)	9 (26.4)	17 (10.7)	0.025
Organ/space SSI, n (%)	6 (17.6)	8 (5.1)	0.021
POPF, n (%)	11 (32.4)	23 (14.6)	0.023
CR-POPF, n (%)	4 (10.8)	4 (5.5)	0.047
<i>Clostridium</i> <i>difficile</i> , n(%)	3 (8.8)	2 (1.3)	0.040

SSI=surgical site infection; POPF=clinically relevant post-operative pancreatic fistulae; CR-POPF=clinically relevant post-operative pancreatic fistulae.

In addition, reductions were noted in the overall rate of POPF (grades A+B+C) from 38.2% versus 19.0% ($p=0.002$). Although there was no difference in the rate of biochemical leak (A), there were reductions in the fistulae of clinical relevance: CR-POPF both individually and on a collective basis at 23.4% versus 6.0% ($p=0.001$).

Of note, the incidence of *Clostridium difficile* infection also reduced after the change in the antibiotic policy from 8.1% to 1.9% ($p=0.006$). A further observation was a reduction in the length of post-operative hospital stay from a median and interquartile range of 7 [5–9] to 6 [4–7] days ($p=0.003$).

After excluding patients with a penicillin allergy ($n=24$) from the post-implementation cohort, cases compliant (158/192) and non-compliant (34/192) to the new antibiotic policy were compared. The overall rate of SSI was 26.4% versus 10.7% in the non-compliant and non-complaint cohorts, respectively ($p=0.025$) and there was also a difference in the OS-SSI rate at 17.6% versus 5.1% ($p=0.021$) (Table 3).

Furthermore, comparing non-compliant and compliant patients, the rates of both overall POPF (32.4 vs. 14.6; $p=0.023$) and CR-POPF (10.8% vs. 5.5%; $p=0.047$) were substantially different. A final observation was that the *Clostridium difficile* rates were lower in the antibiotic-compliant population at 8.8% versus 1.3% ($p=0.040$).

Discussion

The primary finding from this study is that the implementation of an antibiotic prophylaxis policy based on targeted antibiotic therapy to bacteria responsible for SSIs in the targeted population of PD leads to reduction not only of SSIs but also of POPF. The implementation of such a policy in our practice led to a reduction in the incidence of SSI from 26.4% to 14.8%, and when only patients' adherent to the

policy were assessed the rate was only 10.7%. This rate of SSI is less than reported in the NSQIP data (H. Pitt, personal communication, March 18, 2018) and the current surgical literature [4,5] and indicates that intelligent antibiotic prophylaxis targeting bacteria likely to be encountered during PD is critical in preventing SSIs in this cohort.

Kondo et al. [13] examined the effect of changing prophylactic antibiotic policy based on local antibiogram of SSIs observed in their PD patients and noted that a reduction in SSI from 46.6% to 24.1% ($p=0.011$) after the introduction of this policy. An alternate strategy was proposed by Sudo et al. [14] who based perioperative prophylaxis on bile cultures obtained at the time of pre-operative biliary drainage.

It may be questioned as to whether the change in antibiotic policy was the sole driver for the improvement in SSI rates, however, the fact that the SSI rate in the cohort non-compliant with policy at 26.4% is identical to that of the patients undergoing PD prior to the change in prophylaxis would tend to suggest this to be the case. Prior to the implementation of change in antibiotic prophylaxis, the unit was already strictly adhering to SCIP measures [6] and had adopted the use of designated closure kits [7] in all abdominal surgery cases. Interestingly, although the SCIP measures designate antibiotic agents to be given within one hour of incision, they do not identify specific antibiotic prophylaxis for a patient undergoing a PD.

None of the patients in this series had an incision protector in place during surgery. There is evidence that such devices may benefit patients in terms of reducing SSI rates [15]. Although this recent trial looked only at patients with biliary stents, the SSI rate in the cohort in which a wound protector was used was 27.3%, which is similar to the rate in the current study in which cefazolin was used. In the study by Bressan et al. [15] study, the use of antibiotic prophylaxis was not standardized or controlled for on the analysis.

The second interesting finding was the reduction of POPF in the post modification of prophylaxis era, with a decrease from 38.2% to 19% overall, and a reduction from 23.4% to 6.0% in terms of CR-POPF. Again, when only patients whose prophylaxis was adherent to the new policy were considered, the POPF rate was 14.6% compared with 32.4% and the rates of CR-POPF in the compliant and non-complaint groups were 5.5% and 10.8%, respectively. The POPF rate in the ceftriaxone-metronidazole cohort at 5.5% was lower than the current published literature that report rates of 11.3%–19.7%, which are more in keeping with the rates seen in the cefazolin group in the current study [16–18].

Of note, factors said to be predictive of morbidity including both SSI and POPF such as pre-operative biliary stenting [19,20], the performance of open versus laparoscopic surgery [21,22], and the fistula risk score [12] were no different between the pre-and post-implementation groups. Furthermore, no patients in the current study received prophylactic or treatment octreotide [23] Again, these data would indicate that an optimal antibiotic choice may mitigate for certain risk factors.

The fact that 34 of 111 (15.7%) non-penicillin allergic patients in the post-implementation prophylaxis drops group failed to comply with policy was disappointing, because both before and after introducing the change, all members of the surgical staff performing PDs and all surgical residents were educated as to the findings of the initial study, and the

importance of adhering to policy. At the time of this study antibiotic choice was decided at the time of PD during a pre-commencement World Health Organization-style huddle [24], however, an order set has since been developed within the electronic medical record only two options: ceftriaxone and metronidazole and ciprofloxacin and metronidazole for penicillin-allergic patients. It is anticipated that adherence to policy will increase when a re-audit is performed.

A further interesting observation is the reduction in *Clostridium difficile* rates in patients compliant with the approved antibiotic bundle. It may be that the metronidazole is suppressing the bacteria, or the lack of complications is maintaining a more robust immune surveillance thus not slowing an opportunistic infection to develop. Further evaluation of this observation is planned.

As a result of the reduction in rates of OS-SSI and CR-POPF, which are important clinical complications, there was a reduction in the post-operative hospital stay, which in practice would lead to financial savings in addition to the benefit to patients. An additional measure to be considered, and one we have adopted, is to culture the bile at the time of PD in order to obtain confirmation of the organisms present in a particular case. Mohammed et al. [25] reported the importance of obtaining biliary cultures and targeting treatment of bacterobilia, by comparing a standard perioperative prophylaxis policy with a prolonged prophylaxis together with prolonged treatment of patients with bacterobilia. They noted bacterobilia in 59% and that directed treatment decreased the incision infection rate from 12% to 3%.

There is in addition microbiologic data to support a relation between the presence of bacterobilia, POPF, and SSIs. Fong et al. [26], demonstrating a close correlation between organisms cultured from perioperative bile sampling and those subsequently seen in cultures from SSIs, with gut-derived organisms identified in the majority of cases. In a systematic review and meta-analysis, Müsle et al. [27] noted a median incidence of bacterobilia of 58%, and that intra-operative bile cultures and postoperative infections correlated in around 50% of cases. Furthermore, Ohgi et al. [28] studied 264 patients and found in a multivariable analysis that positive intra-operative bile cultures were associated with clinically important pancreatic fistulae. Of great interest was the fact that among the 151 patients with a positive intra-operative bile culture, the same bacteria were detected in the drainage fluid of 100% of the patients on postoperative day one and in 88% of patients on postoperative day three. A causal relation between bacterobilia, SSI, and POPF would therefore appear plausible.

The main weakness of this study is that it is a retrospective series, whereas the optimal design would be a randomized controlled trial such as that currently under way by the combined Americas Hepato-Pancreato-Biliary Association and ACS-NSQIP trial [29]. However, one of the advantages of being a single site study was that all the complications were verified by an experienced pancreatic surgeon, and up- or downgrading of severity was done based on a comprehensive review of the case notes.

Conclusions

A change in the prescribing policy for prophylactic antibiotic agents prior to PD, based on the local microflora,

resulted in a substantial reduction in the SSI rates after resection. In addition, antimicrobial stewardship also resulted in a statistically significant reduction in the overall incidence, as well as the incidence of clinically significant POPF. The lack of complete compliance to policy has led to the development of a fixed preoperative order set with only two antibiotic options for standard and penicillin-allergic patients. After this additional venture, and further education on adherence to the policy a re-audit is in process.

Funding Information

No funding was received.

Author Disclosure Statement

The authors have nothing to disclose.

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