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Is Antisecretory Therapy After Pancreatoduodenectomy Necessary? Meta-analysis and Contemporary Practices of Pancreatic Surgeons

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Abstract
Background Marginal ulcer (MU) is a well-described complication of pancreatoduodenectomy (PD) whose incidence remains unclear. Gastric antisecretory medications likely attenuate the risk of marginal ulceration after PD; however, the true relationship between antisecretory medication and marginal ulceration after PD is not precisely known. The aims of this study were to document the incidence of MU after PD, identify any relationship between MU and gastric antisecretory medication, and survey current practice of MU prophylaxis among experienced pancreatic surgeons.
Methods the MEDLINE, EMBASE, Cochrane Central Registrar of Controlled Trials, and Cochrane Database of Systematic Reviews databases were searched from their inception to May 2014 for abstracts documenting ulceration after pancreatoduodenectomy. Two reviewers independently graded abstracts for inclusion in this review. Contemporary practice was assessed through a four-question survey distributed globally to 200 established pancreatic surgeons.
Results After a review of 208 abstracts, 54 studies were graded as relevant. These represented a cohort of 212 patients with marginal ulcer after PD (n=4794). A meta-analysis of the included references shows mean incidence of ulceration after PD of 2.5 % (confidence interval (CI) 1.8–3.2 %) with a median time to diagnosis of 15.5 months. Pylorus preservation was associated with a MU rate of 2.0 % (CI 1.0–2.9 %), while "classic" PD procedures report an overall rate of 2.6 % (CI 1.6–3.6 %). Documented use of postoperative antisecretory medication was associated with a reduced rate of 1.4 % (CI 0.1–1.7 %). One hundred forty-four of 200 (72 %) surveys were returned, from which it was determined that 92 % of pancreatic surgeons have dealt with this complication, and 86 % routinely prescribe prophylactic antisecretory medication after PD.
Conclusions The incidence of MU after PD is 2.5 % with a median time to occurrence of 15.5 months postoperatively. Gastric antisecretory medication prescription may affect the incidence of MU. The majority of pancreatic surgeons surveyed have encountered MU after PD; most (86 %) routinely prescribe prophylactic gastric antisecretory medication.

Keywords Pancreatoduodenectomy · Pylorus preservation · Marginal ulceration · Antisecretory · Proton pump inhibitors

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Introduction

Marginal ulcer (MU) is a well-described and morbid complication of pancreatoduodenectomy (PD). Despite current broad application of PD, surprisingly few data are available regarding the postoperative incidence of MU. As increasing numbers of PD are performed for non-oncologic indications, this often-delayed complication may even increase in frequency. Etiologic factors affecting the occurrence of MU are related to altered gastrointestinal anatomy: Duodenal resection removes the thick, alkaline-rich mucus buffer provided by Brunner's glands (Fig. 1). As described in Dragstedt's study of ulcer

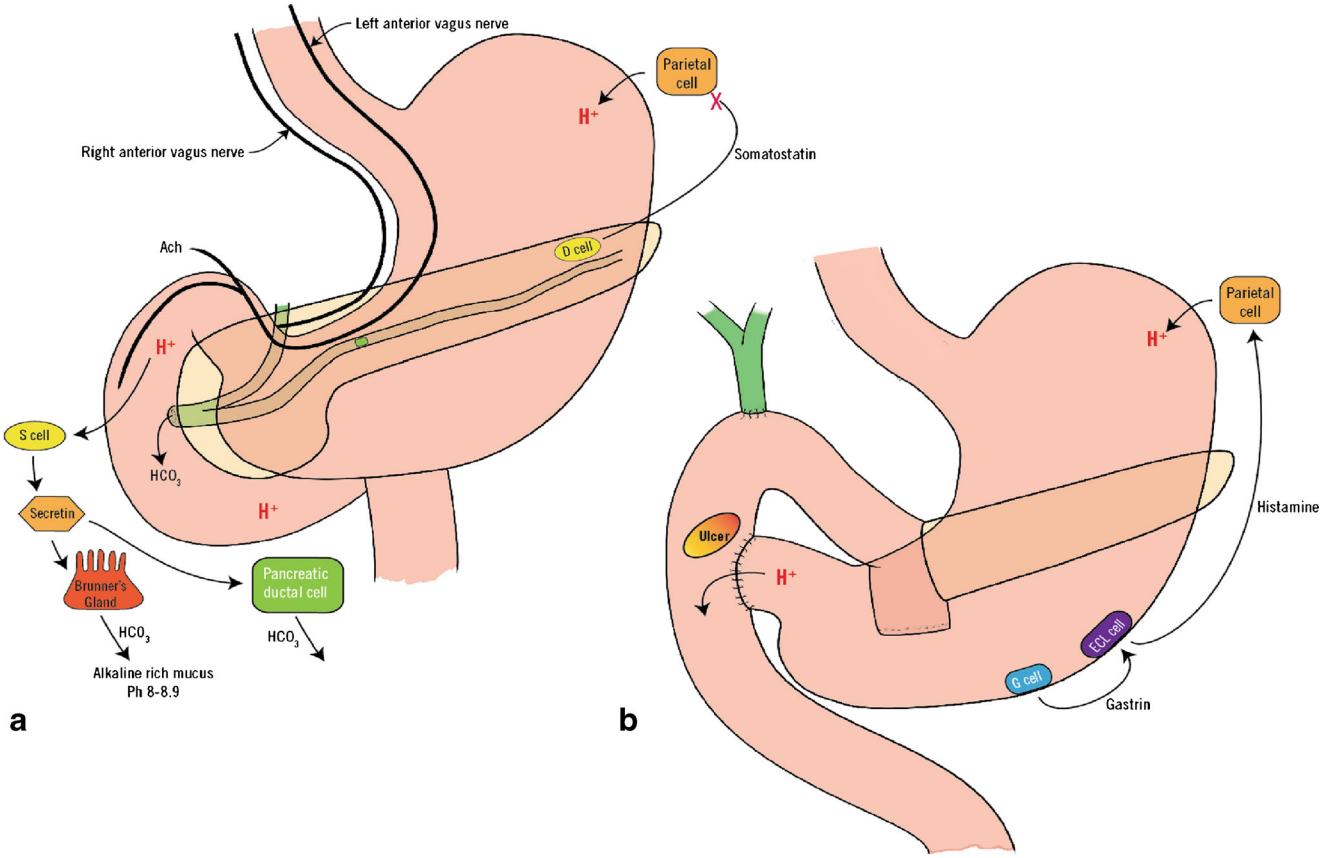

Fig. 1 Marginal ulcer physiology. a Native pancreatic and duodenal wall protection against ulceration. The ulcerogenic hydrogen cation (H^+) is buffered by bicarbonate anion (HCO_3^-) released from pancreatic ductal cells and the duodenal wall. The presence of H^+ in the duodenum stimulates duodenal S cells to release secretin, which has downstream effects on Bruner's gland mucus secretion, and pancreatic ductal cells. Vagal Ach has synergistic action with secretin. Pancreatic D cells release somatostatin, which targets upstream inhibition of H^+ production. b The net loss of acid inhibitory measures after pancreatectomy; PPPD version is depicted. Unchecked acid infusion into the jejunum creates an ulcerogenic state

physiology, un-buffered gastric content can be ulcerogenic to the bowel wall [1].

The importance of anatomical reconstruction after pancreatoduodenectomy has been recognized. For example, as early as 1948, Owens suggested that surgeons should place the gastroenterostomy distal to the pancreatic and biliary anastomoses, citing the importance of bile and pancreatic secretions as alkaline buffers [2]. The discovery of histamine receptor (H_2) blockers and subsequently proton pump inhibitors (PPIs) has provided powerful therapy for peptic ulcer disease.

While marginal ulceration after PD has been identified as a complication of PD, its short- and long-term incidence in the modern era of readily available gastric antisecretory medication has not been reported. The aim of this study was to conduct a systematic review of the published literature to determine the variable incidence of ulceration after PD as well as the relationship of MU with prophylactic gastric antisecretory medication prescription. These data were used to frame a survey of the contemporary practices of high-volume pancreatic surgeons regarding their experience with MU and their pattern of prescribing gastric antisecretory medication after PD.

Materials and Methods

This study was approved by the Indiana University School of Medicine Institutional Review Board.

Data Sources

The MEDLINE, EMBASE, and Cochrane Library were searched from 1946 to May 2014, 1947 to May 2014, and the Cochrane Library through May 2014. The Cochrane Library included the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), and the Database of Abstracts of Reviews of Effects (DARE). For the first search concept, a search hedge was created for surgical procedures which included the terms Whipple, along with terms for pancreatoduodenectomy including plurals and prefix variants such as "pancreato." The ulcer concept was searched in title, abstract, and subject fields and truncated to retrieve ulcer, ulcers, ulceration, etc. A reasonable definition of marginal ulcer is an ulcer occurring within 3 cm of the enteric anastomosis. The third search concept

dealt with postoperative complications. All three concepts were combined and the results limited to humans and to English language. Case reports were eliminated, but case series were included. For all search concepts, a combination of keywords and thesaurus (Medical Subject Headings (MeSH), Emtree Thesaurus) terms were searched. Details of full electronic search strategy are available in supplemental information.

Data Extraction

Three investigators (JRB, TR, and the senior author) independently reviewed the titles and abstracts of all returned references regardless of publication status to identify studies for inclusion in the analysis. All identified articles were examined using a predesigned proforma and the data collected were entered into a database for subsequent analysis. A list of exclusion criteria and gathered data is detailed in Table 1. For the purpose of this analysis, we accepted experienced authors' definition of MU and excluded all studies (n=85) that did not specifically identify a complicating ulcer as "marginal" or document its location with respect to anastomosis. The methodological quality of studies was assessed for a minimum Oxford Center for Evidence-Based Medicine (CEBM) level of 2B. Where appropriate, studies were allocated to separate cohorts for independent meta-analyses of variables. Figure 2 tracks reference flow through the systematic review process.

Statistical Analysis

All included references were allocated to appropriate cohorts for individual meta-analyses of variables. When combining data from these trials, we assumed that the presence of heterogeneity existed prior to pooling and used the random effects model developed by DerSimonian [3]. This model allows for a conservative estimate of the range of effect by adjusting for variability between trials. Individualized random effects meta-analyses were preformed to estimate percentages and 95 % confidence intervals for all endpoints queried.

Table 1 Exclusion criteria applied

Exclusion criteria	
CEBM <2B	N=7
Studies including less than 10 patients	N=6
Data previously published	N=4
Failure to identify or define a MU cohort	N=85
Confounding variable: Zollinger-Ellison pathology	N=34
Mean follow-up duration not specified	N=14
Symptomatic selection bias affecting incidence endpoint	N=4

CEBM Center for Evidence-Based Medicine, *MU* marginal ulcer

Global Survey of Pancreatic Surgeons

The current practice of pancreatic surgeons was queried through an electronic survey. Established pancreatic surgeons were identified through the authors' professional contact and affiliation with pancreatic surgery organizations (Pancreas Club, Society for Surgery of the Alimentary Tract, and the Americas Hepato-Pancreato-Biliary Association). A four-question survey was generated and distributed electronically to 200 established pancreatic surgeons across the world. The questions asked were as follows: (1) How many years have you practiced pancreatic surgery; how many PD have you performed? (2) Do you currently prescribe antisecretory medication for postoperative PD patients and if so for what duration? (3) Has your practice of post-PD antisecretory prescription changed over your career, if so why? (4) Have you ever treated a patient with a marginal ulcer after PD? All data returned from survey response were arranged into a predetermined proforma. This data set was analyzed as an independent and homogenous cohort, subjected to arithmetic analysis without random effects modeling.

Results

Incidence of Marginal Ulcer After PD

In the initial search, 208 abstracts were retrieved; 7 additional abstracts were identified through a review of reference lists. After applying exclusion criteria noted in Table 1, 54 studies were graded as relevant for quantitative review [4–57]. In aggregate, this represented a cohort of 212 patients experiencing ulceration after 4794 PDs. The median CEBM level was 2A. Figure 3a represents a meta-analysis of the included references to show mean incidence of ulceration after PD of 2.5 % (confidence interval (CI) 1.8–3.2 %) with a median time to diagnosis of 15.5 months. Median follow-up time was 22 months (range 5–60) across all studies; all subgroups maintained an 18-month median follow-up time. Pylorus-preserving pancreatoduodenectomy was associated with a MU rate of 2.0 % (CI 1.0–2.9 %), while classic procedures including gastric antrectomy were associated with a MU rate of 2.6 % (CI 1.6–3.6 %). Figure 3b illustrates the relationship between documented use of postoperative antisecretory medication and a reduced MU rate of 1.4 % (CI 0.1–1.7 %).

Contemporary Practice

The survey of contemporary practice was returned by 144 of 200 (72 %) queried pancreatic surgeons representing 11 countries and a collective experience of over 58,000 PDs (Fig. 4). Among respondents, the average number of years practicing

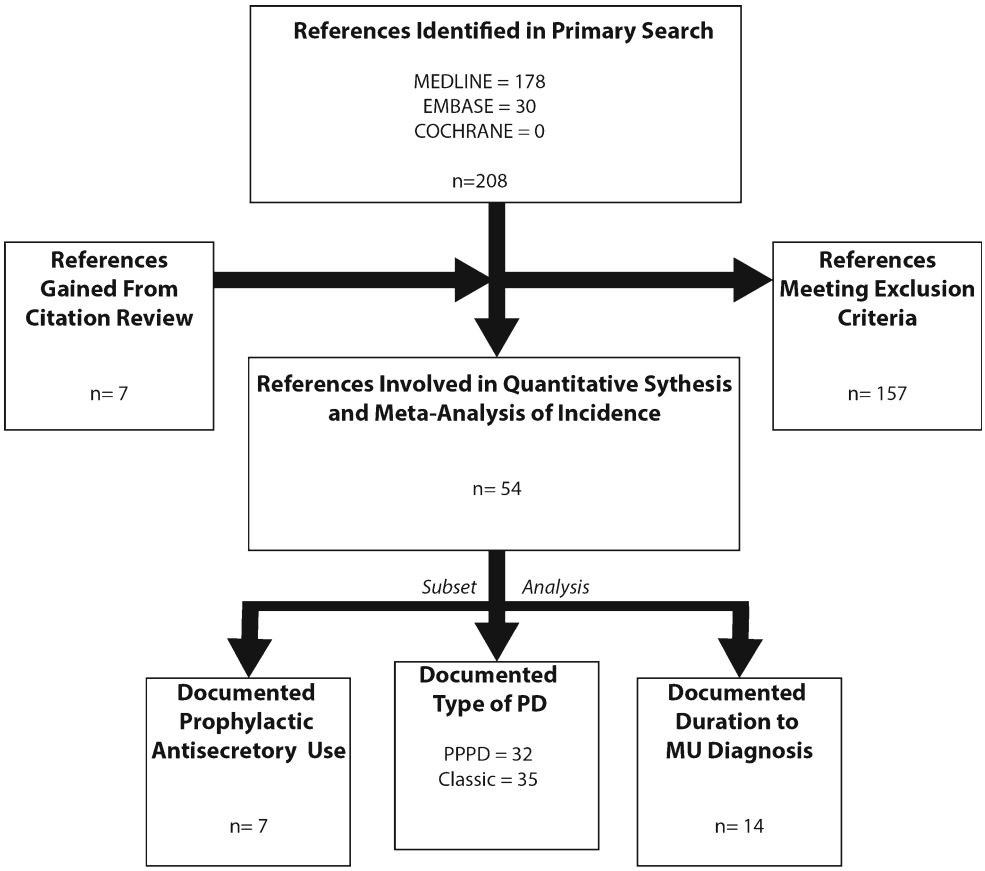

Fig. 2 Flow of references through systematic review

pancreatic surgery was 15 (range 2–40) and the median number of PD performed was 425 (range 23–2000).

The vast majority of pancreatic surgeons (92 % of respondents) encountered marginal ulcer after PD. Figure 5 shows experience with MU relative to years in practice and number of PD performed. Regression analysis suggests that the likelihood of encountering MU approaches 100 % after 425 PDs.

Most pancreatic surgeons (86 %) prescribe antisecretory medication after resection. The duration of antisecretory treatment was variable: 16 % limited treatment to the immediate postoperative period (approximately 7 days), 38 % prescribed antisecretories for 1–12 months, and 46 % routinely prescribed antisecretories for life (Fig. 6).

Twenty-eight percent of pancreatic surgeons reported a change in their practice of post-PD antisecretory prescription during their careers. Of those who did change their routine practice, 74 % increased duration of acid suppression medication and cited an encounter with marginal ulcer as the reason, and 26 % switched from H_2 blocker to PPI (Fig. 7).

Discussion

Marginal ulcer is a well-described and morbid complication of pancreatoduodenectomy. Despite its frequent description within the literature, this is the first study to systematically review the incidence of MU after PD and, specifically, the relationship of MU to postoperative medications. The reported incidence of MU after PD is 2.5 %, with median time to ulceration after PD of 15.5 months. Pylorus-preserving PD trended toward a lower incidence of MU (2.0 %) while the classic PD trended above the mean (2.6 %); these trends did not reach statistical significance. Within this review, the documented use of prophylactic gastric antisecretory medication was associated with a statistically significant reduction in MU after PD. It must be recognized that availability of published data regarding timing, duration, and type of gastric antisecretory therapy is incomplete, and therefore, this report is an observation and may not represent a "cause-effect" relationship. Despite these limitations, it seems that highly experienced pancreatic surgeons have realized this relationship, and the vast majority (86 %) routinely prescribe antisecretory medication after PD. Nearly all (92 %) have encountered MU after PD.

Historical interest in gastric acid production after PD included an initial belief that PD created an inherently hypersecretory state [58] and led to the practice of routine antrectomy and truncal vagotomy [49, 55, 59, 60]. In 1978, Traverso and Longmire popularized pyloric preservation without vagotomy in an attempt to limit jejunal ulceration, a

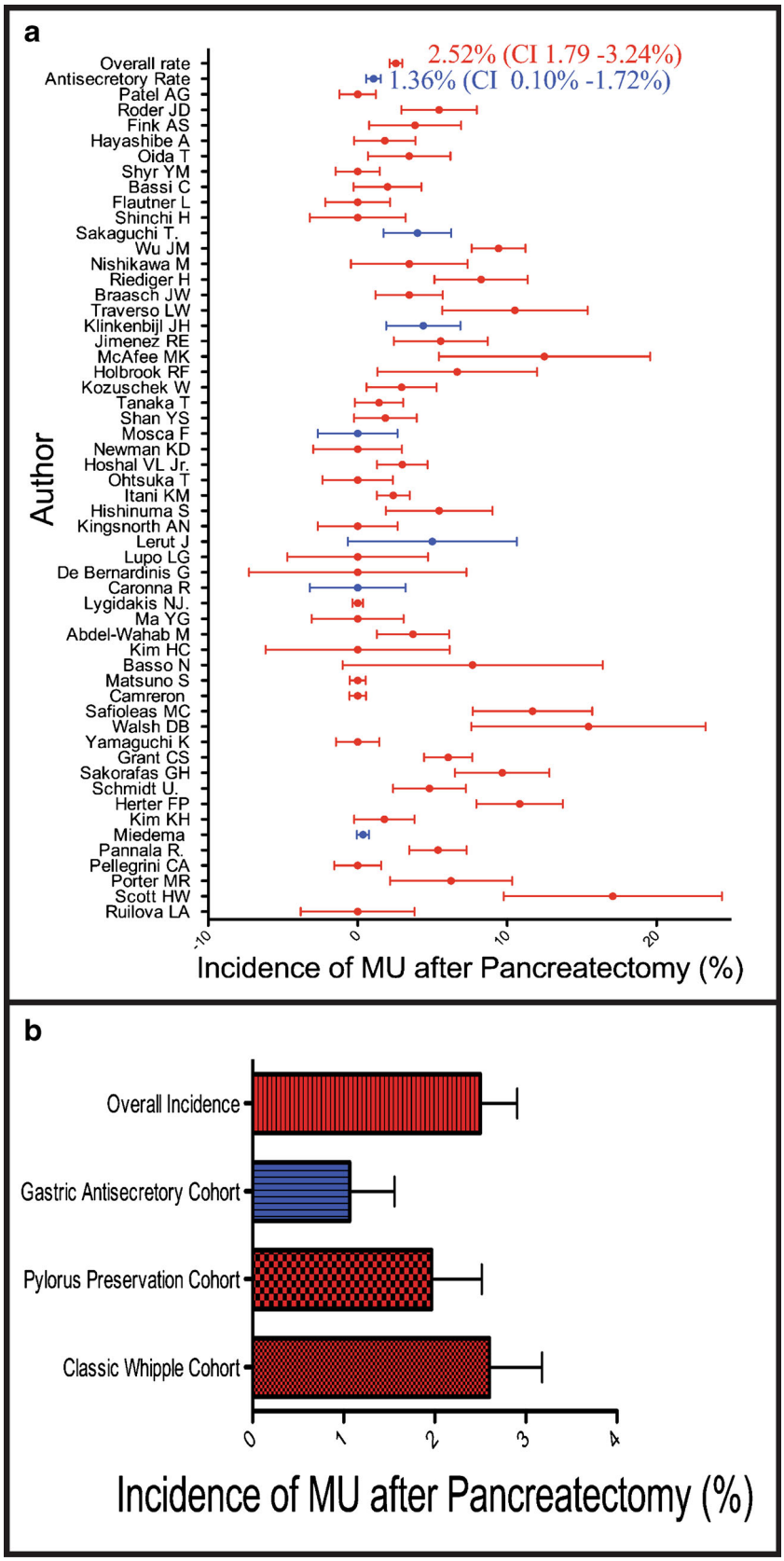

Fig. 3 Incidence of marginal ulcer after pancreatoduodenectomy reported in the literature. **a** All included references [4–57] and **b** aggregate percentages based on operation type (PPPD vs. Classic PD) and postoperative antisecretory prescription are shown

Fig. 4 Institutional representation of survey data. *Dots* represent the 96 institutional affiliations of surgeons responding to survey (n=146)

concept first described by Watson in 1944 [61–63]. After the adoption of pylorus preservation, several studies have documented gastric acid and gastrin levels below normal after classic PD and normal after PPPD [21, 60, 61, 64–66]. The implicit effect of these studies was to divert attention away from the gastric mucosa. Unfortunately, subsequent debates failed to include the role of prophylactic antisecretory agents directed at gastric acid production.

Despite meticulous attention to the anatomical evolution of PD, the literature has afforded much less attention to the role of medical therapy after operation. Effective acid-suppressing medication may decrease the risk of marginal ulceration after gastrojejunostomy [67]. Contemporary literature has paid more attention to the role of antisecretories after gastric bypass bariatric procedures, and several studies have documented a significant protective effect [68, 69]. The incidence of MU after PD is interesting when placed in the context of MU rates observed after gastric bypass (4.6 %) [69]. Similarly, the ability of H_2 blockers and PPI to reverse ulcer physiology effectively is exemplified by their mainstay role in peptic ulcer management.

The efficacy of acid-suppressing medications, especially proton pump inhibitors (PPIs), must be weighed against their potential complications. Increased osteoporotic fractures,

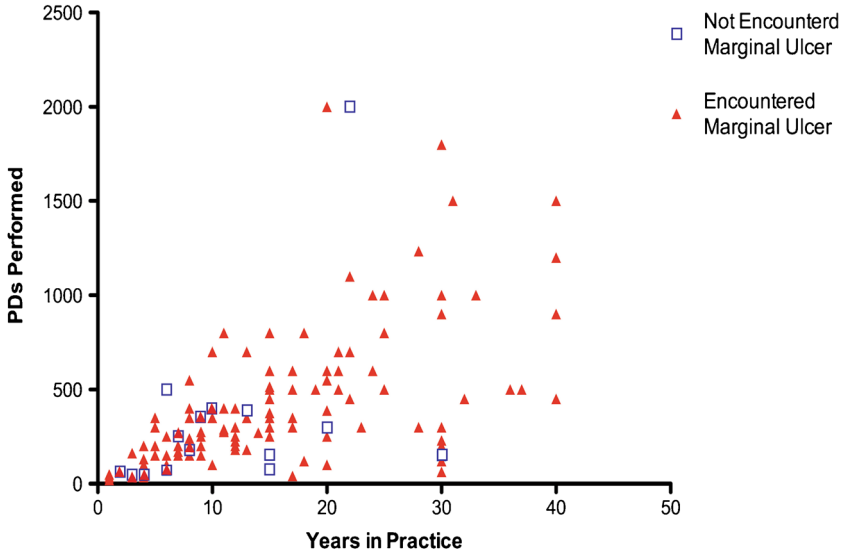

Fig. 5 Experience of pancreatic surgeons with marginal ulcer. Eighty-nine percent of pancreatic surgeons reported to have encountered MU after PD. The likelihood of encountering marginal ulcer approaches 100 % in this sample after 425 PDs

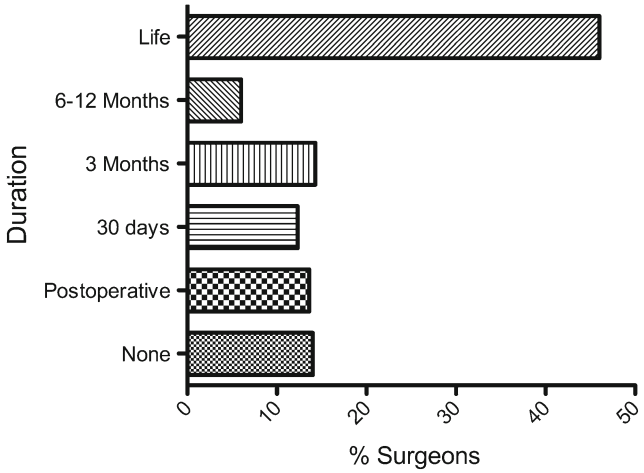

Fig. 6 Antisecretory prescription habits of pancreatic surgeons. Most pancreatic surgeons (86 %) prescribe gastric antisecretory medication. Of those that do, 46 % prescribe for life, 13 % limit to the immediate postoperative period, 12 % for 1 month, 14 % for 3 months, and 8.2 % for 6–12 months

Clostridium difficile infection, and adverse drug-drug interactions have all been reported with long-term PPI use [70, 71]. In addition, PPI use may lead to hypergastrinemia, which has been implicated in the rise of gastroesopheageal malignancy [72, 73]. Although current studies have failed to find a significant relationship between long-term PPI use and gastric cancer [74, 75], theoretical concern is grounded both in concepts of physiology [75] and potential delays in diagnosis.

Several limitations affect the current analysis. Foremost, many larger PD series do not report MU as an endpoint. In the absence of routine endoscopic surveillance, the true incidence of ulceration after PD is almost certainly underreported, and with increasing use of extended or lifelong use of PPIs after PD, many ulcers may not reach clinical significance. Furthermore, the 22-month median follow-up time in the data accrued likely represents the nature of diseases for which PD is performed; the subsequently low rate of ulceration may underestimate the threat of this complication over a longer survival term, particularly in the increasing population that receive PD for non-malignant diagnoses. A second limitation of our data is in the infrequent and inconsistent discussion of antisecretory use by authors. Considering the results of this study's international survey, it is likely that use of prophylactic antisecretory medication is underreported in published PD literature. Finally, one must recognize the capacity of other variables to affect incidence of MU; such factors include smoking, nutritional status, adjuvant chemotherapy, and radiation.

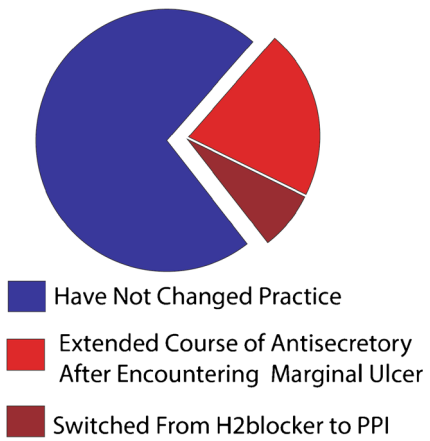

Fig. 7 Changes in prescription habits. Twenty-eight percent of pancreatic surgeons reported changing their practice of post-PD prescription. Of those that did change practice, 74 % increased duration of acid suppression medication, citing an encounter with marginal ulcer as the reason, and 26 % switched from H_2 blocker to PPI

The finding that at least 2.5 % of patients undergoing PD will develop a marginal ulcer highlights the significance of this postoperative complication. Pancreatic surgeons must communicate with patients and their primary care providers to raise awareness of this important problem. Gastric antisecretory medication treatment significantly reduces the incidence of MU after PD. The median time to diagnosis of MU was 15.5 months, suggesting that at least 24 months of prophylactic gastric antisecretory treatment seem prudent.

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