

## Evaluation and Management of Patients With Recurrent Peptic Ulcer Disease After Acid-Reducing Operations: A Systematic Review

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This systematic review examines the evidence for commonly employed strategies of managing patients with recurrent ulcer disease after acid-reducing operations. Particular attention is given to recent evidence relating *Helicobacter pylori* (*H. pylori*) and nonsteroidal anti-inflammatory drugs (NSAIDs) to ulcer recurrence after operative therapy. MEDLINE word searches of the literature from 1966 to 2001 identified 895 articles that cross-reference the terms "peptic ulcer disease (PUD)," "surgery," and "recurrence." Articles were selected for systematic review of evidence relating incomplete vagotomy, NSAIDs, and *H. pylori* to postoperative ulcer recurrence and evidence supporting common medical and surgical strategies. The relationship between incomplete vagotomy and recurrent ulcer disease is suggested by randomized controlled trials and well-designed prospective case series. The evidence that NSAID use is an important pathogenic factor in recurrent ulcer disease includes the relationship between NSAIDs and primary PUD, the occurrence of NSAID-induced ulcers in patients taking proton pump inhibitors, and case series demonstrating virulent ulcer disease in patients taking aspirin despite prior acid-reducing operations. The relationship between *H. pylori* infection and postoperative ulcer recurrence remains uncertain despite multiple controlled trials and well-designed case series that have documented high rates of *H. pylori* infection in postoperative patients. The initial management of patients with recurrent ulcer disease after acid-reducing operations consists of a proton pump inhibitor or a histamine-2 receptor antagonist and antibiotics directed at *H. pylori*, if present. Evidence for this regimen includes prospective randomized trials demonstrating the efficacy of cimetidine in healing ulcers after acid-reducing operations and prospective, randomized studies documenting the efficacy of histamine-2 receptor antagonists and proton pump inhibitors in the management of patients with primary PUD. The critical role that *H. pylori* infection plays in primary PUD and the minimal risks associated with *H. pylori* eradication strongly support the initiation of antibiotic therapy when *H. pylori* is present. The principal indication for operative management of recurrent PUD is the occurrence of ulcer complications that cannot be managed by medical or endoscopic means. The operative management of patients with failed acid-reducing operations is based on ulcer recurrence rates and morbidity and mortality rates in randomized and nonrandomized prospective trials of patients with primary PUD and retrospective case series of patients undergoing remedial operative procedures after various failed acid-reducing operations. (J GASTROINTEST SURG 2003;7:606-626.) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Recurrent peptic ulcer disease, peptic ulcer disease, vagotomy, antrectomy, parietal cell vagotomy

Recurrent peptic ulceration is one of the most frequent causes of unsatisfactory long-term results after operations for peptic ulcer disease (PUD). Although the number of patients requiring elective operations

for PUD has declined dramatically, large numbers of acid-reducing operations have been performed. Furthermore, operations to manage acute complications of ulcer disease are still commonly performed.

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The availability of potent inhibitors of gastric acid secretion and improved understanding of the pathophysiology of primary PUD, particularly with regard to *Helicobacter pylori* (*H. pylori*) and nonsteroidal anti-inflammatory drugs (NSAIDs), has fundamentally altered the therapeutic approach to patients with ulcer disease. The purpose of this article is to review the evidence for commonly employed strategies for evaluating and managing patients with recurrent ulcer disease after acid-reducing operations. Particular attention is given to recent evidence relating *H. pylori* and NSAIDs to ulcer recurrence after operative therapy.

## METHODS

MEDLINE word searches of the literature published from 1966 to 2001 were conducted using the terms “peptic ulcer disease” and “surgery” in combination with “recurrence.” This search yielded 37,283 articles for the term “peptic ulcer disease,” 7385 articles for the surgical treatment of PUD, and 895 articles that cross-referenced the terms “peptic ulcer disease,” “surgery,” and “recurrence.” The MEDLINE abstracts (or titles) of these 895 articles were examined by two of us (R.H.T and G.S.) to identify primary and review articles containing information pertinent to this review. A total of 175 articles were chosen for in-depth review based, in part, on the presence of one of the following characteristics: prospective design, large patient cohort, periods of follow-up longer than 10 years, and publication within the past 10 years. The level of evidence for each of the following questions was assigned using the criteria in Table 1:<sup>1,2</sup> (1) What is the role of incomplete vagotomy, NSAIDs, and *H. pylori* in the pathogenesis of recurrent ulcer disease after acid-reducing operations; (2) what is the best medical treatment for patients with recurrent ulcers after acid-reducing operations; and (3) what is the best operative treatment for patients with recurrent PUD after acid-reducing operations?

## INCIDENCE AND TIMING OF RECURRENT DUODENAL ULCER DISEASE

There are many prospective reports documenting the rate of recurrent ulceration after various acid-reducing operations with long periods of follow-up (Table 2). The incidence of ulcer recurrence is lowest for the most extensive procedures such as truncal vagotomy and antrectomy and higher for nonresectional procedures such as truncal vagotomy and pyloroplasty and parietal cell vagotomy.<sup>3-13</sup> The most common sites for ulcer recurrence are peripyloric, duodenal, and peristomal (i.e., within 1 cm of a gastrojejunostomy). The time to ulcer recurrence is related, at least in part, to the particular operation performed. Most patients who develop recurrent ulcerations after a truncal vagotomy and pyloroplasty or truncal vagotomy and antrectomy do so within the first 3 to 5 postoperative years, whereas patients who have undergone a parietal cell vagotomy appear to be at risk for recurrent ulcer disease for at least 13 years<sup>3,4,6,7,14</sup> (Fig. 1). In one early study, 70% of the recurrences after truncal vagotomy and pyloroplasty, truncal vagotomy and antrectomy, and gastric resection occurred within the first 3 postoperative years.<sup>15</sup> These data are similar to those reported by Jordan et al.<sup>7</sup> in a prospective randomized comparison of parietal cell vagotomy and selective vagotomy and antrectomy. Meisner et al.<sup>3</sup> and Jordan et al.<sup>7</sup> noted a progressive increase in ulcer recurrences after parietal cell vagotomy for at least the first 13 years after the procedure. The monthly risk of ulcer recurrence after parietal cell vagotomy was estimated to be between 0.07% and 0.38%,<sup>7,16,17</sup> and the rate after selective gastric vagotomy and antrectomy was estimated to be 0.008%.<sup>7</sup>

## CLINICAL PRESENTATION

Many patients with recurrent ulcer disease after ulcer surgery are asymptomatic.<sup>18</sup> The others present

**Table 1.** Level of evidence rating<sup>1,2</sup>

Level of evidence	Type of investigation
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled trial without randomization
IIb	Evidence obtained from at least one other type of well-designed quasiexperimental study
III	Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlational studies, and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

**Table 2.** Frequency of recurrent peptic ulcer disease after acid-reducing operations

Reference	Study description	Study design	Level of evidence	Sample size	Average follow-up (yr) or range (yr)	Recurrence rate (%)
Highly selective vagotomy Meisner et al. <sup>3</sup> (1988)	Estimate probability of ulcer recurrence after PCV	Long-term systematic follow-up, case series	III	339	15	27*
Johnston et al. <sup>4</sup> (1991)	Long-term follow-up of patients undergoing PCV	Long-term systematic follow-up, case series	III	305	10–20	15
von Holstein et al. <sup>5</sup> (1987)	Long-term follow-up of patients undergoing PCV	Long-term systematic follow-up, case series	III	100	>10	18
Koruth et al. <sup>6</sup> (1990)	Comparison of PCV and TV & P	Prospective, randomized	Ib	57	12	5
Jordan and Thornby <sup>7</sup> (1994)	Comparison of PCV and SV & A in 200 patients followed over 20 yr	Prospective, randomized	Ib	102	10–20	14
Hoffman et al. <sup>8</sup> (1987)	Long-term prospective follow-up of 135 patients undergoing PCV	Long-term systematic follow-up, case series	III	135	14–18	30
Hoffman et al. <sup>9</sup> (1989)	Comparison of TV and drainage, selective vagotomy and drainage, and PCV in 197 patients	Prospective, randomized	Ib	80	11–15	39*
Macintyre et al. <sup>10</sup> (1990)	Long-term follow-up of patients undergoing PCV 5–15 years postop (82% follow-up)	Long-term systematic follow-up, case series	III	283	12	19
Herrington et al. <sup>11</sup> (1986)	Long-term prospective follow-up of 131 patients undergoing PCV	Long-term systematic follow-up, case series	III	131	6–13	9
Koo et al. <sup>12</sup> (1983)	Comparison of TV & D, TV & A, and PCV in 152 patients	Prospective, randomized	Ib	50	4	16
Koruth et al. <sup>6</sup> (1990)	Comparison of PCV and TV & P in 137 patients	Prospective, randomized	Ib	59	12	7
Hoffman et al. <sup>9</sup> (1989)	Comparison of TV & D, selective vagotomy and drainage and PCV in 197 patients	Prospective, randomized	Ib	78	11–15	28*
Koo et al. <sup>12</sup> (1983)	Comparison of TV & D, TV & A, and PCV in 152 patients	Prospective, randomized	Ib	51	4	12
Truncal vagotomy and drainage Taylor et al. <sup>13</sup> (1990)	Comparison of anterior lesser curve seromyotomy with posterior truncal vagotomy and TV & P in 146 patients	Prospective, randomized	Ib	69	4.5	3

*Table 2 continued.*

**Table 2. Continued**

Reference	Study description	Study design	Level of evidence	Sample size	Average follow-up (yr) or range (yr)	Recurrence rate (%)
Vagotomy and antrectomy Jordan and Thornby <sup>7</sup> (1994)	Comparison of PCV and SV & A in 200 patients followed over 20 yr	Prospective, randomized	Ib	92	10–20	2
Hoffman et al. <sup>9</sup> (1989)	Comparison of TV & D, SV & D, and PCV in 197 patients	Prospective, randomized	Ib	90	11–15	37*
Koo et al. <sup>12</sup> (1983)	Comparison of TV & D, TV & A, and PCV in 152 patients	Prospective, randomized	Ib	51	4	0

PVC = parietal cell vagotomy; SV & A = selective vagotomy and antrectomy; TV & A = truncal vagotomy and antrectomy; TV & D = truncal vagotomy and drainage; TV & P = truncal vagotomy and pyloroplasty.

\*Kaplan-Meier estimates after selective vagotomy and antrectomy.

with recurrent abdominal pain and/or one of the following complications of their disease: hemorrhage, perforation, or gastric outlet obstruction.<sup>14,19–24</sup> The relative frequency of the symptomatic clinical scenarios is shown in Table 3. The following three points deserve emphasis: (1) Most patients with epigastric pain after an operation for PUD do not actually have recurrent ulcers.<sup>23–25</sup> Mosiman et al.<sup>25</sup> found that only about one third of patients with postoperative dyspeptic pain had recurrent ulcers. These investigators and others have noted that the pain of a recurrent ulcer is often indistinguishable from that of other postgastrectomy complications such as impaired gastric emptying (gastroparesis), esophagitis, or bile reflux gastritis.<sup>23–25</sup> (2) Free perforation into the peritoneal cavity is a relatively unusual mode of presentation for patients with recurrent ulcer disease in the absence of aspirin (acetylsalicylic acid [ASA]) or NSAID use, and (3) recurrent ulcers due to ASA, and perhaps other NSAIDs, are associated with a high frequency of severe complications including obstruction, bleeding, and even perforation.<sup>21,26</sup>

## ETIOLOGY

The two most common causes of recurrent ulcer disease are incomplete vagotomy and ulcerogenic medications, particularly NSAIDs. The relationship between *H. pylori* and recurrent ulcer disease is unclear. The evidence relating incomplete vagotomy, NSAID use, and *H. pylori* infection to recurrent ulcer disease after acid-reducing operations is reviewed in Table 4. Less common causes include hypersecretory states, such as gastrinoma, and retained excluded gastric antrum. At the present time, there is

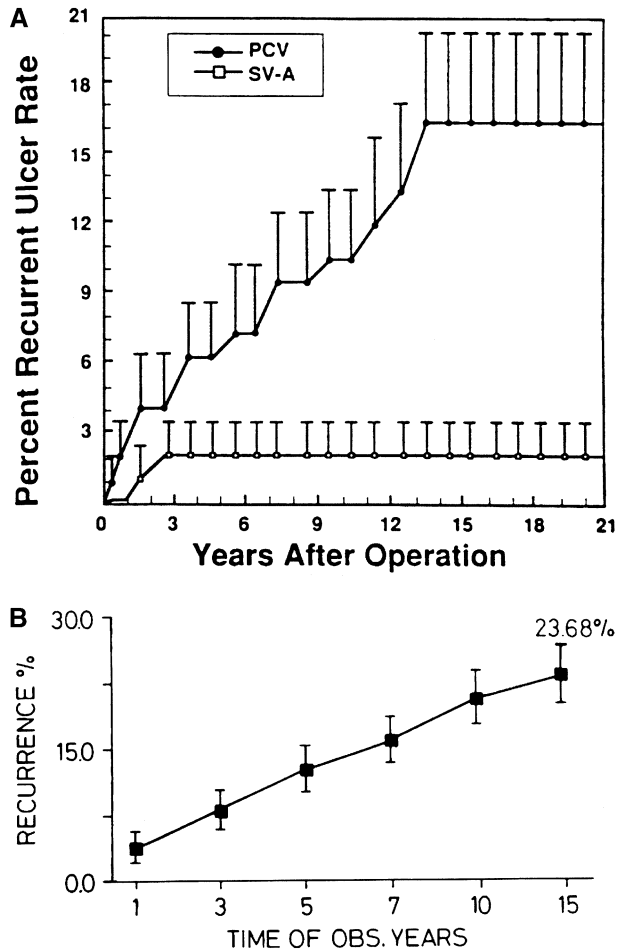
little evidence to suggest that hypercalcemia (in the absence of gastrinoma) and gastric stasis cause recurrent ulcer disease, G-cell hyperplasia, or the presence of a long afferent limb.

## Role of Incomplete Vagotomy in the Pathogenesis of Recurrent Ulcer Disease

There is substantial evidence relating incomplete vagotomy to recurrent ulcer disease after acid-reducing operations.<sup>7,10,27–30</sup> All forms of vagotomy reduce basal acid output and stimulate gastric acid output by 50% to 80%.<sup>7,27–29,31</sup> Gastric resection, with or without vagotomy, reduces acid secretion by as much as 90%.<sup>7,31</sup> This degree of inhibition of acid secretion persists for as long as 10 to 20 years postoperatively.<sup>7,29,31</sup>

The relationship between incomplete vagotomy, persistent acid production, and recurrent ulcer disease is suggested by studies demonstrating greater levels of acid production in patients with ulcer recurrence than in patients without recurrence. For example, a prospective study of 280 patients undergoing parietal cell vagotomy found that 72% of patients with a post-parietal cell vagotomy basal acid output greater than 1.4 mmol/hr developed recurrent ulcer disease compared with only 8% of patients whose basal acid output was less than 1.4 mmol/hr<sup>27</sup> (Fig. 2). Similarly, 18% of the patients in that study with a postoperative peak acid output greater than 12 mmol/hr developed recurrent ulcer disease, whereas only 3% of those with stimulated acid output less than 12 mmol/hr developed a recurrence.<sup>27</sup>

Using another assay of vagal integrity, Feldman et al.<sup>30</sup> found that the ratio of acid output after sham feeding to peak acid output (SAO/PAO) was significantly greater in patients whose ulcers recurred post-



**Fig. 1. A,** Frequency and timing of ulcer recurrence after parietal cell vagotomy (PCV) or selective vagotomy and antrectomy (SV-A). Jordan and Thornby<sup>7</sup> reported the results of a prospective, randomized comparison between parietal cell vagotomy (n = 100) and selective vagotomy and antrectomy (n = 100). Each curve represents the expected probability plus 1 standard error for ulcer recurrence. The monthly average recurrence rate was 0.069% for parietal cell vagotomy and 0.0083% for vagotomy and antrectomy. (From Jordan PH Jr, Thornby J. Twenty years after parietal cell vagotomy or selective vagotomy antrectomy for treatment of duodenal ulcer: Final report. *Ann Surg* 1994;220:283–296.) **B,** Frequency and timing of ulcer recurrence after parietal cell vagotomy using Kaplan-Meier plots  $\pm$  1 standard deviation. Meisner et al.<sup>3</sup> reported these data based on observations in 339 patients undergoing parietal cell vagotomy followed for a median period of 108 months (range 1 to 197 months). Ulcers recurred in 62 (18.3%) of the 339 patients. (From Meisner S, Jorgensen LN, Sensen HE. The Kaplan and Meier and the Nelson estimate for the probability of ulcer recurrence 10 and 15 years after parietal cell vagotomy. *Ann Surg* 1988;207:1–3.)

operatively than in those without a recurrence. More important, of the five patients with ulcer recurrence and a high SAO/PAO, repeat vagotomy dramatically reduced acid production and prevented ulcer recur-

rence. Stenquist et al.<sup>28</sup> reported that a high postoperative SAO/PAO predicted early (within 5 years postoperatively) but not late (>5 years) ulcer recurrence, suggesting the importance of other factors such as NSAID use in late ulcer recurrence. The latter observation is consistent with studies demonstrating the recurrence of ulcers in patients with complete vagotomies and the lack of a difference in the average (or median) gastric acid output between patients who have a recurrence of ulcers and those who do not.<sup>7,21,31–33</sup>

### Role of NSAIDs in the Pathogenesis of Recurrent Peptic Ulcer Disease

Evidence relating NSAID use to recurrent ulcer disease after acid-reducing operations includes the following: (1) the well-known association between NSAIDs and complicated primary PUD;<sup>34–36</sup> (2) the suggestion that overt or surreptitious NSAID use is responsible for recurrent ulcers after the effective eradication of *H. pylori*;<sup>37</sup> (3) the observation that NSAID-induced ulcers occur in patients in whom gastric acid secretion is significantly suppressed by the administration of high-dose proton pump inhibitors (PPIs);<sup>38,39</sup> and (4) two observational studies documenting the occurrence of virulent recurrent ulcer disease in patients taking ASA despite prior operations that profoundly reduced gastric acid secretion.<sup>21,26</sup> Hirschowitz and Lanas<sup>21</sup> reported 30 patients who chronically used ASA and developed recurrent ulcer disease after various acid-reducing operations. The rate of ulcer recurrence was 80% to 90% despite the fact that patients undergoing remedial procedures of increasing complexity had progressively greater reductions in gastric acid production. In this study the ulcerations were multiple, deep, and caused stenosis of the gastric outlet. Most important, the only patients who had healing of their ulcers were those who stopped taking ASA. These observations are consistent with those reported by Perrault et al.<sup>26</sup> in a case series.

The quantity of ASA required to produce recurrent ulceration, particularly in the hypochlorhydric stomach, is unknown. In the study by Hirschowitz and Lanas,<sup>21</sup> the patients took 1 to 3.5 gm per day (serum salicylate levels of 3 to 30.4 mg/100 ml), suggesting that the virulent ulcer disease reported in their study was induced by large doses of ASA. In a recent study by Cryer and Feldman,<sup>40</sup> in normal volunteers with an intact stomach, they found that even very low doses of ASA (10 mg/day) reduce gastric mucosal prostaglandin levels by 60% and cause gastroduodenal mucosal injury. These data are consistent with epidemiologic and autopsy studies suggest-

**Table 3.** Symptoms associated with recurrent ulcers after acid-reducing operations

Reference	Sample size	Pain (%)	Bleeding (%)	Obstruction (%)	Perforation (%)	Notes
Schirmer et al. <sup>14</sup> (1982)	166	45	41	12	1	One patient presented with diarrhea
Kinney et al. <sup>19</sup> (1988)	42	55	40	5	0	—
Lee et al. <sup>20</sup> (1998)	93	58	42	—	—	—
Hirschowitz <sup>21</sup> (1998)*	30	—	23	43	23	Other symptoms (e.g. pain) are not described in 11% of patients.
Heppell et al. <sup>22</sup> (1983)	120	43	27	19	7	Other symptoms of recurrent ulcer disease are not described in 4% of patients

\*Aspirin-associated ulcers.

ing that ASA dosages as low as 75 to 325 mg/day (or even 325 mg every other day) may cause gastrointestinal ulcers and bleeding.<sup>41,42</sup> Whether patients with ulcers who undergo prior acid-reducing operations are more vulnerable (or protected) against ASA-induced ulcers is uncertain.

### Role of *H. pylori* in the Pathogenesis of Recurrent Peptic Ulcer Disease

In contrast to the well-known pathogenic role that *H. pylori* plays in primary PUD,<sup>43-45</sup> the relationship between *H. pylori* infection and recurrent ulcer disease after acid-reducing operations is unclear. The prevalence of *H. pylori* infection after vagotomy without gastric resection is 65% to 98% up to 14 years postoperatively, and the prevalence of infection after gastric resection ranges from 18% to 49% up to 20 years postoperatively.<sup>20,46-52</sup> There are surprisingly few data relating persistent colonization to recurrent ulcer disease. Several studies have found that the prevalence of *H. pylori* infection in patients with recurrent ulcer disease is similar to that in patients without recurrent disease.<sup>20,46-52</sup> These studies are summarized in Table 4.

Even in the presence of an incomplete vagotomy, it remains unclear whether *H. pylori* significantly increases the risk of ulcer recurrence. In one study of 122 patients undergoing vagotomy, who were followed for up to 14 years, the only patients who developed ulcer recurrence were those with incomplete vagotomy, irrespective of the status of the *H. pylori*. Only one in four patients with both persistent *H. pylori* infection and an incomplete vagotomy developed recurrent ulcer disease.<sup>48</sup> These data suggest that acid-reducing operations, per se, do not affect gastric *H. pylori* infection and that patients who were infected preoperatively remain infected after their ulcer oper-

ations. Despite these data, the relationship between *H. pylori* and the recurrence of ulcers postoperatively remains of concern, particularly given recent data suggesting that patients with *H. pylori* infections are more susceptible to NSAID-induced gastric mucosal injury than are patients without *H. pylori* infection.<sup>53</sup>

### Unusual Causes of Recurrent Ulcer Disease After Acid-Reducing Operations

**Retained Gastric Antrum.** Gastric antrum retained within the duodenal stump after gastric resection and Billroth II gastrojejunostomy is a very rare but important cause of recurrent ulcer disease. In these instances, the excluded antral mucosa is constantly bathed by alkaline duodenal and pancreatic fluid, resulting in the continuous secretion of gastrin and hence gastrin-mediated acid hypersecretion. The diagnosis should be suspected in patients with recurrent ulcer disease and hypergastrinemia after gastric resection and a Billroth II gastrojejunostomy. A sodium 99m-technetium pertechnetate scan demonstrating retained antral tissue within the end of the afferent loop confirms the diagnosis. The diagnosis may also be made endoscopically by histologically documenting pyloric or gastric mucosa at the end of the afferent loop. Excision of the retained antral tissue is curative. This complication can be avoided by frozen-section evaluation of the duodenal margin at the time of the initial resection. Identification of Brunner's glands at the distal resection margin confirms complete excision of the antrum.

**Gastrinoma.** Although gastrinoma is a rare cause of primary PUD, it assumes much greater importance in patients with recurrent ulceration, particularly after gastric resection. Multiple or jejunal ulcerations, rugal hypertrophy, and a history of diarrhea are important diagnostic clues. About one fourth of

**Table 4.** Evidence that incomplete vagotomy, nonsteroidal anti-inflammatory drugs, and *Helicobacter pylori* are important factors in the pathogenesis of recurrent ulcer disease after acid-reducing operations

Reference	Study description	Study design	Level of evidence
<b>Incomplete vagotomy</b>			
Jordan and Thornby <sup>7</sup> (1994)	Comparison of PCV and SV & A in 200 patients followed over 20 yr; ulcer recurrence and acid secretion higher in PCV group	Prospective, randomized	Ib
Macintyre et al. <sup>10</sup> (1990)	Long-term follow-up of patients undergoing PCV 5–15 years postop (82% follow-up); higher recurrence rate with incomplete vagotomy	Long-term systematic follow up, case series	III
Cohen et al. <sup>27</sup> (1993)	Quantitation of gastric acid release both pre- and postop in patients undergoing PCV with correlation between acid secretion and ulcer recurrence (N = 280 patients)	Case series with acid studies	IIb
Stenquist et al. <sup>28</sup> (1994)	Quantitation of postop sham acid output in 98 patients after PCV recurrence rate with complete vagotomy = 8%; with incomplete vagotomy = 23%.	Case series with acid studies	IIb
Braghetto et al. <sup>29</sup> (1988)	Comparison of PCV and extended PCV in 80 patients with duodenal ulcers; all patients had postop acid studies; low recurrence rate; acid studies similar in both groups	Prospective, randomized	Ib
Feldman et al. <sup>30</sup> (1980)	Quantitation of sham feeding to peak acid output in 50 nonvatomized subjects and 15 vagotomized patients with duodenal ulcers; all 5 patients with acid studies diagnostic of incomplete vagotomy underwent repeat vagotomy with significant reduction in acid secretion and cure of their ulcer disease	Case series with acid studies	IIb
<b>NSAID use</b>			
Hirschowitz and Lanas <sup>21</sup> (1998)	Series of 30 patients with recurrent ulcer disease after acid-reducing operations; with continued NSAID use ulcer recurrence is the rule despite complete vagotomy	Case series with salicylate levels	III
Perrault et al. <sup>26</sup> (1988)	Case report of 5 patients with recurrent ulcer after acid-reducing operations; All had surreptitious use of NSAIDs	Case series with salicylate levels	III
<b><i>Helicobacter pylori</i></b>			
Lee et al. <sup>20</sup> (1998)	No clear correlation between <i>H. pylori</i> and ulcer recurrence after acid-reducing operations	Prospective series with <i>H. pylori</i> studies	IIb
Peetsalu et al. <sup>46</sup> (1991)	Determination of <i>H. pylori</i> infection in patients with ulcers after ulcer operations; no correlation between <i>H. pylori</i> and recurrent ulcers	Case series	IIb
Leivonen et al. <sup>47</sup> (1997)	No clear correlation between <i>H. pylori</i> and ulcer recurrence after acid-reducing operations in 155 patients	Case series	III
Peetsalu et al. <sup>48</sup> (1998)	14-year follow-up of 122 patients after PCV; <i>H. pylori</i> status and endoscopic Congo red studies performed; no correlation between <i>H. pylori</i> status and recurrent ulcers	Case series	IIb
Leivonen et al. <sup>49</sup> (1998)	90 patients followed 5+ years after gastrectomy for ulcer disease; negative correlation between <i>H. pylori</i> and recurrent ulcers	Case series	III
Schilling et al. <sup>50</sup> (1999)	Patients undergoing gastroscopy for ulcer symptoms; 50 with prior ulcer surgery, 50 controls; <i>H. pylori</i> found in 37% with ulcer recurrence, 73% with primary ulcers	Case-control study	IIa
Csendes et al. <sup>51</sup> (1996)	31 patients with PCV, 133 with primary ulcers; 81% of primary ulcers <i>H. pylori</i> +, 71% of PCV patients <i>H. pylori</i> + despite no ulcer recurrence	Case series	IIb

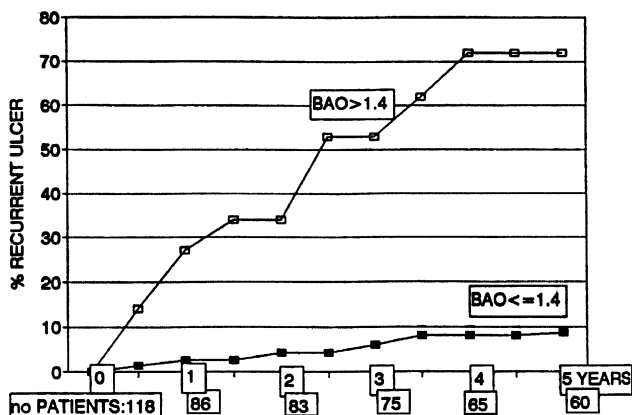


Fig. 2. Relationship between elevated basal acid output (BAO) and recurrence of PUD after parietal cell vagotomy. These data show the actuarial recurrent ulceration rate in 118 patients undergoing parietal cell vagotomy. Those patients with a BAO greater than 1.4 mmol/hr had a significantly higher rate of ulcer recurrence than did those with a BAO less than 1.4 mmol/hr. (From Cohen F, Valleur P, Serra J, Brisset D, Chiche L, Hautefeuille P. Relationship between gastric acid secretion and the rate of recurrent ulcer after parietal cell vagotomy. *Ann Surg* 1993;217:253-259.)

patients with gastrinomas have multiple endocrine neoplasia-1 (MEN-1) and 40% to 60% of patients with MEN-1 will have a gastrinoma. Thus the presence of hypercalcemia and hyperparathyroidism in a patient with recurrent ulcer disease strongly suggests the diagnosis of gastrinoma and MEN-1.

**Hypercalcemia and Hyperparathyroidism.** With the exception of patients with MEN-1, there are few published data to suggest that patients with hypercalcemia and hyperparathyroidism have an increased risk of PUD. Although experimentally induced hypercalcemia may stimulate gastrin release and gastric acid secretion,<sup>53</sup> basal and stimulated gastric acid secretion and serum gastrin levels are not significantly elevated in patients with chronic hypercalcemia associated with hyperparathyroidism.<sup>54</sup> Furthermore, in the absence of MEN-1 syndrome, there are few epidemiologic data to support a relationship between hyperparathyroidism and PUD.<sup>55</sup>

**Impaired Gastric Emptying.** An association between impaired gastric emptying, gastroparesis, and recurrent ulcer disease (especially gastric ulcers) has been suggested since the early days of gastric surgery. It is postulated that gastric distention and retained food increase gastrin release and thus acid secretion.<sup>56,57</sup> Although at one time it was thought to be responsible for as many as 12% of cases of recurrent ulceration,<sup>15</sup> at present the relationship between delayed gastric emptying and recurrent PUD is unclear. The principal evidence against the notion that impaired gastric emptying causes recurrent gastric

ulcers is the high rate of ulcer recurrence in patients with gastric outlet obstruction treated only by revision of the anastomosis.<sup>23,58</sup> It is likely that in most patients with gastric outlet obstruction and recurrent ulcer disease, outlet obstruction is the consequence, and not the cause, of ulcer recurrence.

**Long Afferent Loop After Billroth II Gastrectomy.** The presence of a long afferent loop in a Billroth II reconstruction has often been mentioned as cause of recurrent ulceration. The long afferent loop is proposed to cause deficient buffering of the acidic gastric juice in the jejunal limb resulting in ulceration. Although there is elegant experimental evidence in dogs from the 1950s supporting this mechanism,<sup>59,60</sup> only a few cases reported in the literature in humans are attributed to this cause.<sup>61</sup> In these reports, the definition of long afferent limb is imprecise. Based on the paucity of solid evidence in humans, we do not consider a long afferent limb to be an important cause of recurrent postoperative peptic ulcers.

**Antral G-Cell Hyperplasia (Pseudo-Zollinger-Ellison Syndrome).** This syndrome is described in patients with excessive gastrin release and therefore exaggerated acid production. It is believed to result from an excessive number of antral G-cells without an extragastric source of gastrin. The hallmarks of the syndrome are excessive acid and gastrin production in response to meals, a negative secretin stimulation test for gastrinoma, a virulent course of ulcer disease, and resolution of the syndrome with antrectomy. The existence of this entity remains controversial. Despite a number of articles published on the topic, only two case series clearly rule out gastrinoma by provocative testing,<sup>62,63</sup> and only one of these includes postoperative recurrent ulcers.<sup>63</sup> Further complicating the use of this diagnosis is the fact that both series predate the recognition of *H. pylori* as an important etiologic agent in PUD, and hence do not include data on *H. pylori* status. Of note, *H. pylori* infection has been shown to increase the gastrin and acid response to food,<sup>64,65</sup> raising the possibility that G-cell antral hyperplasia may, in fact, represent *H. pylori* infection. Based on the paucity of published evidence, we believe that G-cell antral hyperplasia cannot be regarded as a significant cause of recurrent postoperative ulcers.

## INITIAL DIAGNOSTIC EVALUATION

A detailed history and physical examination will identify symptoms of ulcer disease or evidence of complications, for example, hematemesis and melena, anemia, vomiting, or weight loss. A thorough medical history may also provide insight into the cause of

the ulcer recurrence, for example, the use of ulcerogenic medications or Zollinger-Ellison syndrome. In the absence of symptoms and signs of perforation and peritonitis, the diagnosis of ulcer recurrence is best made by esophagogastroduodenoscopy (EGD). In addition to documenting the presence and location of the ulcer, this study may provide valuable information regarding ulcer etiology and the presence of *H. pylori*. Multiple ulcers and those in atypical locations strongly suggest the presence of a hypersecretory syndrome or the use of NSAIDs. Retained food, a gastric bezoar, or a stenotic anastomosis suggests associated impairment of gastric emptying. Endoscopic biopsy of gastric ulcers is of particular importance in detecting cancer. Last, EGD is invaluable in the evaluation and treatment of patients bleeding from ulcer disease.

Upper gastrointestinal barium contrast studies are of limited value in diagnosing recurrent ulcer disease after acid-reducing operations. Various investigators have documented that this study has a sensitivity and specificity of less than 50% in detecting ulcers in the postoperative setting. The impaired accuracy of this test is due principally to the difficulty in detecting ulcerations in the presence of postoperative deformities of the stomach and duodenum. Contrast radiographs may, however, provide important information in the evaluation of patients with suspected gastric outlet obstruction and in those whose postoperative anatomy is uncertain.

A fasting serum gastrin level should be obtained in all patients with recurrent ulcer disease to identify patients with gastrin-mediated hypersecretory syndromes. With rare exceptions,<sup>66</sup> a normal fasting serum gastrin concentration excludes the possibility of Zollinger-Ellison syndrome, whereas a serum gastrin level greater than 1000 pg/ml, combined with a fasting gastric pH below 2.5,<sup>67</sup> is virtually diagnostic. Of note, achlorhydria alone may be associated with markedly elevated serum gastrin levels, and hence it is important to quantify gastric pH in patients with markedly elevated serum gastrin concentrations. Patients with lesser degrees of hypergastrinemia will require provocative testing with a secretin stimulation test to confirm the diagnosis of gastrinoma. Patients with retained gastric antrum typically have fasting serum gastrin concentrations two to four times the normal range; in these instances, a secretin stimulation test will be negative.

## INITIAL MANAGEMENT

In the usual scenario in which a patient presents with recurrence of upper abdominal pain and endos-

copy demonstrates recurrent ulcer disease, medical therapy consists of a PPI or histamine-2 receptor antagonist (H2-RA) and antibiotics directed at *H. pylori*, if present. The use of a PPI or H2-RA for managing patients with recurrent PUD after acid-reducing operations is based on the following evidence: (1) early prospective randomized clinical trials demonstrating the efficacy of acid suppression with H2-RAs in healing ulcers after acid-reducing operations<sup>68-70</sup> and (2) clinical trials documenting the efficacy of H2-RAs and PPIs in the management of patients with primary ulcer disease<sup>71-75</sup> and ulcers associated with the use of NSAIDs.<sup>38,39,76</sup> These studies are reviewed in Table 5. To our knowledge, no studies have directly examined the use of PPIs in the management of patients with recurrent ulcer disease after acid-reducing operations. The optimal duration of treatment with a PPI or H2-RA is unknown. In one early prospective randomized clinical trial, cessation of cimetidine after 1 year of treatment was associated with a 71% rate of ulcer recurrence.<sup>70</sup> This study supports the use of long-term maintenance PPI or H2-RA therapy in patients with ulcer disease after acid-reducing operations; however, these data were generated before the importance of *H. pylori* and NSAIDs was recognized in the pathogenesis of ulcer disease.

Although no data directly support the eradication of *H. pylori* in patients with postoperative ulcer recurrence, the critical role that this infection plays in primary PUD,<sup>37,43-45</sup> the possibility that *H. pylori* promotes NSAID-induced mucosal injury,<sup>53</sup> and the minimal risks associated with *H. pylori* eradication strongly support the use of antibiotic therapy, for example, the addition of amoxicillin and clarithromycin to the PPI for 14 days in the presence of *H. pylori*. The presence of *H. pylori* may be documented by histologic evaluation of gastric biopsies or, alternatively, by serologic, breath, or fecal tests.

A thorough review of the patient's medication use (both prescription and nonprescription) must be performed to identify ulcerogenic medications. Patients and their families should be carefully counseled regarding the various over-the-counter preparations containing NSAIDs, the important relationship between NSAID use and ulcer disease, and the necessity of discontinuing these medications. Serum salicylate levels may be useful in identifying patients with surreptitious ASA use as a pathogenic factor in ulcer recurrence, but this test is of no value in identifying nonaspirin NSAIDs or in detecting the use of low-dose ASA regimens. Hirschowitz and Lanas<sup>21</sup> report that serum salicylate testing of patients from the Southeastern United States with recurrent ulcers found at least as many patients who were sur-

**Table 5.** Evidence supporting various medical treatments for recurrent ulcer disease after acid-reducing operations

Treatments	Evidence	Reference	Study description	Study design	Level of evidence
Acid suppression with H <sub>2</sub> -RAs or PPIs	Prospective studies demonstrating healing of postop ulcers with H <sub>2</sub> -RAs	Gugler et al. <sup>68</sup> (1979)	Randomized, double-blind multicenter trial in which 15 patients with postop recurrent ulcers were treated with cimetidine (1 g/day for 8 wk) or placebo; ulcers healed in 7 of 8 cimetidine-treated patients and only 1 of 8 placebo-treated patients	Prospective, randomized, double-blind multicenter	Ib
		Stage et al. <sup>69</sup> (1983)	Randomized, double-blind trial in which 23 of 24 patients with postop recurrent ulcers who had their ulcers healed with ranitidine (150 mg bid for 6 wk) were randomized to ranitidine (q hs) or placebo; Ulcers re-occurred in 9 patients within 4 months and recurrences were significantly more frequent in placebo-treated patients than in those receiving ranitidine ( $P = 0.01$ )	Prospective, randomized, double-blind	Ib
		Koo et al. <sup>70</sup> (1982)	Prospective, nonrandomized comparison of 46 patients with postop recurrent ulcers who received cimetidine (1 g/day for 6–12 wk, then 400 mg q hs as maintenance therapy) (N = 23) or underwent repeat operation (N = 23); discontinuation of cimetidine after 1 yr was associated with ulcer recurrence in 71.4% of patients	Prospective, nonrandomized	IIb
	Prospective studies demonstrating healing of primary PUD with H <sub>2</sub> -RAs	Binder et al. <sup>71</sup> (1978)	Multicenter, prospective, randomized, double-blind, placebo-controlled trial comparing cimetidine and placebo in the healing of duodenal ulcers in 308 patients; after 2 wk of therapy, 56% of cimetidine-treated patients and 37% of patients receiving placebo had healing of their ulcers ( $P < 0.05$ )	Prospective, nonrandomized double-blind	Ib

Table 5 continued.

Table 5. Continued

Treatments	Evidence	Reference	Study description	Study design	Level of evidence
		Legerton <sup>72</sup> (1984)	Review of prospective studies demonstrating the efficacy of H <sub>2</sub> -RA in the healing of duodenal and gastric ulcers	Review of prospective clinical trials	IV
		Gitlin et al. <sup>73</sup> (1987)	Multicenter, prospective, randomized, double-blind, placebo-controlled trial comparing famotidine vs. placebo in the healing of duodenal ulcers; 8 wk of treatment with famotidine resulted in the healing of 82% of ulcers vs. 45% for placebo	Prospective, randomized, double-blind trial	Ib
	Prospective studies demonstrating healing of primary PUD and NSAID-induced ulcers with PPIs	Hawkey et al. <sup>38</sup> (1998)	Double-blind comparison of omeprazole (40 mg q d) or misoprostol (200 µg qid) in healing NSAID-induced ulcers in 935 patients; at 8 wk of therapy, the overall healing rates were similar between the omeprazole and misoprostol groups (75% and 71%, respectively); maintenance therapy with omeprazole was associated with fewer ulcer recurrences than misoprostol (39% vs. 52%, respectively; $P = 0.001$ )	Prospective, randomized, double-blind trial	Ib
		Dekkers et al. <sup>74</sup> (1999)	Prospective randomized, double-blind, multicenter trial comparing rabeprazole and omeprazole in 205 patients with duodenal ulcers; the ulcer healing rates after 4 wk of treatment for rabeprazole and omeprazole were 98% and 93%, respectively	European, multicenter, randomized, double-blind trial	Ib
		Poynard et al. <sup>75</sup> (1995)	Meta-analysis of five randomized double-blind clinical trials comparing lansoprazole with ranitidine or famotidine in the treatment of acute duodenal ulcers; The 4 wk healing rate of lansoprazole was 85% compared with 75% healing rate for H <sub>2</sub> -RA ( $P < 0.01$ ; odds ratio = 2.27, 95% confidence interval 1.5–3.2)	Meta-analysis of five randomized double-blinded trials	Ia

Table 5 continued.

Table 5. Continued

Treatments	Evidence	Reference	Study description	Study design	Level of evidence
Eradication of <i>H. pylori</i>	Prospective studies demonstrating healing of primary PUD by eradication of <i>H. pylori</i>	Hentschell et al. <sup>44</sup> (1993)	Prospective, randomized comparison of ranitidine, amoxicillin, and metronidazole vs. ranitidine and placebo in 104 patients with <i>H. pylori</i> infection and duodenal ulcers; after 6 wk of treatment, the ulcers were healed in 92% of patients receiving antibiotics + ranitidine and 75% of patients receiving ranitidine alone ( $P = 0.01$ ); over the next 12 months ulcer recurrence was significantly more frequent in those patients with persistent <i>H. pylori</i> infection when compared with those without <i>H. pylori</i> (85 vs. 2%, respectively; $p < 0.001$ ).	Prospective, randomized, double-blind trial	Ib
		Van der Hulst et al. <sup>37</sup> (1997)	Prospective follow-up of 247 patients with PUD and <i>H. pylori</i> infection; none of the 141 patients in whom <i>H. pylori</i> was eradicated developed recurrent ulcer disease over 2.5 yr follow-up	Prospective, case series	IIb
		Graham et al. <sup>45</sup> (1992)	Prospective, randomized comparison of ranitidine + triple therapy (bismuth subsalicylate, tetracycline, metronidazole) vs. ranitidine alone in 109 <i>H. pylori</i> -infected patients; the probability of ulcer recurrence for patients receiving triple therapy was significantly less than that for patients receiving ranitidine alone (12% vs. 95% for duodenal ulcers; 13% vs. 74% for gastric ulcers); 50% of patients receiving ranitidine alone had ulcer recurrence within 12 weeks of healing, whereas ulcer recurrence in the triple-therapy group could be related to failure to eradicate <i>H. pylori</i> infection or NSAID use	Prospective, randomized trial	Ib

repeatedly using ASA as patients who admitted to ASA use.

NSAID use, including low-dose ASA, should ideally be discontinued during the period of ulcer healing, if feasible. Once ulcer healing has been documented endoscopically, non-NSAID analgesic agents, such as acetaminophen or tramadol, should be substituted for the NSAIDs. If these are ineffective, then nonacetylated NSAIDs, such as salsalate, nabumetone, etodolac, or a cyclooxygenase (COX)-2-specific NSAID, such as celecoxib or rofecoxib, should be considered because they are associated with a lower rate of ulcer disease compared to traditional (non-COX-2 selective) NSAIDs. If a traditional NSAID is required, a rare event nowadays, then prophylactic combination therapy with either misoprostol or a PPI should be administered.<sup>38</sup> Consideration should be given to substituting clopidogrel for low-dose aspirin for cardiovascular prophylaxis. Because of the potential for even low doses of ASA to contribute to peptic ulceration<sup>41,42</sup> and the recognition that prior ulcer disease is an important risk factor for NSAID-induced gastrointestinal complications,<sup>77</sup> patients continued on low-dose ASA and not switched to clopidogrel should receive ulcer prophylaxis with misoprostol or a PPI.

## INDICATIONS FOR OPERATIVE MANAGEMENT AND PREOPERATIVE EVALUATION

### Indications for Operative Management

Historically, the indications for operative management of recurrent PUD are the failure of medical therapy or the occurrence of complications that cannot be managed nonoperatively. Literature from the late 1970s and early 1980s suggested that approximately 20% of patients with recurrent ulcer disease require operative management.<sup>23,68-70</sup> Although more recent figures are lacking, we believe the frequency of operative management of recurrent ulcer disease is much lower today, especially for patients with nonhealing ulcers in the absence of complications. Clearly, the adequacy of prior medical management and the elimination of risk factors for ulcer recurrence (e.g., NSAID use) are important considerations in determining whether a patient is an appropriate candidate for operative therapy—that is, recalcitrant ulcer disease must be refractory to an appropriate course of medical treatment. Based on recent experiences, the predominant indication for remedial surgery is severe ulcer-related complications such as bleeding and gastric outlet obstruction, with medically refractory ulcer disease being less common than in previous decades.<sup>21,26,78</sup>

## Preoperative Considerations

In general, the management of patients with recurrent ulcer disease entails the use of the operative procedure with the lowest risk of recurrence that the patient is medically able to tolerate. Various options are available to allow the surgeon to tailor the remedial procedure to the specific needs of the patient. The preoperative evaluation should provide insight into the etiology of the patient's recurrent ulcer disease, the nature of his or her previous operative procedure, the presence of complications of the ulcer, and an understanding of the patient's overall medical conditions that affect his or her ability to tolerate the surgical procedure.

## Etiology of Recurrent Ulcer Disease

The initial assessment of patients with recurrent ulcer disease may provide information that is useful in determining the cause of the ulcer, such as NSAID use, gastrinoma, or retained antrum, however, it will not document the adequacy of the prior vagotomy. Because most patients with recurrent ulcer disease are managed successfully with medication, including many with an incomplete vagotomy, assessment of the vagotomy by quantitating gastric acid secretion becomes important only when surgical treatment is contemplated. Historically, the most commonly used methods of assessing the completeness of vagotomy are the measurement of basal and stimulated acid secretion with or without sham feeding. The current unavailability of pentagastrin severely limits the capability of measuring stimulated or peak acid output and perhaps the widespread applicability of these tests.

**Basal and Stimulated Gastric Acid Secretion Without Sham Feeding.** Gastric secretory analysis is performed by fluoroscopically positioning a nasogastric (or orogastric) tube so that the tip of the tube is in the gastric antrum or in the distal gastric remnant in the case of an antrectomy. Basal acid secretion (BAO) is determined by measuring the volume and pH of gastric juice for 1 hour, usually in 15-minute aliquots. With the use of a standardized table, pH is converted to millimoles of hydrogen ions per liter of gastric juice and BAO is expressed as millimoles of hydrogen ions per hour. After measurement of the BAO, PAO is determined by measuring gastric acid secretion for 1 hour after the subcutaneous administration of 6 to 10  $\mu\text{g}/\text{kg}$  of pentagastrin. PAO is calculated as the sum of the two greatest consecutive 15-minute acid outputs multiplied by two (to express the results in millimoles per hour). BAO greater than 2 mmol/hr and/or a PAO greater than 12 mmol/hr suggests persistent vagal innervation of the stomach.<sup>27</sup>

**Basal and Stimulated Acid Secretion With Sham Feeding.** Sham feeding stimulates gastric acid secretion solely via vagal pathways, and thus measurement of gastric acid secretion after sham feeding is a sensitive and reliable physiologic test of the completeness of vagotomy.<sup>28,30</sup> This test is performed by measuring BAO for 1 hour, after which a steak meal and 300 ml of water are presented to the patient who then chews but does not swallow the food. This sham feeding is carried out for 30 minutes during which time GAO (sham acid output [SAO]) is measured every 15 minutes for 1 hour (30 minutes during and 30 minutes after sham feeding). PAO is then determined by measuring acid secretion for 1 hour after the subcutaneous injection of 12  $\mu\text{g}/\text{kg}$  pentagastrin, if available. Feldman et al.<sup>79</sup> found that the SAO/PAO ratio of 50 unoperated normal subjects had a normal distribution with a mean of 0.39, a standard deviation of  $\pm 0.11$ , and a range of 0.11 to 0.83. From these measurements it was predicted that 95% of subjects with normal vagal innervation of the stomach would have SAO/PAO ratios greater than 0.10. Thus patients with SAO/PAO ratios less than 0.10 are considered to have complete vagotomies, whereas individuals with ratios greater than 0.10 have incomplete vagotomies. Interpretation of the sham feeding test assumes a normal or near-normal fasting serum gastrin concentration. Patients with Zollinger-Ellison syndrome or retained gastric antrum may have SAO/PAO ratios greater than 0.1, even after complete vagotomy.<sup>23</sup>

### Nature of the Previous Operative Procedure

It is critical that the surgeon understand the exact nature of the previous operative procedure before the remedial operation is performed. This information may be gleaned by carefully reviewing the previous operative note and pathology report. The endoscopic findings and a barium contrast study may also provide useful information regarding the extent of the prior resection and the particular postoperative anatomy.

### Presence of Complications of Ulcer Disease

The presence of complications of the recurrent ulcer disease strongly influences the appropriateness of various remedial operative procedures. For example, a bleeding peptic ulcer that cannot be controlled endoscopically necessitates an abdominal approach for ligation of the bleeding vessel and often a more extensive acid-reducing procedure. Ulcer recurrence causing gastric outlet obstruction necessitates both revision of the anastomosis and a more extensive acid-reducing procedure. In those patients presenting with ulcer

perforation, the degree of contamination and the hemodynamic stability of the patient clearly influence the appropriateness of a particular remedial procedure. For example, hemodynamic instability and/or marked contamination of the upper abdomen favors simple closure of the gastrointestinal perforation without attempt at resection and reanastomosis.

### Presence of Medical Comorbidity

The accurate assessment of the operative risk-benefit ratio is crucial to the successful management of patients with postoperative recurrent PUD. The presence of chronic medical diseases may significantly increase the risk of perioperative morbidity and mortality. This risk, in turn, influences the specific procedure chosen. For example, an elderly frail patient with an incomplete truncal vagotomy and adequate gastric drainage would tolerate a thoracoscopic truncal vagotomy better than a truncal vagotomy and antrectomy. In this setting, the surgeon would do well to accept the slightly higher risk of recurrent ulcer disease associated with repeat vagotomy alone for the less "risky" thoracoscopic procedure.

## OPERATIVE MANAGEMENT

The choice of a particular operation for a patient with recurrent ulcer disease is based on the following tenets: (1) the remedial procedure should be that with the lowest recurrence risk that the patient is medically able to tolerate; (2) the procedure should be tailored to the particular needs of the patient based on the adequacy of the prior vagotomy and drainage procedure, medical comorbidity, presence of complications of the ulcer, and the extent of the prior resection; and (3) non-acid-reducing procedures such as local ulcer excision, revision of drainage procedures alone, and closure of perforations are associated with high failure rates.<sup>23,24,58</sup>

Commonly recommended operative procedures for various failed initial acid-reducing operations are described in Table 6. These operative options are based on the following evidence: (1) ulcer recurrence rates and mortality rates for particular operative procedures in prospective randomized and nonrandomized clinical trials of patients treated for primary PUD (Table 2) and (2) retrospective studies documenting the incidence of ulcer recurrence, early and late complications, and mortality rates associated with various remedial operative procedures (Table 6).

Patients with an incomplete vagotomy and recurrent ulcer disease after truncal vagotomy and pyloroplasty or parietal cell vagotomy may be treated by

**Table 6.** Evidence supporting specific remedial operations for patients with recurrent peptic ulcer disease

Remedial operation	Study description	Level of evidence	Sample size	Operative mortality	Recurrence rate (%)	Visick grade (I or II; excellent or good)	Visick grade (III or IV; fair or poor)
Truncal vagotomy alone							
Schirmer et al. <sup>14</sup> (1982)	Retrospective case series of 166 patients undergoing reoperation between 1951 and 1980 at Duke University Hospital for ulcer recurrence after various acid-reducing operations; average follow-up 12.3 yr	III	59	0 (0.0%)	10 (16.9)	—	—
Heppell et al. <sup>22</sup> (1983)	Retrospective case series of 120 patients undergoing reoperation between 1970 and 1975 at Mayo Clinic for ulcer recurrence after various acid-reducing operations. >5 yr follow-up available for only 27 patients (22.5%)	III	62	2 (3.2%)	6 (10%)	37 (60%)	14 (23%)
Stabile and Passaro <sup>58</sup> (1976)	Detailed literature review from 1950 to 1974 cataloguing the results of more than 3400 surgically treated cases of recurrent ulcers after various operations	IV	888	10 (1.1%)	135 (15.2%)	571 (64.3%)	90 (10.1%)
Ingvar et al. <sup>80</sup> (1986)	Retrospective case series of 40 consecutive patients undergoing reoperation between 1971 and 1980 at University Hospital, Lund, Sweden, for ulcer recurrence after PCV	III	16	0 (0.0%)	1 (6.25%)	14 (87.5%)	2 (12.5%)*
Truncal vagotomy + antrectomy							
Schirmer et al. <sup>14</sup> (1982)	Retrospective case series of 166 patients undergoing reoperation between 1951 and 1980 at Duke University Hospital for ulcer recurrence after various acid-reducing operations; average follow-up was 12.3 yr	III	31	1 (3.2%)	6 (19.4%)	—	—

Table 6 continued.

Table 6. Continued

Remedial operation	Study description	Level of evidence	Sample size	Operative mortality	Recurrence rate (%)	Visick grade (I or II; excellent or good)	Visick grade (III or IV; fair or poor)
Heppell et al. <sup>22</sup> (1983)	Retrospective case series of 120 patients undergoing reoperation between 1970 and 1975 at Mayo Clinic for ulcer recurrence after various acid-reducing operations; >5 yr follow-up available for only 27 patients (22.5%)	III	35	0 (0.0%)	1 (2.9%)	20 (57%)	7 (20%)
Stabile and Passaro <sup>58</sup> (1976)	Detailed literature review from 1950 to 1974 cataloguing the results in more than 3400 surgically treated cases of recurrent ulcer following various operations.	IV	76	6 (7.9%)	6 (7.9%)	48 (63.2%)	6 (7.9%)
Resection or re-resection only							
Schirmer et al. <sup>14</sup> (1982)	Retrospective case series of 166 patients undergoing reoperation between 1951 and 1980 at Duke University Hospital for ulcer recurrence after various acid-reducing operations; average follow-up was 12.3 yrs	III	25	0 (0.0%)	3 (12.0%)	—	—
Heppell et al. <sup>22</sup> (1983)	Retrospective case series of 120 patients undergoing reoperation between 1970 and 1975 at Mayo Clinic for ulcer recurrence after various acid-reducing operations; >5 yr follow-up available for only 27 patients (22.5%)	III	23	2 (8.7%)	2 (8.7%)	8 (35%)	9 (39%)
Stabile and Passaro <sup>58</sup> (1976)	Detailed literature review from 1950 to 1974 cataloguing the results in more than 3400 surgically treated cases of recurrent ulcer following various operations.	IV	1344	53 (3.9%)	191 (14.2%)	894 (66.5%)	99 (7.4%)

Table 6 continued.

Table 6. *Continued*

Remedial operation	Study description	Level of evidence	Sample size	Operative mortality	Recurrence rate (%)	Visick grade (I or II; excellent or good)	Visick grade (III or IV; fair or poor)
Browder et al. <sup>78</sup> (1997)	Retrospective case series of 20 patients with recurrent ulcers after gastric resection more than 10 years previously (average time to recurrence 21 yr)	III	20	0 (0.0%)	0 (0.0%)	16 (80%)	4 (20%)
Ingvar et al. <sup>80</sup> (1986)	Retrospective case series of 40 consecutive patients undergoing reoperation between 1971 and 1980 at University Hospital, Lund, Sweden for ulcer recurrence after PCV	III	17	0	1 (6%)	14 (82%)	3 (18%) <sup>†</sup>
Hoffman et al. <sup>84</sup> (1986)	Retrospective case series of 60 patients with recurrent ulcers after vagotomy (PCV = 23; TV or SV & D = 37) treated with partial gastrectomy; average follow-up was 8 yr	III	51	1 (1.67%)	4 (7.8%)	30 (59%)	21 (41%)

\*Five patients required remedial operations to treat ulcer recurrence (n = 1) or severe postgastrectomy symptoms/complications (n = 4).

<sup>†</sup>Four patients required remedial operations to treat gastric outlet obstruction.

antrectomy with or without truncal vagotomy. These procedures have a relatively low incidence of ulcer recurrence and a modest risk of morbidity and mortality.<sup>14,22,23,58,80,81</sup> For patients with a failed truncal vagotomy and pyloroplasty with adequate gastric drainage and an incomplete vagotomy, transthoracic or thoracoscopic vagotomy represent very good surgical options, particularly in relatively high-risk patients.<sup>23,82,83</sup> Thoracoscopy is generally well tolerated and avoids the potential morbidity of repeat dissection within the esophageal hiatus and upper abdomen necessitated by an abdominal approach. Operative revision after parietal cell vagotomy is thought to be associated with lower morbidity risk than other initial acid-reducing procedures.<sup>11</sup>

Historically, the operative approach in patients with ulcer recurrence after a truncal vagotomy and antrectomy or a distal gastrectomy is partial gastric resection. Recurrent PUD after truncal vagotomy and antrectomy or partial gastrectomy strongly suggests the presence of confounding factors such as NSAID use or a hypersecretory state. Recent studies have documented the importance of ASA abuse in the etiology of such

virulent ulcer disease and very high rates of ulcer recurrence after even very aggressive operative intervention.<sup>21,26</sup> In the past, this situation has been managed operatively by further gastric resection that may necessitate subtotal or even total gastrectomy. Unfortunately, severe postgastrectomy symptoms after these extensive procedures occur in as many as 20% to 40% patients.<sup>14,22,58,78,80,84</sup> Patients with recurrent ulcer disease and an incomplete vagotomy may benefit from a thoracoscopic truncal vagotomy so long as NSAID use has been eliminated and there is no evidence of gastric stasis or gastric outlet obstruction. Again, this thoracic approach avoids a difficult dissection in the upper abdomen and eliminates a likely cause of ulcer recurrence. In those instances where ulcer recurrence is accompanied by gastric outlet obstruction, vagotomy and revision of the anastomosis (with further gastric resection) are necessary to relieve the mechanical obstruction and further reduce gastric acid secretion.

Ulcer recurrence after adequate resection for gastric ulcer disease strongly suggests the use of NSAIDs or the presence of a hypersecretory state such as that associated with a gastrinoma or retained excluded

gastric antrum. Also, patients who have undergone resection for gastric ulcers appear to have a threefold increase in the risk of gastric adenocarcinoma when followed for more than 25 years after a Billroth II reconstruction.<sup>85</sup> Clearly, an aggressive diagnostic approach, including endoscopic biopsy, is necessary in patients with gastric ulcers. In general, the operative approach in patients with recurrent benign gastric ulcers has been further gastric resection. However, the postgastroectomy complications associated with extended gastric resection and the relative high frequency of NSAID use in these patients (with its attendant negative effect on surgical outcomes) should relegate extended gastric resection for recurrent gastric ulcer disease to a very small cohort of patients.

## RESULTS OF REMEDIAL OPERATIONS

Numerous retrospective studies have evaluated the results of remedial ulcer operations performed between 1950 and 1985.\* The results of the largest studies are reviewed in Table 6. Unfortunately, there are very few recent data on the results of operations for recurrent PUD and no prospective data.

### Ulcer Recurrence

Overall the frequency of ulcer recurrence varies from 8% to 22%. The likelihood of ulcer recurrence is dependent on the remedial procedure performed with the highest rates associated with repeat vagotomy alone and lower rates associated with repeat vagotomy and antrectomy or distal gastrectomy. Revision of a gastroenterostomy alone or any other non-acid-reducing operation is associated with a high rate of ulcer recurrence.<sup>23,58</sup> Patients who continue to take ASA (and probably other NSAIDs) after the operative management of their ulcer disease appear to be at particularly high risk for recurrence (80% to 90%) regardless of the operative procedure performed. The virulence of the ulcer disease is suggested by the high rate of gastric outlet obstruction, perforation, and death in these patients.<sup>21,26</sup>

### Operative Mortality

Early studies reported that the overall mortality rate of operations for recurrent ulcer disease was 2% to 4%. In the collected review by Stabile and Passaro,<sup>58</sup> the operative mortality rate for truncal vagot-

omy and antrectomy, partial gastric resection, and vagotomy and drainage was between 2.2% and 3.7% depending on the procedure.<sup>58</sup> Similar results are reported in more recent smaller studies.<sup>19,78</sup> Browder et al.<sup>78</sup> had no deaths among 20 patients with recurrent ulcers who underwent gastric resection with or without vagotomy. The presence of a complication of ulcer disease mandating an emergency operation significantly increases the risk of operative mortality and likely has a greater effect on mortality than the magnitude of the operative procedure.<sup>14,22</sup> For example, in a study by Heppell et al.,<sup>22</sup> among 120 patients there was one death after 107 elective procedures and three deaths after 13 emergency operations. In contrast, a more recent study by Kinney et al.<sup>19</sup> reported no deaths among 20 patients who were undergoing either elective or emergency treatment of recurrent ulcer disease.

### Quality of Life

The chronic postoperative complications of both primary and remedial acid-reducing operations include diarrhea, dumping, chronic abdominal pain syndromes, impaired gastric emptying, osteoporosis, and anemia. Most investigators report that 60% to 80% of patients who undergo remedial operations for recurrent PUD will have either no symptoms or only occasional mild symptoms (Visick grades I and II), whereas 20% to 40% will have severe or incapacitating symptoms including ulcer recurrence (Visick grades III and IV). Excluding ulcer recurrence, approximately 10% to 20% of patients undergoing remedial operative procedures will have chronic symptoms that have a significant impact on the patients' life (Visick grades III and IV—without ulcer recurrence).\*

## SUMMARY

Patients with symptoms suggestive of recurrent PUD after acid-reducing operations should undergo a careful medical history and physical examination with particular attention to identifying evidence of complications of ulcer disease. Given the frequent use of NSAIDs and the importance of these agents in the pathogenesis of recurrent PUD, patients must be carefully questioned regarding their use and treatment with less ulcerogenic analgesics and anti-inflammatory agents instituted. EGD is performed to docu-

\*References 14,15,19-22,58,78,80-84.

\*References 14,15,19-22,58,78,80-84.

ment the presence of an ulcer and determine the presence or absence of *H. pylori*. Serum is obtained for a fasting gastrin determination to identify unusual but treatable causes of recurrent ulceration. In the absence of achlorhydria, fasting serum gastrin concentrations greater than 1000 pg/ml are virtually diagnostic of a hypersecretory syndrome. For those patients with recurrent PUD, treatment is initiated with a PPI or H<sub>2</sub>-RA and, if *H. pylori* infection is documented, antibiotic therapy is used. Repeat EGD is usually performed 6 to 8 weeks later to document ulcer healing. If the ulcer is healed, the patient is treated with long-term maintenance acid suppression with a PPI or H<sub>2</sub>-RA. Operative management is considered for those patients with nonhealing symptomatic ulcers or those who develop a complication of their ulcer disease that cannot be managed nonoperatively. The most appropriate surgical procedure depends on the exact nature of the previous operation, the adequacy of the previous vagotomy, the presence of gastric stasis or outlet obstruction, and the presence of significant medical comorbidity. In general, the preferred operative approach will be that with the lowest rate of ulcer recurrence which the patient is able to tolerate. In most good-risk patients with an incomplete vagotomy, this will be a repeat vagotomy and antrectomy. In those patients with significant medical illnesses and ulcer disease related to an incomplete vagotomy, a thoracoscopic truncal vagotomy may be preferable, provided that the patient has had a previous and still functional emptying procedure such as pyloroplasty or gastrojejunostomy. Patients who develop ulcer recurrence after more extensive procedures, such as truncal vagotomy and antrectomy or truncal vagotomy and partial gastric resection, must be strongly suspected of using either NSAIDs or ASA or having a hypersecretory state such as a gastrinoma or a retained gastric antrum.

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