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COMPLICATIONS OF ENDOSCOPIC BILIARY SPHINCTEROTOMY

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ABSTRACT

Background Endoscopic sphincterotomy is commonly used to remove bile-duct stones and to treat other problems. We prospectively investigated risk factors for complications of this procedure and their outcomes.

Methods We studied complications that occurred within 30 days of endoscopic biliary sphincterotomy in consecutive patients treated at 17 institutions in the United States and Canada from 1992 through 1994.

Results Of 2347 patients, 229 (9.8 percent) had a complication, including pancreatitis in 127 (5.4 percent) and hemorrhage in 48 (2.0 percent). There were 55 deaths from all causes within 30 days; death was directly or indirectly related to the procedure in 10 cases. Of five significant risk factors for complications identified in a multivariate analysis, two were characteristics of the patients (suspected dysfunction of the sphincter of Oddi as an indication for the procedure and the presence of cirrhosis) and three were related to the endoscopic technique (difficulty in cannulating the bile duct, achievement of access to the bile duct by "precut" sphincterotomy, and use of a combined percutaneous-endoscopic procedure). The overall risk of complications was not related to the patient's age, the number of coexisting illnesses, or the diameter of the bile duct. The rate of complications was highest when the indication for the procedure was suspected dysfunction of the sphincter of Oddi (21.7 percent) and lowest when the indication was removal of bile-duct stones within 30 days of laparoscopic cholecystectomy (4.9 percent). As compared with those who performed fewer procedures, endoscopists who performed more than one sphincterotomy per week had lower rates of complications (8.4 percent vs. 11.1 percent, $P=0.03$).

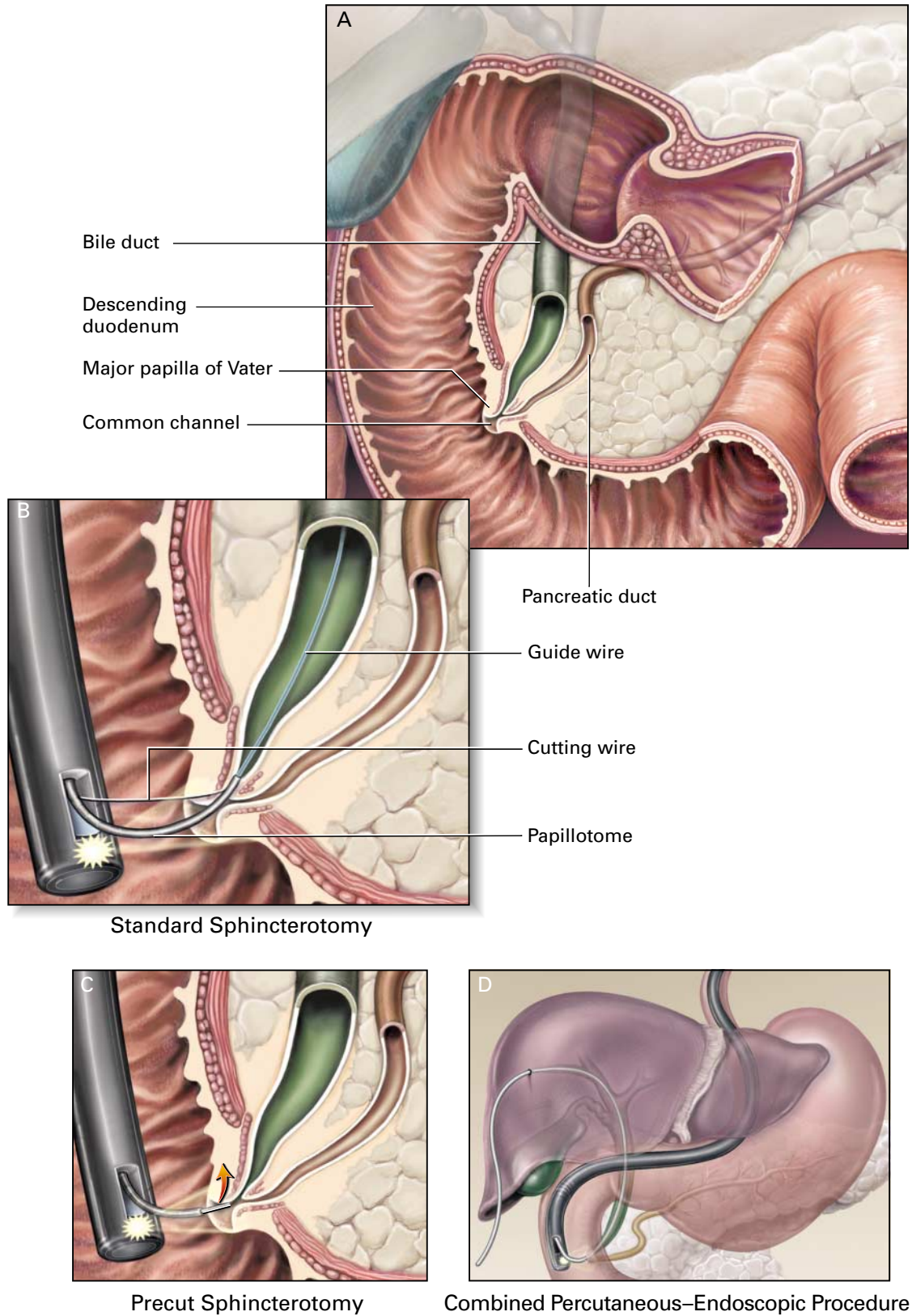
Conclusions The rate of complications after endoscopic biliary sphincterotomy can vary widely in different circumstances and is primarily related to the indication for the procedure and to endoscopic technique, rather than to the age or general medical condition of the patient. (N Engl J Med 1996;335:909-18.)

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SINCE its introduction into endoscopic retrograde cholangiopancreatography (ERCP) in 1974,^{1,2} endoscopic biliary sphincterotomy has become a common procedure; approximately 150,000 such procedures are performed annually in the United States. Sphincterotomy is most commonly performed to remove bile-duct stones and is often substituted for surgical exploration of the common bile duct in patients undergoing laparoscopic cholecystectomy.³⁻⁶ Sphincterotomy is also performed to facilitate the placement of stents through malignant and benign biliary strictures and for other biliary and pancreatic problems, including dysfunction of the sphincter of Oddi.⁷⁻¹³ This controversial syndrome of unknown cause involves functional or structural abnormalities of the sphincter of Oddi. It is most often suspected as a cause of recurrent abdominal pain after cholecystectomy in women, whether or not there is objective evidence of biliary or pancreatic disease. Because the response to

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Standard Sphincterotomy

Precut Sphincterotomy

Combined Percutaneous-Endoscopic Procedure

Figure 1. Endoscopic Biliary Sphincterotomy, or "Papillotomy," as Performed under Endoscopic and Fluoroscopic Guidance.

Panel A shows the major anatomical structures. Standard sphincterotomy (Panel B) requires successful retrograde cannulation of the bile duct, confirmed by injection of radiocontrast material; once obtained, access is often secured by passing a guide wire into the duct. The biliary sphincter is then incised by means of electrocautery through a traction-type papillotome, with the cutting wire bowed against the roof of the papilla.

If the bile duct cannot be cannulated and access is necessary, two alternative, nonsurgical methods are available: "precut" sphincterotomy or a combined percutaneous–endoscopic procedure.

Precut sphincterotomy involves the endoscopic dissection of the papilla with a variety of techniques to gain access to the bile duct; if access is achieved, sphincterotomy is usually completed with a standard papillotome.^{14–17} In the needle–knife pre-cut method (Panel C), a fine cutting wire extending several millimeters from the catheter tip (shown in the common channel) is used to unroof the papilla in incremental layers until the bile duct is exposed; a small-diameter plastic stent (not shown) is sometimes placed into the pancreatic duct before precutting to protect pancreatic drainage.¹⁶ The arrow shows the usual direction of the incision. A less common method of precutting, not shown, involves the use of a modified traction-type papillotome with the cutting wire extending to the tip; the papillotome is wedged into the papillary orifice, and incremental incisions are made in the direction of the bile duct.

The combined percutaneous–endoscopic approach (Panel D) involves the puncture of the liver by a radiologist, with transhepatic antegrade passage of a guide wire through the bile duct into the duodenum so that the endoscopist can complete the sphincterotomy in the standard fashion.¹⁸

sphincter ablation is variable in these patients, manometry of the sphincter of Oddi, in which a perfusion catheter is used to measure pressures in the biliary and pancreatic sphincters, is sometimes performed to help determine whether sphincterotomy is indicated.^{7,10,11}

Sphincterotomy, or papillotomy, is a technically complex endoscopic procedure performed under visual and fluoroscopic guidance (Fig. 1). The usual approach involves deep insertion of a cannula into the bile duct through the ampulla of Vater, followed by electrocautery to incise the sphincter of Oddi. Bile-duct cannulation can sometimes be difficult and can lead to inadvertent but repeated cannulation or injection of the pancreas. If the bile duct cannot be cannulated by the usual approach and access is felt to be necessary, the papilla can be dissected to expose the bile duct with use of a variety of techniques known collectively as "precut" sphincterotomy.^{14–17} Alternatively, a radiologist can puncture the liver and pass a guide wire antegradely through the bile duct into the duodenum so that the endoscopist may complete the sphincterotomy; this is referred to as a combined percutaneous–endoscopic procedure.¹⁸

Sphincterotomy and associated pancreatic and biliary instrumentation can cause pancreatitis, hemor-

rhage, perforation, and other complications. Many factors, such as a small diameter of the common bile duct, have been suggested as increasing the risk of these outcomes, primarily on the basis of expert opinion, retrospective data, and a few prospective studies of highly selected groups of patients.^{19–26} It is unclear whether these risk factors apply to community practice outside referral centers or are independently significant.²⁷ Precise identification of conditions predisposing patients to complications is important in order to improve the safety of sphincterotomy and to allow optimal decision making with respect to alternative therapies. We prospectively investigated risk factors for complications of biliary sphincterotomy and the outcomes of these complications in a variety of settings.

METHODS

We conducted a prospective cohort study of sphincterotomy at 16 institutions in the United States and 1 in Canada, of which 6 were private and 11 were affiliated with universities. The protocol was approved by an institutional review board at each of the participating centers.

Patients

During periods lasting 6 to 24 months in 1992 through 1994, participating endoscopists enrolled consecutive patients who were undergoing biliary sphincterotomy. All sphincterotomies performed in an attempt to establish access to the bile duct were included. Not included were patients in whom attempts at biliary cannulation without sphincterotomy failed and those who underwent pancreatic sphincterotomy.

Collection and Verification of Data

Data were collected at the time of the procedure, before discharge, and approximately 30 days after sphincterotomy; patients were interviewed and charts were reviewed by means of a standardized questionnaire; data were entered into a 150-variable data base. The accuracy of data was verified by various methods, including cross-checks for internal consistency among complications, length of the hospital stay, and information on the patient questionnaire.

Definitions

Complications of sphincterotomy were defined as any adverse events related to the ERCP procedure during which sphincterotomy was performed and that required more than one night of hospitalization. Events not directly related to the sphincterotomy incision, such as sequelae of stent insertion, were included as miscellaneous complications.

Definitions of individual complications were similar to those of Cotton et al.¹⁹ Unless otherwise specified, the severity of complications was graded according to the length of hospitalization and the degree of intervention required. Mild complications required 2 to 3 days of hospitalization; moderate complications required 4 to 10 days of hospitalization; and severe complications required more than 10 days of hospitalization, necessitated surgical or invasive radiologic intervention, or contributed to death.

Procedure-induced pancreatitis was defined as new or worsened abdominal pain and a serum concentration of pancreatic enzymes (amylase or lipase) that was two or more times the upper limit of normal that required more than one night of hospitalization. Continuation of preexisting acute pancreatitis was not included as a complication. Hemorrhage was considered clinically significant only if there was clinical (not just endoscopic) evidence

of bleeding, such as melena or hematemesis, with an associated decrease of at least 2 g per deciliter in the hemoglobin concentration, or the need for a blood transfusion. Hemorrhage following the procedure was presumed to result from sphincterotomy unless another cause was documented. Cholangitis was defined as an elevation in the temperature to more than 38°C that was thought to have a biliary cause, without concomitant evidence of acute cholecystitis. Acute cholecystitis was considered a complication if there were no suggestive clinical or radiographic signs before the procedure and if emergency cholecystectomy was subsequently required. Perforation included retroperitoneal or bowel-wall perforation documented by any radiographic technique.

The decision to perform sphincterotomy was made by the participating endoscopists on the basis of clinical, endoscopic, and radiologic findings. Malignant biliary stricture did not require histologic confirmation. Suspected dysfunction of the sphincter of Oddi was defined as a clinical or manometric diagnosis of a functional or structural abnormality of the sphincter of Oddi suspected to be the cause of recurrent abdominal pain.

Statistical Analysis

Of 2420 patients in the cohort, 73 (3.0 percent) were lost to follow-up and were therefore excluded from our analysis; the study group thus consisted of 2347 patients. Mean values are presented with their standard deviations. The primary outcomes analyzed were complications within 30 days of the procedure. For each outcome, potentially relevant risk factors were assessed by univariate analysis with the chi-square statistic in the case of categorical variables and simple logistic regression in the case of continuous variables. Significance was indicated by a two-tailed P value of less than 0.05. Significant predictors in the univariate analysis were then included in a forward, stepwise multiple logistic-regression model to identify the most important risk factors for pancreatitis, hemorrhage, and complications overall; patients for whom relevant data were missing were excluded from the multivariate analyses.²⁸

RESULTS

The mean number of sphincterotomy procedures performed at each center ranged from 0.2 to 16.0 per endoscopist per week. The experience of endoscopists with ERCP ranged from approximately 100 to 10,000 previous cases. Indications for sphincterotomy were a stone in the common bile duct in the case of 1600 patients (68.2 percent), including 263 (11.2 percent) with pancreatitis due to gallstones; placement of a biliary stent for malignant obstruction in 310 patients (13.2 percent); treatment of suspected dysfunction of the sphincter of Oddi in 272 (11.6 percent); placement of a stent or dilation of benign strictures in 98 (4.2 percent); and miscellaneous other conditions in 184 (7.8 percent). More than one indication for sphincterotomy was recorded for 117 patients (5.0 percent).

Of the 2347 patients who underwent biliary sphincterotomy, complications occurred in 229 (9.8 percent) (Table 1). Death from all causes within 30 days occurred in 55 patients (2.3 percent), and death was thought to be directly or indirectly related to ERCP in 10 cases (0.4 percent). Of 10 procedure-related deaths, 5 occurred in patients who were at least 70 years of age, 4 in patients under 70 who had serious coexisting medical conditions, and 1 in a patient under 70 with no serious coexisting conditions.

TABLE 1. COMPLICATIONS OF ENDOSCOPIC BILIARY SPHINCTEROTOMY IN 2347 PATIENTS.

TYPE OF COMPLICATION	PATIENTS WITH COMPLICATIONS	PATIENTS WITH SEVERE COMPLICATIONS	PATIENTS WITH FATAL COMPLICATIONS
		number (percent)	
Pancreatitis	127 (5.4)	9 (0.4)	1 (<0.1)
Hemorrhage	48 (2.0)	12 (0.5)	2 (0.1)
Perforation	8 (0.3)	5 (0.2)	1 (<0.1)
Cholangitis	24 (1.0)	2 (0.1)	1 (<0.1)
Cholecystitis	11 (0.5)	3 (0.1)	1 (<0.1)
Miscellaneous*	25 (1.1)	8 (0.3)	5 (0.2)
Any†	229 (9.8)	38 (1.6)	10 (0.4)

*Miscellaneous complications included cardiopulmonary complications (in 6 patients); complications of combined percutaneous access (in 3 patients: bile leak in 1 and intrahepatic bleeding in 2); ductal perforations by guide wires (in 3); stent malfunctions (in 3); ileus (in 3); papillary obstruction (in 2); diarrhea induced by antibiotics (in 2); indeterminate abdominal fluid collections (in 2); and infection of a pancreatic pseudocyst (in 1). The deaths in this category were caused by cardiopulmonary events (arrhythmia in 1 patient, aspiration pneumonia in 1, and acute chest syndrome in sickle cell disease in 1) or were stent-related (in 2).

†Some patients had more than one complication.

Pancreatitis

Procedure-induced pancreatitis occurred in 127 patients (5.4 percent); it was mild in 53 (2.3 percent), moderate in 65 (2.8 percent), and severe in 9 (0.4 percent). Of the nine severe cases of pancreatitis (defined as requiring more than 10 days of hospitalization or a drainage procedure), all except one involved suspected sphincter dysfunction (seven cases), the use of precutting techniques (four cases), or both. One patient required percutaneous drainage of a pseudocyst, three required surgical drainage or débridement, and one patient with concomitant retroperitoneal perforation died.

The results of our analysis of risk factors for pancreatitis are shown in Table 2. Of 16 variables evaluated, 13 were significant according to the univariate analysis; of 5 that remained significant in the multivariate analysis, 2 were characteristics of the patients (suspected dysfunction of the sphincter of Oddi and younger age), and 3 were related to difficulty in obtaining biliary access (difficult cannulation, a higher number of injections of contrast medium into the pancreas, and use of precutting techniques). Pancreatitis occurred in 19.1 percent of patients with suspected dysfunction of the sphincter of Oddi, the most powerful risk factor in the multivariate analysis, as compared with 3.6 percent of patients with other indications for sphincterotomy ($P<0.001$).

Sex was a significant factor in the univariate analysis, but not in the multivariate analysis; 85 percent of patients with dysfunction of the sphincter of Oddi

TABLE 2. RISK FACTORS FOR PANCREATITIS AFTER SPHINCTEROTOMY IN THE UNIVARIATE AND MULTIVARIATE ANALYSES.*

RISK FACTOR	PATIENTS WITH PANCREATITIS (N=127)	ALL PATIENTS (N=2347)	UNIVARIATE P VALUE	ADJUSTED ODDS RATIO (95% CI)†
Significant in the multivariate analysis				
Suspected dysfunction of sphincter of Oddi — no. (%)	52 (41)	272 (12)	<0.001	5.01 (2.73–9.22)
Younger age — yr‡	51.7±17.8	60.4±19.1	<0.001	2.14 (1.41–3.25)
Pre-cut sphincterotomy — no. (%)	17 (13)	111 (5)	<0.001	4.34 (1.73–10.88)
Difficulty of cannulation§	1.9±0.8	1.4±0.7	<0.001	2.40 (1.07–5.36)
No. of pancreatic contrast injections¶	3.5±3.9	1.8±2.9	<0.001	1.35 (1.04–1.75)
Significant in the univariate analysis only				
Acinarization of pancreas — no. (%)	10 (8)	34 (1)	<0.001	
Sphincter of Oddi manometry — no. (%)	29 (23)	171 (7)	<0.001	
History of ERCP-induced pancreatitis — no. (%)	14 (11)	77 (3)	<0.001	
Female sex — no. (%)	97 (76)	1441 (61)	<0.001	
History of pancreatitis — no. (%)	37 (29)	422 (18)	<0.001	
Guide wire used for cannulation — no. (%)	19 (27)	211 (15)	0.004	
Distal bile-duct diameter — mm	8.4±4.0	9.3±4.4	0.02	
History of allergy to contrast material — no. (%)	7 (6)	62 (3)	0.04	
Not significant				
Use of multiple cannulation devices — no. (%)	21 (30)	372 (27)	0.57	
Mean case volume of endoscopist ≤1/wk — no. (%)	63 (50)	1189 (51)	0.81	
Direction of incision 2 to 3 o'clock — no. (%)**	3 (2)	56 (2)	0.99	

*Only risk factors with P values below 0.05 in the univariate analysis were included in the multivariate analysis. Numbers and percentages of patients and means are based on available data. Data were missing for more than 10 patients for the following variables: difficulty and method of cannulation (data not collected in the initial 952 cases), bile-duct diameter (missing in 73 cases), and number of pancreatic contrast injections (missing in 15 cases). Plus-minus values are means ±SD. ERCP denotes endoscopic retrograde cholangiopancreatography.

†Odds ratios have been adjusted for the effect of the other variables in the model. CI denotes confidence interval.

‡The odds ratio is for a 30-year-old as compared with a 70-year-old.

§The difficulty of cannulation was graded on a 3-point scale, as follows: 1 = easy (≤5 attempts), 2 = moderately difficult (6–15 attempts), and 3 = difficult (>15 attempts). The odds ratio is for difficult as compared with easy cannulation.

¶The odds ratio is for four injections of pancreatic contrast material as compared with none.

||Acinarization denotes the appearance of acinar opacification on radiography of the pancreas.

**Endoscopic visual orientation of the papillotome cutting wire was to the 2- to 3-o'clock position.

were female. Similarly, having undergone sphincter of Oddi manometry during the same procedure was not an independent risk factor in the multivariate analysis; in patients with suspected sphincter disease, the 134 patients who underwent manometry before sphincterotomy (biliary in 94 and pancreatic in 82, the latter performed with an aspirating catheter²⁹) and the 138 who did not undergo manometry had similar rates of pancreatitis (18 percent and 20 percent, respectively). Acinarization (the appearance of pancreatic acinar opacification on radiography, resulting from high-pressure injection of contrast medium) was not significant (P=0.06) in the multivariate analysis, probably because of the low prevalence of this factor and its association with other indicators of difficult cannulation. Pancreatitis was related to the diameter of the bile duct in the univariate analysis, but only in the subgroup of patients with suspected sphincter dysfunction; pancreatitis occurred in 12 percent of patients in whom

the diameter of the duct was large (>10 mm), 18 percent of those in whom it was normal (6–10 mm), and 31 percent of those in whom it was small (≤5 mm).

Hemorrhage

Clinically significant hemorrhage occurred in 48 patients (2.0 percent) and was mild (i.e., there was no need for transfusion) in 14 (0.6 percent), moderate (up to 4 units of blood were needed) in 22 (0.9 percent), and severe (i.e., it necessitated the transfusion of 5 or more units of blood, surgery, or angiography) in 12 (0.5 percent). Most bleeding (85 percent of the cases) and all episodes of severe bleeding occurred after sphincterotomy performed to remove stones. Clinical recognition of hemorrhage was delayed from 1 to 10 days after sphincterotomy in 52 percent of the patients in whom it was diagnosed. Twenty-one patients underwent one or more subsequent endoscopic procedures in an attempt to con-

trol bleeding, and surgery was required in two. Death due to delayed bleeding occurred in two patients with Child–Pugh class C cirrhosis³⁰ despite aggressive endoscopic and angiographic intervention.

The results of our analysis of risk factors for hemorrhage are shown in Table 3. Of five risk factors that were significant in the multivariate analysis, three were characteristics of patients (the presence of coagulopathy or active cholangitis before the procedure and anticoagulant therapy within three days after the procedure), and one was probably related to technique (the endoscopist's case volume was ≤ 1 per week). The fifth risk factor was the occurrence of any observed bleeding during the procedure, a common event during sphincterotomy. Cirrhosis, which is often accompanied by coagulopathy, was not independently significant in the multivariate analysis ($P=0.06$).

Other Complications

Cholangitis occurred after sphincterotomy in 24 patients (1.0 percent). Significant risk factors in the univariate analysis were combined percutaneous–endoscopic procedures ($P<0.001$), stenting of ma-

lignant strictures ($P<0.001$), and failed biliary access or drainage ($P<0.001$). Of eight patients with retroduodenal or bowel-wall perforations, three required surgery. Newly diagnosed cholecystitis requiring emergency cholecystectomy occurred in 11 patients (0.5 percent), up to 16 days after sphincterotomy. Cholecystitis was considered severe in two patients who underwent sphincterotomy for indications other than stones and in one who died after surgery. Other than the presence of stones in the gallbladder in 10 of 11 patients, no predictors of cholecystitis were identified. Miscellaneous other complications are listed in Table 1.

Complications of Precutting and Combined Percutaneous–Endoscopic Procedures

Precutting techniques were used to attempt bile-duct access in 111 sphincterotomy procedures (4.7 percent), but these techniques were not used at three centers. Techniques included needle–knife precut (Fig. 1), either with prophylactic placement of a pancreatic stent (15 cases) or without such stenting (77 cases), and use of a specialized traction papillotomy with the cutting wire extending to the tip (19

TABLE 3. RISK FACTORS FOR HEMORRHAGE AFTER SPHINCTEROTOMY IN THE UNIVARIATE AND MULTIVARIATE ANALYSES.*

RISK FACTOR	PATIENTS WITH HEMORRHAGE (N=48)	ALL PATIENTS (N=2347)	UNIVARIATE P VALUE	ADJUSTED ODDS RATIO (95% CI)†
Significant in the multivariate analysis				
Coagulopathy before procedure — no. (%)‡	10 (21)	120 (5)	<0.001	3.32 (1.54–7.18)
Anticoagulation within 3 days after procedure — no. (%)§	4 (8)	37 (2)	<0.001	5.11 (1.57–16.68)
Cholangitis before procedure — no. (%)	17 (35)	339 (14)	<0.001	2.59 (1.38–4.86)
Mean case volume of endoscopist ≤ 1 /wk — no. (%)	35 (73)	1189 (51)	0.002	2.17 (1.12–4.17)
Bleeding during procedure — no. (%)¶	23 (48)	678 (29)	0.004	1.74 (1.15–2.65)
Significant in the univariate analysis only				
Cirrhosis — no. (%)	5 (10)	73 (3)	0.003	
Stone as indication for procedure — no. (%)	41 (85)	1600 (68)	0.01	
Periapillary diverticulum — no. (%)	14 (29)	382 (16)	0.02	
Distal bile-duct diameter — mm	10.7 \pm 5.5	9.3 \pm 4.4	0.03	
Not significant				
Extension of previous sphincterotomy — no. (%)	3 (6)	101 (4)	0.50	
Ampullary tumor — no. (%)	1 (2)	36 (2)	0.75	
Length of incision — mm	10.0 \pm 3.0	9.9 \pm 3.7	0.82	
Aspirin or NSAID use within 3 days — no. (%)	6 (12)	292 (12)	0.99	

*Only risk factors with P values below 0.05 in the univariate analysis were included in the multivariate analysis. Numbers and percentages of patients and means are based on available data. Data were missing for more than 10 patients for the following variables: bile-duct diameter (missing in 73 cases), length of incision (missing in 36 cases), and bleeding at the time of the procedure (missing in 32 cases). Plus–minus values are means \pm SD.

†Odds ratios have been adjusted for the effect of the other variables in the model. CI denotes confidence interval.

‡Coagulopathy was defined as a partial-thromboplastin or prothrombin time more than two seconds above the normal value, a platelet count of $<80,000$ per cubic millimeter, or ongoing hemodialysis.

§Anticoagulation consisted of oral warfarin or intravenous heparin therapy.

¶This category includes patients with any bleeding observed endoscopically during sphincterotomy, ranging from self-limited oozing to severe bleeding requiring immediate endoscopic hemostasis.

||This category includes patients who received aspirin or a nonsteroidal antiinflammatory drug (NSAID) within three days before or after sphincterotomy.

cases).¹⁴⁻¹⁶ Precut sphincterotomy followed prolonged attempts at cannulation (more than 15) in 71 of the 111 patients (64.0 percent) and resulted in successful bile-duct access during the same procedure in 73 patients (65.8 percent overall; success rate, 90.0 percent for endoscopists who averaged more than one sphincterotomy per week, as compared with 52.1 percent for endoscopists with lower case volumes; $P < 0.001$).

Complications occurred after 24.3 percent of precut sphincterotomies; 3.6 percent of patients had severe pancreatitis. When precutting techniques were used for suspected dysfunction of the sphincter of Oddi (in 17 patients) pancreatitis was significantly more common than when the procedure was performed for other indications (94 patients; rate of pancreatitis, 35.3 percent vs. 11.3 percent; $P = 0.01$); severe complications of any kind were also significantly more common (23.5 percent vs. 2.1 percent, $P < 0.001$). Combined percutaneous–endoscopic access was used for 31 procedures (1.3 percent), but only in patients with strictures or stones. In such patients, combined percutaneous–endoscopic procedures had an overall complication rate that was similar to the rate for precut sphincterotomy (22.6 percent vs. 22.3 percent), but there were more severe complications with the combined procedure (6.5 percent vs. 2.1 percent).

Complications of Sphincterotomy for Common-Bile-Duct Stones

Among the 1600 patients with bile-duct stones or gallstone pancreatitis, rates of complications were similar (8.1 percent overall) regardless of whether sphincterotomy was performed before, after, or without cholecystectomy. In the subgroup of 487 patients who underwent sphincterotomy within 30 days before or after laparoscopic cholecystectomy, there were no severe complications, and the overall complication rate was significantly lower than for the other 1113 patients with choledocholithiasis (4.9 percent vs. 9.5 percent, $P < 0.001$), of whom the majority had either undergone prior open cholecystectomy ($n = 400$) or had the gallbladder left intact for at least 30 days after sphincterotomy ($n = 547$). The patients who underwent sphincterotomy in tandem with laparoscopic cholecystectomy were comparatively younger (mean [\pm SD] age, 51.3 ± 19.8 vs. 64.4 ± 17.8 years, $P < 0.001$) and had smaller bile-duct diameters (8.7 ± 3.3 vs. 10.0 ± 4.4 mm, $P < 0.001$) than the other patients with choledocholithiasis.

Overall Rates of Complications

Risk factors for all types of complication are shown in Table 4. Of 21 risk factors evaluated, 12 were significant in the univariate analysis, and 5 in the multivariate analysis; of the latter, 2 were related to the patients (cirrhosis and suspected sphincter dysfunction), and 3 were related to technique (difficulty of cannulation, and use of precut sphincterotomy or combined percutaneous–endoscopic access). Overall, complications occurred in 21.7 percent of patients undergoing sphincterotomy for dysfunction of the sphincter of Oddi, as compared with 8.2 percent of patients with other indications ($P < 0.001$); the rates of severe complications were 3.7 percent and 1.3 percent, respectively ($P < 0.001$). The 11 university-affiliated centers had higher rates of complications, but different case mixes, than the 6 private practices (frequency of sphincter of Oddi dysfunction, 16.0 percent vs. 4.0 percent; $P < 0.001$); the type of center was not significantly related to the incidence of complications in the multivariate analysis ($P = 0.61$).

Complications in Relation to Endoscopists' Case Volume

When the 5 centers whose staff physicians each performed an average of more than one sphincterotomy per week were compared with the 12 lower-volume centers, there were fewer difficult cannulations at the more experienced centers (7.1 percent vs. 14.6 percent, $P < 0.001$), as well as lower mean numbers of pancreatic-duct injections (1.4 vs. 2.1, $P < 0.001$), fewer failures of biliary access or drainage after sphincterotomy (1.2 percent vs. 5.4 percent, $P < 0.001$), fewer hemorrhages (1.1 percent vs. 2.9 percent, $P = 0.002$), fewer severe complications (0.9 percent vs. 2.3 percent, $P = 0.01$), and fewer overall complications (8.4 percent vs. 11.1 percent, $P = 0.03$). There were no significant differences in the rates of pancreatitis (5.5 percent vs. 5.3 percent); sphincterotomy was performed more often for dysfunction of the sphincter of Oddi (13.1 percent vs. 10.1 percent, $P = 0.02$) at the more experienced centers. Case volume was not independently significant in the overall multivariate model, probably because factors related to technique and case volume were closely linked. In a multivariate model based only on data available before the procedure and excluding details of intraoperative technique, low case volume was independently associated with a higher overall rate of complications ($P = 0.01$; odds ratio, 1.43; 95 percent confidence interval, 1.07 to 1.89).

DISCUSSION

The type and frequency of complications of endoscopic biliary sphincterotomy varied widely according to the clinical context in which the procedure was performed. The overall rate of complications (9.8 percent), although similar to the rates in previous reports,^{8-13,19-21} was derived from procedures involving a broad spectrum of patients, indications, and endoscopists. It included a substantial number of delayed and indirectly related events, which are often not discovered or recognized as complications of sphincterotomy without prospective investigation.^{31,32}

Pancreatitis is the most common complication of

TABLE 4. RISK FACTORS FOR COMPLICATIONS OF SPHINCTEROTOMY IN THE UNIVARIATE AND MULTIVARIATE ANALYSES.*

RISK FACTOR	PATIENTS WITH COMPLICATIONS (N=229)	ALL PATIENTS (N=2347)	UNIVARIATE P VALUE	ADJUSTED ODDS RATIO (95% CI)†
Significant in the multivariate analysis				
Difficulty of cannulation‡	1.8±0.8	1.4±0.7	<0.001	3.05 (1.83–5.08)
Precut sphincterotomy — no. (%)	27 (12)	111 (5)	<0.001	3.61 (1.78–7.34)
Combined percutaneous–endoscopic procedure — no. (%)	7 (3)	31 (1)	0.01	3.40 (1.04–11.13)
Suspected dysfunction of sphincter of Oddi — no. (%)	59 (26)	272 (12)	<0.001	2.90 (1.70–4.94)
Cirrhosis — no. (%)	14 (6)	73 (3)	0.006	2.93 (1.48–5.90)
Significant in the univariate analysis only				
No. of pancreatic contrast injections	2.7±3.4	1.8±2.9	<0.001	
Acinarization of pancreas — no. (%)§	11 (5)	34 (1)	<0.001	
Failed biliary access or drainage — no. (%)¶	18 (8)	78 (3)	<0.001	
Indication other than bile-duct stone	99 (43)	747 (32)	<0.001	
Age — yr	56.9±18.5	60.4±19.1	0.01	
University-affiliated center — no. (%)	158 (69)	1453 (62)	0.02	
Mean case volume of endoscopist ≤1/wk — no. (%)	132 (58)	1189 (51)	0.03	
Not significant				
Coagulopathy before procedure — no. (%)	18 (8)	120 (5)	0.05	
Emergency procedure — no. (%)	11 (5)	171 (7)	0.13	
Billroth II gastrectomy or Roux-en-Y anastomosis — no. (%)	8 (3)	50 (2)	0.13	
Cholangitis before procedure — no. (%)	26 (11)	339 (14)	0.16	
Periampullary diverticulum — no. (%)	31 (14)	382 (16)	0.24	
Female sex — no. (%)	148 (65)	1441 (61)	0.29	
No. of coexisting illnesses	1.4±1.5	1.5±1.5	0.44	
Participation of a trainee in procedure — no. (%)	81 (35)	852 (36)	0.76	
Distal bile-duct diameter — mm	9.2±4.8	9.3±4.4	0.90	

*Only risk factors with P values below 0.05 in the univariate analysis were included in the multivariate analysis. Numbers and percentages of patients and means are based on available data. Data were missing for more than 10 patients for the following variables: difficulty and method of cannulation (data not collected in the initial 952 cases), bile-duct diameter (missing in 73 cases), and number of pancreatic contrast injections (missing in 15 cases). Plus-minus values are means ±SD.

†Odds ratios have been adjusted for the effect of the other variables in the model. CI denotes confidence interval.

‡The difficulty of cannulation was graded on a 3-point scale, as follows: 1 = easy (≤5 attempts); 2 = moderately difficult (6–15 attempts); and 3 = difficult (>15 attempts). The odds ratio is for difficult as compared with easy cannulation.

§Acinarization denotes the appearance of acinar opacification on radiography of the pancreas.

¶This category includes 38 patients in whom access to the bile duct was not achieved after precut sphincterotomy and 40 in whom biliary decompression failed despite successful access to the bile duct.

||Coagulopathy was defined as a partial-thromboplastin or prothrombin time more than two seconds above the normal value, a platelet count of <80,000 per cubic millimeter, or ongoing hemodialysis.

ERCP and sphincterotomy.^{20-22,33-35} Two of the most important risk factors — suspected dysfunction of the sphincter of Oddi and relatively young age — were characteristics of the patients. Other risk factors were related to difficulty in cannulating the bile duct. Thus, the risk of pancreatitis was influenced by the technique of the endoscopist, and much of the injury to the pancreas appeared to result from the process of cannulating the bile duct rather than from the sphincterotomy itself.

A relatively young age increased susceptibility to pancreatitis after sphincterotomy; the progressive decline in pancreatic exocrine function with aging³⁶ may protect older patients from injury. A small bile-duct diameter, often found in younger patients,³⁷ has been emphasized as a risk factor in studies from re-

ferral centers.^{24,25} We found, however, that a small duct diameter increased the risk of pancreatitis only in the subgroup of patients with suspected dysfunction of the sphincter of Oddi.

It is unclear why pancreaticobiliary instrumentation confers such a marked, independent increase in the risk of pancreatitis in patients with suspected dysfunction of the sphincter of Oddi^{24,25,33,38}; it is possible that the absence of biliary tract disease may itself increase risk. Sphincter of Oddi manometry is not performed at many centers, in part because of concern that the infusion techniques may damage the pancreas.³⁹ Our results suggest that sphincterotomy preceded by manometry as it was performed, using an aspirating catheter to limit intraductal pressure in the pancreas,²⁹ did not involve any greater

risk than sphincterotomy performed empirically for this syndrome.

Precut sphincterotomy is a controversial technique.¹⁴ It is used by some endoscopists to obtain access to the common bile duct when other methods have failed, but it is avoided by others who fear damage to adjacent structures, especially the pancreas. Proponents have argued that any increase in complications with this technique can be attributed to excessive attempts at bile-duct cannulation before it is used.¹⁵ Even after adjusting for such variables, we found that the use of precut sphincterotomy independently increased the risk of complications, especially when dysfunction of the sphincter of Oddi was suspected. Nonetheless, when performed by experienced endoscopists in patients with definite biliary obstruction, precutting, unlike changing to a percutaneous approach, usually allowed the completion of biliary decompression during one procedure, and it seldom led to severe complications.

Clinically significant hemorrhage occurred primarily after sphincterotomy for bile-duct stones.⁴⁰ Independent risk factors for hemorrhage included all coagulopathies (but not the use of aspirin or related drugs in the usual doses),^{41,42} bleeding during the procedure,⁴³ and low case volume on the part of the endoscopist, which may have reflected less precise control of the incision or less effective endoscopic control of bleeding once it occurred. Risk factors did not include a longer incision or enlargement of a previous sphincterotomy. These observations do not support the view that bleeding results from incision through an aberrant retroduodenal artery^{19-21,44} but instead suggest delayed sloughing of an incomplete coagulum.

There has been concern about the additive risk of performing sphincterotomy in conjunction with laparoscopic cholecystectomy, especially in young patients with small bile ducts.⁴⁻⁶ We found that the endoscopic removal of bile-duct stones in tandem with laparoscopic cholecystectomy was relatively safe, regardless of the patient's age or the diameter of the duct. Such patients may make up a group with less complex choledocholithiasis, since their ductal stones may be discovered incidentally by routine preoperative or intraoperative imaging; by virtue of being considered fit for surgery, they are less likely than other patients to have cirrhosis or other conditions that increase risk.⁴⁵

The overall rate of complications after sphincterotomy, unlike that for most surgical procedures, did not increase with age or the number of coexisting medical conditions,²³ except for cirrhosis.⁴⁵ In fact, the risk of pancreatitis was highest among the youngest and otherwise healthiest patients — that is, those with suspected dysfunction of the sphincter of Oddi. Nonetheless, death occurred almost exclusively in the elderly or very ill.

Complications of sphincterotomy were closely related to endoscopic technique, which was in turn related to the case volume and, presumably, the skill and training of the endoscopist. Complications represent only one facet of procedural outcome; we did not study the success rates for all biliary endoscopic procedures that were attempted.⁴⁶⁻⁴⁸ Such additional information, as well as adjustment for case mix, would be necessary for a more complete assessment of the outcomes of sphincterotomy performed by different endoscopists.

In summary, the incidence and type of complications of endoscopic biliary sphincterotomy can vary widely in different circumstances. Complications appear to be related primarily to the clinical indication for the procedure and to the technical skill of the endoscopist, rather than to the age or general medical condition of the patient. These findings should be considered when clinicians interpret other studies, decide between alternative therapies, and inform patients about the risks of sphincterotomy.

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APPENDIX

The following centers, listed in descending order of the number of patients enrolled (in parentheses), participated in the study. The participating staff endoscopists, other than the coauthors, are also listed. Wellesley Hospital, Toronto (544); St. Cloud Clinic of Internal Medicine, St. Cloud, Minn. (246) — B.E. Currier, S.W. Hutton, P.E. Nelson, and R.C. Salières; Duluth Clinic, Duluth, Minn. (238) — J. Aas and R.V. Erickson; Indiana University Medical Center, Indianapolis (196) — G.A. Lehman; Digestive Health Care, Minneapolis (193) — R.J. Yanda; Hennepin County Medical Center, Minneapolis (186) — O.W. Cass; University of Pittsburgh, Pittsburgh (156) — R.R. Schade, M. Rabinowitz, and H. Wright; Marshfield Clinic, Marshfield, Wis. (139) — G.P. Mayeux; University of California at Los Angeles, Los Angeles (86); Medical University of South Carolina, Charleston (71) — W.H. Marsh and B.J. Hoffman; Park Nicollet Clinic, Minneapolis (64) — L.L. Stahnke; Minneapolis Veterans Affairs Medical Center, Minneapolis (63); California Pacific Medical Center, San Francisco (57) — M.S. Verhille, D.H. Augustyn, S.C. Steady, and R.G. Gish; Arizona Health Science Center, Tucson (36) — P.E. Jaffe; University of Minnesota Hospital and Clinic, Minneapolis (36) — J.A. Vennes; University of Utah Medical Center, Salt Lake City (22); St. Paul–Ramsey Medical Center, St. Paul, Minn. (14).

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