

Recurrent Acute Pancreatitis: An Algorithmic Approach to Identification and Elimination of Inciting Factors

LEHEL SOMOGYI,*[†] STEPHEN P. MARTIN,* THANGHAM VENKATESAN,*[†]
and CHARLES D. ULRICH II*^{†,§}

Departments of *Medicine and [§]Pathobiology and Molecular Medicine, University of Cincinnati Medical Center, and
[†]Cincinnati VA Medical Center, Cincinnati, Ohio

The established and putative causes of acute pancreatitis are legion. Most cases are attributable to acute or chronic alcohol ingestion, choledocholithiasis, medications, and metabolic derangements.¹⁻³ Other causes are uncommon, situational, or the subject of ongoing controversy (e.g., pancreas divisum, sphincter of Oddi dysfunction).¹⁻³ Recent studies show that mutations in the cationic trypsinogen gene are responsible for an autosomal dominant form of recurrent acute and chronic pancreatitis, termed hereditary pancreatitis (HP).⁴⁻⁸ Other groups have demonstrated a significant increase in the frequency of mutations in the cystic fibrosis gene (cystic fibrosis transmembrane conductance regulator [CFTR]) in patients with recurrent acute and chronic pancreatitis of otherwise unexplained etiology.⁹⁻¹³ Improving technology has enhanced our ability to image the pancreas and biliary system by non-invasive means.¹⁴⁻¹⁶ Unfortunately, despite these advances in knowledge and imaging, the clinical management of acute pancreatitis consists of intravenous hydration; monitoring of hemodynamic status, electrolytes, and acid-base balance; narcotic analgesics; antiemetics; enteral or parenteral nutrition; and antibiotic prophylaxis in the setting of necrosis.¹⁷⁻¹⁹

Evaluation of patients with recurrent acute pancreatitis requires systematic identification and/or elimination of correctable inciting factors. This article provides (1) a comprehensive yet concise overview of the causes of recurrent acute pancreatitis; (2) a detailed review of data relevant to implicated medications, the controversial issues of pancreas divisum and sphincter of Oddi dysfunction, and the role of genetic testing; (3) a guideline for evaluation of patients during the initial episode of acute pancreatitis; and (4) a consensus algorithm within which putative inciting factors may be identified and eliminated. Our guidelines pertain only to patients with recurrent acute pancreatitis in the absence of obvious evidence of chronic pancreatitis; Etamad and Whitcomb²⁰ discuss the latter in a review in this issue.

Causes of Recurrent Acute Pancreatitis

Virtually any factor capable of causing an initial episode of acute pancreatitis has the potential to incite recurrent episodes. Choledocholithiasis and alcohol use are the most common causes of acute pancreatitis, accounting for more than 70% of all cases.²¹ Established and suspected causes of recurrent acute pancreatitis can be segregated into toxic-metabolic, mechanical, and miscellaneous categories (Table 1).^{1-3,21-33} A number of inciting factors, specifically medications, pancreas divisum, sphincter of Oddi dysfunction, and genetic mutations, warrant further discussion.

Many medications have been implicated as causes of acute pancreatitis. However, the literature on the subject is conflicting because most of the information is found within individual case reports and/or small case series with wide variation in practice standards. The first 2 columns in Table 2 list medications for which there is general agreement on some association or a strong association with acute pancreatitis. To qualify for these lists, the drug must have been cited as causative in at least 3 articles. However, the strongest link between a drug and pancreatitis is provided by rechallenge (Table 2).³³⁻³⁷ With some drugs, the risk of pancreatitis is dose dependent (e.g., didanosine); in others, a hypersensitivity reaction may occur independent of the dose (e.g., 6-mercaptopurine). The overwhelming majority of cases are classified as idiosyncratic.

Pancreas divisum is the most common anatomic variant of the pancreas, occurring in up to 14% of individ-

Abbreviations used in this paper: CFTR, cystic fibrosis transmembrane conductance regulator; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HP, hereditary pancreatitis; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PSH, pancreatic sphincter hypertension; SOM, sphincter of Oddi manometry.

© 2001 by the American Gastroenterological Association

0016-5085/01/\$35.00

doi:10.1053/gast.2001.22333

Table 1. Causes of Recurrent Acute Pancreatitis

Established	Suspected	Investigational
Toxic-metabolic	Mechanical	Miscellaneous
Alcohol	SOD	CFTR mutations in the absence of overt CF
Hypertriglyceridemia	Pancreas divisum	
Hypercalcemia		
Medications		
Organophosphates		
Scorpion toxin		
Methylene chloride		
Mechanical	Miscellaneous	
Choledocholithiasis/microlithiasis	Autoimmune	
Periampullary/ampullary obstruction (e.g., diverticulum, cyst, polyp, tumor, stenosis, infection, Crohn's, blind loop)		
Pancreatic duct obstruction (e.g., tumor, mucinous ductal ectasia, nonneoplastic stricture)		
Congenital malformations (e.g., annular pancreas)		
Trauma		
Miscellaneous		
Vascular (e.g., hypotension, vasculitis, hypercoagulable state, embolism)		
Infections (e.g., CMV, TB, coxsackie virus, mumps, HIV, parasites)		
HP		
Tropical pancreatitis		
CF		

SOD, sphincter of Oddi dysfunction; CF, cystic fibrosis; CMV, cytomegalovirus; TB, tuberculosis; HIV, human immunodeficiency virus. Data from references 1–3, 21–33.

uals in autopsy series.³⁸ This variant arises from failure of fusion of the dorsal and ventral pancreatic ducts in the second month of gestation, causing the majority of pancreatic juice volume (80%–95%) to flow via the duct of Santorini (dorsal duct) through the minor papilla. Its importance as an etiology of pancreatitis remains controversial. Although one large retrospec-

tive series showed no correlation between pancreas divisum and recurrent acute pancreatitis,³⁹ other studies show a statistically significant higher prevalence of pancreas divisum in this patient population.^{40–43} The pertinent results of these studies are summarized in Table 3 and are highly suggestive of a cause-effect relationship.

Table 2. Medications That Cause Acute Pancreatitis

General agreement on some association	General agreement on strong association	At least 1 positive rechallenge documented
Asparaginase	Azathioprine	α-Methyl dopa
Corticosteroids	Didanosine	5-Aminosalicylate
Metronidazole	Estrogens	Azathioprine
Salicylates	Furosemide	Cimetidine
Thiazides	Mercaptopurine	Cytosine arabinoside
	Pentamidine	Dexamethasone
	Sulfonamides	Ethinylestradiol/lynestrenol
	Tetracycline	Furosemide
	Valproic acid	Isoniazid
		Mercaptopurine
		Metronidazole
		Norethindrone/mestranol
		Pentamidine
		Procainamide
		Stibogluconate
		Sulfamethazole
		Sulfamethoxazole
		Sulindac
		Tetracycline
		Trimethoprim/sulfamethoxazole
		Valproic acid

Data from references 33–37.

Table 3. Evidence That Pancreas Divisum Is Associated With Acute Pancreatitis

Study, yr	Prevalence in recurrent acute pancreatitis	Prevalence in controls	Study type	N
Morgan et al., 1999 ⁴⁰	49%	12% ($P < 0.0001$)	Retrospective	38
Bernard et al., 1990 ⁴¹	50%	<5% ($P < 0.001$)	Retrospective	137
Brenner et al., 1990 ⁴²	13%	4.8% ($P < 0.05$)	Retrospective	86
Delhay et al., 1985 ³⁹	7.5%	5.5% (NS)	Retrospective	335
Richter et al., 1981 ⁴³	12%	2.9% ($P < 0.005$)	Retrospective	125

The proposed mechanism for pancreas divisum causing pancreatitis is that pancreatic juice flow is obstructed at the level of an inadequately patent or stenosed minor papilla, resulting in ductal hypertension.⁴⁴ Improving flow with stenting and/or sphincterotomy would reduce this ductal hypertension and potentially improve pain or reduce subsequent episodes of recurrent pancreatitis.⁴⁵ Indeed, studies evaluating the treatment of patients suffering from recurrent pancreatitis and pancreas divisum with minor papilla stenting, sphincterotomy, or both show a decrease in the frequency of subsequent pancreatitis episodes (Table 4).^{22,46,47} Although most of the studies are retrospective and uncontrolled, it is difficult to argue that pancreas divisum plays no role in recurrent acute pancreatitis. As such, part of the evaluation and treatment of recurrent acute pancreatitis should include endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) to exclude pancreas divisum. Techniques attempting to better document the functional significance of pancreas divisum by comparing ductal images before and after secretin stimulation require further study (e.g., ultrasonography, magnetic resonance imaging [MRI]).

The role of sphincter of Oddi dysfunction also remains controversial. Despite this fact, ERCP with sphincter of Oddi manometry (SOM) has become a routine practice at specialty centers in the evaluation of patients with recurrent acute pancreatitis.⁴⁵ Studies published only in abstract form claim relief of symptoms after biliary sphincterotomy even though abnormal basal sphincter pressure may be confined to the pancreatic duct segment. This benefit may be seen in more than 50% of patients (Table 5).^{48–52} More recently, performance of manometry in both sphincters, with subsequent biliary and pancreatic sphincterotomy, the latter if pancreatic pressures are

elevated, has been advocated as more beneficial than biliary sphincterotomy alone.^{53,54}

Patients with pancreatic sphincter of Oddi dysfunction may be classified similarly to those with biliary sphincter of Oddi dysfunction. Type I patients have documented recurrent attacks of pancreatitis with a dilated pancreatic duct and slow drainage associated with ampullary stenosis.⁵⁵ They have the best results from sphincterotomy and generally do not require SOM.⁵⁶ Type II patients experience recurrent acute pancreatitis and have elevated basal sphincter pressures (more than 40 mm Hg) on manometry in the absence of stenosis. Guelrud et al.⁵⁷ found that these patients did best if endoscopic biliary sphincterotomy and pancreatic sphincterotomy were performed during the same session (86% improvement vs. 28% improvement with biliary sphincterotomy alone; $P < 0.05$) or if pancreatic sphincterotomy was performed at a later date (77% vs. 28%; $P < 0.05$).⁵⁷

Patients with sphincter of Oddi dysfunction have a higher incidence of postsphincterotomy pancreatitis, which occurs up to 5 times more frequently than in patients undergoing biliary sphincterotomy for other indications.⁵⁸ Sherman et al.⁵⁹ suggest that in addition to biliary sphincterotomy, the use of needle-knife pancreatic sphincterotomy over a pancreatic stent reduces the risk of significant post-ERCP pancreatitis compared with biliary sphincterotomy alone in this high-risk group (3.8% vs. 10.4%; $P = 0.03$).⁵⁹ Pancreatic sphincter hypertension has been implicated in the pathophysiology of post-ERCP pancreatitis. Placement of a pancreatic stent after biliary sphincterotomy significantly decreased the risk of post-ERCP pancreatitis (from 26% to 2%; $P = 0.003$) in a prospective, controlled trial of 80 patients with pancreatic sphincter hypertension diag-

Table 4. Studies of Endoscopic Therapy of Pancreas Divisum in Recurrent Acute Pancreatitis

Study, yr	N (mean follow-up)	Intervention (minor papilla)	Recurrence	Symptom relief	Stent-induced changes
Ertan, 2000 ⁴⁷	25 (2 yr)	Stenting	6/25 (24%)	19/25 (76%)	84%
Lans et al., 1992 ²²	10 (2.4 yr)	Stenting	1/10 (10%)	9/10 (90%)	0%
Lehman et al., 1993 ⁴⁶	17 (1.7 yr)	Sphincterotomy with stent	3/17 (18%)	14/17 (82%)	50%

Table 5. Studies of Endoscopic Therapy of Sphincter of Oddi Dysfunction in Recurrent Acute Pancreatitis

Study, yr	N (follow-up)	Intervention	Efficacy	Recurrence	Complications
Catalano et al., 1993 ⁴⁹	10 (NA)	Sphincterotomy	7/10 (70%)	2/10 (20%)	33% post-ERCP pancreatitis
Sherman, 1992 ⁵⁰	7 (0.7 yr)	Sphincterotomy	4/4 (100%)	0%	NS
Venu et al., 1989 ⁵¹	17 (3 yr)	Sphincterotomy	16/17 (94%)	1/17 (6%)	NS
Toouli et al., 1985 ⁵²	28 (NA)	Observation	16/28 (57%)	NS	NS

nosed by SOM.⁶⁰ Only patients with a nonpatent accessory duct developed pancreatitis in the group without stents, suggesting that a patent accessory (minor) papilla may effectively decompress the main duct via the accessory pancreatic duct (of Santorini) when drainage at the major papilla is inadequate.

Taking all of these factors into consideration raises a provocative question: if (1) sphincter of Oddi dysfunction is a cause of pancreatitis and (2) diagnosis with SOM places the patient at significant risk of morbidity, should patients with otherwise negative evaluation (including ERCP) undergo empiric biliary sphincterotomy? The data above suggest that this maneuver may reduce morbidity while achieving up to 50% efficacy.

Finally, from the standpoint of inherited predisposition, a diagnosis of HP can be made solely on the basis of family history and age at onset.^{6,7,61} Approximately 50% of kindreds with phenotypic characteristics of HP exhibit causative mutations in the cationic trypsinogen gene.^{6,7,62} In one large kindred with an established genotype, 87.5% of family members previously categorized as having HP based on phenotype had the genotype.⁶³ Stated another way, 12.5% of family members carried an incorrect diagnosis of HP. The rate of cationic trypsinogen gene mutations in patients lacking a sufficient family history with disease categorized as idiopathic appears to vary from 0% to 15% depending on the proximity of the testing center to kindreds with known HP.^{64–66} With respect to CFTR, the increased frequency of mutations in patients with recurrent acute pancreatitis of otherwise unclear etiology suggests that a cause–effect relationship may soon be established.^{9–13}

Genetic testing is controversial outside of approved protocols attempting to (1) further elicit the epidemiology of known gene mutations and (2) identify novel genetic mutations in kindreds lacking alterations in cationic trypsinogen and/or CFTR. This is because we currently have nothing to offer these patients for disease prevention, treatment, or surveillance other than smoking cessation, which presumably reduces cancer risk.^{67–70} Genetic testing may play a role in confirming the diagnosis in suspected cases of HP in which other more invasive tests are being considered.^{20,71} However, because

the phenotypic penetrance of HP is 80%,⁶ it is our belief that a limited search for other correctable inciting factors is reasonable. The role of testing for cationic trypsinogen gene mutations on family planning is controversial, and its impact on insurability must be considered.

Evaluation During the Initial Episode of Acute Pancreatitis

Our guidelines for evaluating patients with an initial episode of acute pancreatitis are contained in the algorithm in Figure 1. A thorough history and physical examination, when combined with a focused laboratory evaluation and biliary ultrasonography, may identify inciting factors such as acute or chronic alcohol use, choledocholithiasis, use of medications, overt cystic fibrosis, blunt abdominal trauma, exposure to toxins (e.g., organophosphates, scorpion toxin, methylene chloride), and hypotension. With regard to alcohol, an emerging concept is that a single episode of binge drinking may be sufficient to induce an episode of acute pancreatitis.² The previous dogma based on historical and histopathologic evidence was that consistent ingestion of alcohol for a prolonged period (e.g., 5 years or longer) was

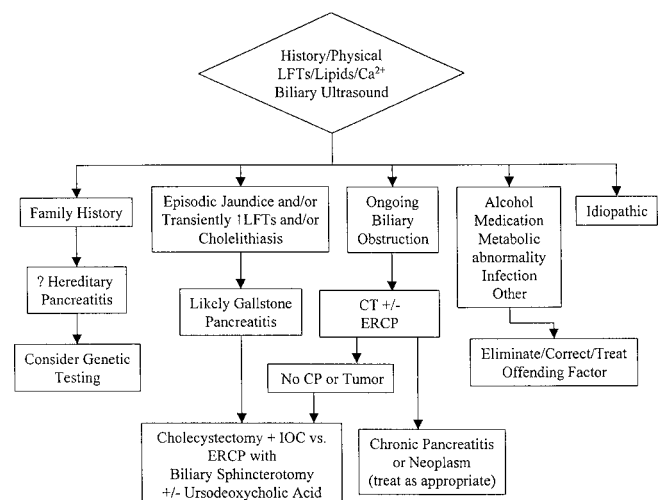


Figure 1. Algorithm facilitating identification and elimination of factors inciting an initial episode of acute pancreatitis. LFT, liver function test; IOC, intraoperative cholangiogram; CP, chronic pancreatitis.

required to “prime” the pancreas before an episode of pancreatitis.^{2,72,73}

Signs, symptoms, laboratory values, and/or biliary ultrasound findings may be indicative of malignancy, perampullary or ampullary obstruction, a hypercoagulable state, vasculitis, embolism, or infection. Consideration of an infectious etiology is particularly appropriate in immunosuppressed patients. The geographic origin or location of the patient may bring tropical pancreatitis and helminths (e.g., ascaris) into the differential diagnosis. A history of (1) a single 1st- or 2nd-degree relative with unexplained early-onset pancreatitis (at age <20 years); (2) a 1st- or 2nd-degree relative with multiple episodes of unexplained pancreatitis; or (3) 2 or more relatives with unexplained or presumed HP should raise the issue of genetic testing.

The evidence available should guide intervention. Discontinuation of the use of alcohol and certain medications, avoidance of toxins, and correction of metabolic abnormalities are appropriate. Although difficult to document in some cases, antibiotic/antiviral treatment of a primary infection may be warranted (e.g., pancreatitis in the setting of active cytomegalovirus or tuberculosis infection). Abdominal computed tomography (CT) should be performed in patients whose condition does not improve 48–72 hours after symptom onset.¹⁷ Urgent ERCP is warranted only in a setting in which biochemical and/or radiologic evidence of ongoing pancreaticobiliary obstruction accompanies lack of clinical improvement.^{74–76} In a setting in which there is biochemical or radiologic evidence of ongoing obstruction or choledocholithiasis but the patient is improving clinically, ERCP should be performed before the patient is discharged. If chronic pancreatitis and/or neoplasia is evident, the problem should be managed appropriately. If choledocholithiasis is apparent, biliary sphincterotomy and stone extraction are warranted. If chronic pancreatitis, neoplasia, and choledocholithiasis are all absent in the setting of biochemical and/or radiologic evidence of biliary obstruction, the possible presence of ampullary stenosis and/or sphincter of Oddi dysfunction must be considered. Based on available expertise, SOM vs. empiric sphincterotomy should be the next step in management.

If episodic jaundice precedes the episode of pancreatitis; liver function test results (aspartate aminotransferase and alanine aminotransferase, alkaline phosphatase, total and direct bilirubin) are transiently abnormal; and/or cholelithiasis, choledocholithiasis, or biliary sludge^{3,23} is documented, cholecystectomy is warranted. This should be performed after the episode of pancreatitis and sys-

temic complications have resolved completely. A laparoscopic approach is preferable and should be accompanied by an intraoperative cholangiogram. This approach should be taken independent of endoscopic intervention during the episode of pancreatitis (e.g., biliary sphincterotomy and stone extraction, which eliminates the risk of reflux-related cholecystitis). If the patient is not a surgical candidate, ERCP with biliary sphincterotomy and possible therapy with ursodeoxycholic acid²⁴ must suffice.

Identification and Elimination of Inciting Factors in Recurrent Acute Pancreatitis

Based on the studies published to date, members of our Pancreatic Disease Center at the University of Cincinnati follow the working algorithm illustrated in Figure 2. This algorithm has been modified based on the recommendations of members of the Midwest Multi-Center Pancreatic Study Group (see Acknowledgment). As such, it represents the consensus of numerous experts in the field. Although some would argue with certain aspects of this algorithm, we believe it represents a reasonable framework for systematic identification and elimination of inciting factors in recurrent acute pancreatitis. This algorithm is meant to guide decision making and should not supersede a more directed approach

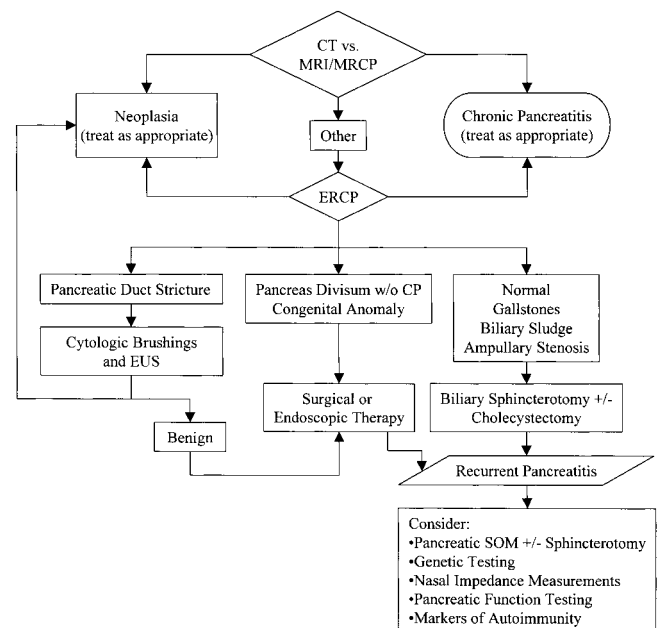


Figure 2. Algorithm facilitating stepwise identification and elimination of factors inciting recurrent acute pancreatitis. This represents a consensus resulting from the input of numerous members of the Midwest Multi-Center Pancreatic Study Group in combination with an extensive review of the current literature. CP, chronic pancreatitis.

Table 6. Diagnostic Tests in Chronic Pancreatitis: Strengths and Weaknesses

Tests	Strengths	Weaknesses
Established		
Secretin test	Most sensitive of all Functional information	Not widely available Time and labor intensive No structural information
ERCP	Best defines ductal anatomy Therapeutic potential	Less sensitive than secretin test Risk of pancreatitis High cost No functional information No information about the parenchyma
CT	Provides some information about the parenchyma as well as the pancreatic duct	Moderate cost and sensitivity No functional information
Serum trypsin	Simple, inexpensive Useful in diagnosis of steatorrhea	Low sensitivity in early disease
Evolving		
EUS	Provides information about the parenchyma as well as pancreatic duct Less invasive than ERCP	Highly operator dependent No functional information Sensitivity/specificity not well defined against pancreatic histology
Intraductal secretin test	Can be performed at the time of ERCP	Inaccurate as peak bicarbonate secretion often occurs beyond the 15-minute collection time typically used
Fecal elastase	Simple Inexpensive	Suboptimal accuracy False-positives in nonpancreatic steatorrhea Not available in the United States
MRI/MRCP	Better definition of ductal anatomy compared with CT Noninvasive	Limited sensitivity for early chronic pancreatitis Limited parenchymal information No functional information Lacks therapeutic potential

Data from references 14–16, 70, 77–84.

driven by a high index of clinical suspicion in certain cases.

The first step in the evaluation of patients with recurrent acute pancreatitis is the exclusion of chronic pancreatitis and malignancy. The review by Etemad and Whitcomb²⁰ in this issue discusses the strengths and weaknesses of diagnostic options with regard to chronic pancreatitis. Table 6 provides the reader of this review with a brief comparison of the tests available.^{14–16,70,77–84} Although we lack a test that will provide both structural and functional information about the gland, the strengths and weaknesses suggest that CT and MRI/MRCP are the initial imaging modalities of choice.^{14–16,81} Both are listed for obvious reasons. CT provides a view of the biliary system and pancreatic parenchyma (including calcifications and tumors) and may or may not visualize the pancreatic duct, even when dilated. MRI/MRCP facilitates high-resolution imaging of main biliary and pancreatic ducts at the expense of parenchymal detail. The level of experience, quality of instrumentation, and software all influence the images obtained using this modality. Thus the option of either CT or MRI/MRCP at the beginning of the algorithm. If chronic pancreatitis or malignancy is evident, it should be managed appropriately.

In the absence of chronic pancreatitis or malignancy, ERCP is the next logical step. The major issues to be dealt with at this point are early chronic pancreatitis, unappreciated malignancy, pancreatic duct stricture, pancreas divisum in the absence of chronic pancreatitis, cholelithiasis/microlithiasis, ampullary stenosis, other types of sphincter of Oddi dysfunction, and uncommon congenital anomalies. Acknowledging the associated 5%–10% risk of pancreatitis,⁵⁸ it is clear that ERCP is the only modality that combines identification and the potential for elimination of these inciting factors. It is also the only test capable of diagnosing chronic pancreatitis involving secondary ductal branches. Endoscopic ultrasonography (EUS) by itself is an unproven modality for diagnosing chronic pancreatitis.⁸⁴ Pancreatic function testing is not widely available and lacks specificity in the absence of tangible evidence of ductal or parenchymal abnormalities consistent with chronic pancreatitis.^{20,79} The accuracy of EUS and pancreatic function testing in combination remains in question pending correlation with histopathology. With respect to tumors, some may argue for the superiority of EUS based on its ability to both detect and stage pancreatic malignancy.⁷⁰ However, it is extremely unusual for a pancreatic tumor to cause

acute pancreatitis in the absence of obvious ductal obstruction. The sensitivity of ERCP in this cohort is high, and cytologic brushings, while lacking sensitivity, are specific.¹⁷ Biliary stent placement, as well as pancreatic stent placement,⁸⁵ should be considered as a palliative measure at the time of tumor detection.

Not infrequently, a pancreatic duct stricture of indeterminate nature is visualized by ERCP. Brushings from the stricture should be obtained and a pancreatic duct stent placed for palliation and to reduce the risk of post-ERCP pancreatitis.^{17,85,86} EUS is then performed in an attempt to discern the presence or absence of malignancy.⁷⁰ Optimal yield in this procedure is dependent on resolution of the pancreatic parenchymal changes associated with acute pancreatitis, which may take weeks. Even in the absence of positive cytologic brushing and EUS evidence of malignancy, we believe the stricture must eventually be dealt with surgically. We and others have not observed the same curative success with pancreatic duct stent placement reported by Cremer et al.⁸⁷ and others.⁸⁸ We also share concerns for stent-induced ductal deformity in the setting of repeated stent placement.⁸⁹ Surgery is definitive in confirming the stricture as malignant or benign.

Pancreas divisum in the absence of chronic pancreatitis may respond to a trial of transpapillary pancreatic duct stent placement through the minor papilla and/or sphincterotomy of the minor papilla. If episodes of pancreatitis recur and no other inciting factors are identified, surgical sphincteroplasty of the minor papilla should be considered.⁹⁰ Resection of the pancreatic head is a final logical option that has not yet been proven beneficial in this cohort. The potential morbidity and mortality associated with such procedures (e.g., Whipple, pylorus-preserving pancreaticoduodenectomy) cannot be ignored.

In patients with recurrent acute pancreatitis and either a normal cholangiopancreatogram, evidence of choledocholithiasis, or ampullary stenosis, we advocate biliary sphincterotomy. This addresses the issues of choledocholithiasis, microlithiasis, ampullary stenosis, and other types of biliary sphincter of Oddi dysfunction. It does so without the need for bile aspirate crystal analysis (a less than fully reliable test at even the most accomplished centers)^{91,92} or SOM, which carries with it the potential for significant morbidity.^{58,93} Whenever possible, biliary sphincterotomy should be accompanied by cholecystectomy. This will eliminate the risk of reflux-related cholecystitis associated with biliary sphincterotomy.⁹⁴ The only downsides to this approach are the immediate risks of sphincterotomy,⁵⁸ the potential for stenosis of the sphincterotomy site (operator dependent), and the theo-

retical concern of cholangiocarcinoma (no objective confirmatory evidence).⁹⁴

If pancreatitis recurs, consideration should be given to pancreatic SOM and, if results are abnormal, pancreatic sphincterotomy. Genetic testing,⁷¹ nasal impedance measurements,¹² pancreatic function testing,^{79,95} and analysis of markers of autoimmunity^{31,96} may also be appropriate at this time. These tests are listed last in our algorithm based on the morbidity associated with pancreatic SOM, the limited clinical impact of positive genetic testing, the lack of a uniform gold standard correlate for pancreatic function testing in the setting of normal radiologic imaging results, and the paucity of cases of autoimmune pancreatitis reported in the literature. If the results of all of these tests are negative, the patient can be truly considered to have one of the now <10% of cases classified as idiopathic recurrent acute pancreatitis.³

Summary

Recurrent acute pancreatitis represents a challenging clinical problem associated with significant morbidity, impairment in quality of life, and expense. If unchecked, recurrent episodes of acute pancreatitis may lead to chronic pancreatitis. In this work we have combined the opinion of experts in pancreatology and an extensive review of the literature to develop a logical algorithm that facilitates the stepwise identification and elimination of inciting factors using current technology. The approach taken in recurrent acute pancreatitis is clearly dependent on adequate and appropriate evaluation and treatment of the patient with an initial episode of acute pancreatitis. Future advances in the treatment of these patients will almost certainly depend on improved imaging modalities, prospective clinical trials assessing the efficacy of endoscopic and surgical intervention, a better understanding of mutations and pathophysiologic mechanisms responsible for recurrent acute pancreatitis, and the development of novel, effective preventive and therapeutic strategies.¹⁸

References

1. Gorelick F. Acute pancreatitis. In: Yamada T, ed. Textbook of gastroenterology. 2nd ed. Philadelphia: Lippincott, 1995:2064–2065.
2. Bank S, Indaram A. Causes of acute and recurrent pancreatitis. Clinical considerations and clues to diagnosis. *Gastroenterol Clin North Am* 1999;28:571–589.
3. Sakorafas GH, Tsiotou AG. Etiology and pathogenesis of acute pancreatitis: current concepts. *J Clin Gastroenterol* 2000;30:343–356.
4. Gorry MC, Ghabaizedeh D, Furey W, Gates LK, Preston RA, Aston CE, Zhang Y, Ulrich CD, Ehrlich GD, Whitcomb DC. Mutations in the

- cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. *Gastroenterology* 1997;113:1063–1068.
5. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, Martin SP, Gates LK, Amann ST, Toskes PP, Liddle R, McGrath K, Uomo G, Post JC, Ehrlich GD. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet* 1996;14:141–145.
 6. Ulrich CD, Kopras E, Wu Y, Ward S. Hereditary pancreatitis: epidemiology, molecules, mutations, and models. *J Lab Clin Med* 2000;136:260–274.
 7. Whitcomb DC. Genetic predispositions to acute and chronic pancreatitis. *Med Clin North Am* 2000;84:531–547.
 8. Chen JM, Ferec C. Molecular basis of hereditary pancreatitis. *Eur J Hum Genet* 2000;8:473–479.
 9. Cohn JA, Friedman KJ, Noone PG, Knowles MR, Silverman LM, Jowell PS. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. *N Engl J Med* 1998;339:653–658.
 10. Sharer N, Schwarz M, Malone G, Howarth A, Painter J, Super M, Braganza J. Mutations in the cystic fibrosis gene in patients with chronic pancreatitis. *N Engl J Med* 1998;339:645–652.
 11. Choudari CP, Lehman GA, Sherman S. Pancreatitis and cystic fibrosis gene mutations. *Gastroenterol Clin North Am* 1999;28:543–549.
 12. Cohn JA, Bornstein JD, Jowell PS. Cystic fibrosis mutations and genetic predisposition to idiopathic chronic pancreatitis. *Med Clin North Am* 2000;84:621–631.
 13. Bishop MD, Ahmed N, Ellis L, Shea J, Hopper I, Haber G, Ross C, Zielenski J, Tsui L-C, Durie PR, Freedman SD. Cystic fibrosis (CF) genotype and phenotype testing in idiopathic chronic and recurrent acute pancreatitis (abstr). *Pancreas* 1999;19:416.
 14. Adamek HE, Albert J, Breer H, Weitz M, Schilling D, Riemann JF. Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. *Lancet* 2000;356:190–193.
 15. Varghese JC, Liddell RP, Farrell MA, Murray FE, Osborne H, Lee MJ. The diagnostic accuracy of magnetic resonance cholangiopancreatography and ultrasound compared with direct cholangiography in the detection of choledocholithiasis. *Clin Radiol* 1999;54:604–614.
 16. Sica GT, Braver J, Cooney MJ, Miller FH, Chai JL, Adams DF. Comparison of endoscopic retrograde cholangiopancreatography with MR cholangiopancreatography in patients with pancreatitis. *Radiology* 1999;210:605–610.
 17. Martin SP, Ulrich CD. Pancreatic disease in the elderly. *Clin Geriatr Med* 1999;15:579–605.
 18. Ulrich CD. Medical management of acute pancreatitis: strategies, reality, and potential. *Curr Gastroenterol Rep* 2000;2:115–119.
 19. Martin SP, Ulrich CD. Complicated acute pancreatitis. *Curr Treatment Options Gastroenterol* 1999;2:215–225.
 20. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001;120:682–707.
 21. Steinberg W, Tenner S. Acute pancreatitis. *N Engl J Med* 1994;330:1198–1210.
 22. Lans J, Geenen J, Johanson J, Hogan W. Endoscopic therapy in patients with pancreas divisum and acute pancreatitis: a prospective, randomized, controlled clinical trial. *Gastrointest Endosc* 1992;38:430–434.
 23. Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. *N Engl J Med* 1992;326:589–593.
 24. Ros E, Navarro S, Bru C, Garcia-Puges A, Valderrama R. Occult microlithiasis in “idiopathic” acute pancreatitis: prevention of relapses by cholecystectomy or ursodeoxycholic acid therapy. *Gastroenterology* 1991;101:1701–1709.
 25. Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am* 1990;19:783–791.
 26. Heiss FW, Shea JA. Association of pancreatitis and variant ductal anatomy: dominant drainage of the duct of Santorini. *Am J Gastroenterol* 1978;70:158–162.
 27. Chuttani R, Carr-Locke DL. Pathophysiology of the sphincter of Oddi. *Surg Clin North Am* 1993;73:1311–1322.
 28. Lehman GA, Sherman S. Sphincter of Oddi dysfunction. *Int J Pancreatol* 1996;20:11–25.
 29. Hill ID, Lebenthal E. Congenital abnormalities of the exocrine pancreas. In: Go VLW, ed. *The pancreas: biology, pathobiology, and disease*. New York: Raven, 1993:1029–1040.
 30. Lloyd-Jones W, Mountain JC, Warren KW. Annular pancreas in the adult. *Ann Surg* 1972;176:163–170.
 31. Taniguchi T, Seko S, Okamoto M, Hamasaki A, Ueno H, Inoue F, Nishida O, Miyake N, Mizumoto T. Association of autoimmune pancreatitis and type 1 diabetes: autoimmune exocrinopathy and endocrinopathy of the pancreas. *Diabetes Care* 2000;23:1592–1594.
 32. Morohoshi T, Held G, Kloppel G. Exocrine pancreatic tumours and their histological classification. A study based on 167 autopsy and 97 surgical cases. *Histopathology* 1983;7:645–661.
 33. Tenner SM, Steinberg WM. Drug-induced acute pancreatitis. In: Beger HG, Warshaw AL, Russell RCG, Buchler M, Carr-Locke DL, Neoptolemos JP, Sarr MG, eds. *The pancreas*. Oxford: Blackwell Science, 1998:331–342.
 34. Underwood TW, Frye CB. Drug-induced pancreatitis. *Clin Pharm* 1993;12:440–448.
 35. Runzi M, Layer P. Drug-associated pancreatitis. *Pancreas* 1996;13:100–109.
 36. Banks P. Acute and chronic pancreatitis. In: Feldman M, Scharshmidt BF, Sleisenger MH, eds. *Sleisenger and Fordtran’s gastrointestinal and liver disease: pathophysiology/diagnosis/management*. 6th ed. Philadelphia: Saunders, 1998:809–862.
 37. Steinberg WM. Acute drug and toxin induced pancreatitis. *Hosp Pract* 1985;20:95–102.
 38. Smanio T. Proposed nomenclature and classification of the human pancreatic ducts and duodenal papillae. Study based on 200 postmortems. *Int Surg* 1969;52:125–134.
 39. Delhaye M, Engelholm L, Cremer M. Pancreas divisum: congenital anatomic variant or anomaly? Contribution of endoscopic retrograde dorsal pancreatography. *Gastroenterology* 1985;89:951–958.
 40. Morgan D, Logan K, Baron T, Koehler R, Smith J. Pancreas divisum: implications for diagnostic and therapeutic pancreatography. *Am J Roentgenol* 1999;173:193–198.
 41. Bernard JP, Sahel J, Giovannini M, Sarles H. Pancreas divisum is a probable cause of acute pancreatitis: a report of 137 cases. *Pancreas* 1990;5:248–254.
 42. Brenner P, Duncombe V, Ham JM. Pancreatitis and pancreas divisum: aetiological and surgical considerations. *Aust NZ J Surg* 1990;60:899–903.
 43. Richter JM, Schapiro RH, Mulley AG, Warshaw AL. Association of pancreas divisum and pancreatitis, and its treatment by sphincteroplasty of the accessory ampulla. *Gastroenterology* 1981;81:1104–1110.
 44. Warshaw AL. Pancreas divisum and pancreatitis. In: Beger HG, Warshaw AL, Russell RCG, Buchler M, Carr-Locke DL, Neoptolemos JP, Sarr MG, eds. *The pancreas*. Oxford: Blackwell Science, 1998:364–374.
 45. Shah RJ, Martin SP. Endoscopic retrograde cholangiopancreatography in the diagnosis and management of pancreatic diseases. *Curr Gastroenterol Rep* 2000;2:133–145.
 46. Lehman GA, Sherman S, Nisi R, Hawes RH. Pancreas divisum: results of minor papilla sphincterotomy. *Gastrointest Endosc* 1993;39:1–8.
 47. Ertan A. Long-term results after endoscopic pancreatic stent

- placement without pancreatic papillotomy in acute recurrent pancreatitis due to pancreas divisum. *Gastrointest Endosc* 2000;52:9–14.
48. Sherman S, Jamidar P, Reber H. Idiopathic acute pancreatitis: endoscopic approach to diagnosis and treatment (abstr). *Am J Gastroenterol* 1993;88:1541.
 49. Catalano MF, Sivak MV, Falk GW, Howerton HD, Achkar E. Idiopathic pancreatitis: diagnostic role of sphincter of Oddi manometry (SOM) and response to endoscopic sphincterotomy (ES) (abstr). *Gastrointest Endosc* 1993;39:310A.
 50. Sherman S. Idiopathic acute recurrent pancreatitis: endoscopic approach to diagnosis and therapy (abstr). *Gastrointest Endosc* 1992;38:261A.
 51. Venu RP, Geenen JE, Hogan W, Stone J, Johnson GK, Soergel K. Idiopathic recurrent pancreatitis an approach to diagnosis and treatment. *Dig Dis Sci* 1989;34:56–60.
 52. Toouli J, Roberts-Thomson IC, Dent J, Lee J. Sphincter of Oddi motility disorders in patients with idiopathic recurrent pancreatitis. *Br J Surg* 1985;72:859–863.
 53. Koksall R, Lo S, Solatni S. Utility of sphincter manometry in sphincterotomy for pancreatic sphincter dysfunction (abstr). *Gastrointest Endosc* 1997;45:544A.
 54. Eversman D, Fogel EL, Rusche M, Sherman S, Lehman G. Frequency of abnormal pancreatic and biliary sphincter manometry compared with clinical suspicion of sphincter of Oddi dysfunction. *Gastrointest Endosc* 1999;50:637–641.
 55. Sherman S, Troiano FP, Hawes RH, O'Connor KW, Lehman GA. Frequency of abnormal sphincter of Oddi manometry compared with the clinical suspicion of sphincter of Oddi dysfunction. *Am J Gastroenterol* 1991;86:586–589.
 56. Kuo W-H, Pasricha P, Kalloo A. The role of sphincter of Oddi manometry in the diagnosis and therapy of pancreatic disease. *Gastrointest Endosc Clin North Am* 1998;8:79–85.
 57. Guelrud M, Plaz J, Mendoza S, Beker B, Rojas O, Rossiter G. Endoscopic treatment in type II pancreatic sphincter dysfunction (abstr). *Gastrointest Endosc* 1995;52:398A.
 58. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996;335:909–918.
 59. Sherman S, Eversman D, Fogel E, Gottlieb K, Earle D. Sphincter of Oddi dysfunction (SOD): needle-knife pancreato-biliary sphincterotomy over pancreatic stent (NKOPS) has a lower post-procedure pancreatitis rate than pull-type biliary sphincterotomy (BES) (abstr). *Gastrointest Endosc* 1997;45:148A.
 60. Tarnasky P, Palesch Y, Cunningham J, Mauldin P, Cotton P, Hawes R. Pancreatic stenting prevent pancreatitis after biliary sphincterotomy in patients with Sphincter of Oddi dysfunction. *Gastroenterology* 1998;115:1518–1524.
 61. Perrault J. Hereditary pancreatitis. Historical perspectives. *Med Clin North Am* 2000;84:519–529.
 62. Whitcomb DC, Applebaum S, Bartness MA, Ford MA, Thompson B, Aston CE, Midwest Multicenter Pancreatic Study Group (MMPSPG). Mutations associated with pancreatitis in families in the United States—the MMPSPG study (abstr). *Pancreas* 1998;17:459.
 63. Sossenheimer MJ, Aston CE, Preston RA, Gates LK, Jr, Ulrich CD, Martin SP, Zhang Y, Gorry MC, Ehrlich GD, Whitcomb DC. Clinical characteristics of hereditary pancreatitis in a large family, based on high-risk haplotype. The Midwest Multicenter Pancreatic Study Group (MMPSPG). *Am J Gastroenterol* 1997;92:1113–1116.
 64. Böhm A-K, Reinheckel T, Rosenstrauch D, Halangk W, Schulz HU. Screening for a point mutation of cationic trypsinogen in patients with pancreatic diseases (abstr). *Digestion* 1999;60:369.
 65. Ockenga J, Stuhmann M, Ballmann M, Teich N, Keim V, Dork T, Manns MP. Mutations of the cystic fibrosis gene, but not cationic trypsinogen gene, are associated with recurrent or chronic idiopathic pancreatitis. *Am J Gastroenterol* 2000;95:2061–2067.
 66. Simon P, Zimmer KP, Domschke W, Lerch MM. Cationic trypsinogen mutations in patients with idiopathic pancreatitis (abstr). *Pancreas* 1999;19:438.
 67. Lowenfels AB, Maisonneuve P, Whitcomb DC. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. *Med Clin North Am* 2000;84:565–573.
 68. Gates LK Jr. Preventive strategies and therapeutic options for hereditary pancreatitis. *Med Clin North Am* 2000;84:589–595.
 69. Howes N, Greenhalf W, Neoptolemos J. Screening for early pancreatic ductal adenocarcinoma in hereditary pancreatitis. *Med Clin North Am* 2000;84:719–738.
 70. Martin SP, Ulrich CD. Pancreatic cancer surveillance in a high-risk cohort. Is it worth the cost? *Med Clin North Am* 2000;84:739–747.
 71. Applebaum SE, Kant JA, Whitcomb DC, Ellis IH. Genetic testing. Counseling, laboratory, and regulatory issues and the EUROPAC protocol for ethical research in multicenter studies of inherited pancreatic diseases. *Med Clin North Am* 2000;84:575–588.
 72. Ammann RW, Muellhaupt B, Meyenberger C, Heitz PU. Alcoholic nonprogressive chronic pancreatitis: prospective long-term study of a large cohort with alcoholic acute pancreatitis (1976–1992). *Pancreas* 1994;9:365–373.
 73. Singh M, Simsek H. Ethanol and the pancreas: current status. *Gastroenterology* 1990;98:1051–1062.
 74. Fan ST, Lai EC, Mok FP, Lo CM, Zheng SS, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N Engl J Med* 1993;328:228–232.
 75. Neoptolemos J, London N, Slater N, Carr-Locke D, Fossard D, Moosa A. A prospective study of ERCP and endoscopic sphincterotomy in the diagnosis and treatment of gallstone acute pancreatitis. A rational and safe approach to management. *Arch Surg* 1986;121:697–702.
 76. Nowak A, Nowakowska-Dulawa E, Marek TA. Final results of the prospective, randomized, controlled study on endoscopic sphincterotomy versus conventional management in acute biliary pancreatitis (abstr). *Gastroenterology* 1995;108(suppl):A380.
 77. Forsmark CE, Toskes PP. What does an abnormal pancreatogram mean? *Gastrointest Endosc Clin North Am* 1995;5:105–123.
 78. Amann ST, Bishop M, Curington C, Toskes PP. Fecal pancreatic elastase 1 is inaccurate in the diagnosis of chronic pancreatitis. *Pancreas* 1996;13:226–230.
 79. Hayakawa T, Kondo T, Shibata T, Noda A, Suzuki T, Nakano S. Relationship between pancreatic exocrine function and histological changes in chronic pancreatitis. *Am J Gastroenterol* 1992;87:1170–1174.
 80. Sahai AV, Zimmerman M, Aabakken L, Tarnasky PR, Cunningham JT, van Velse A, Hawes RH, Hoffman BJ. Prospective assessment of the ability of endoscopic ultrasound to diagnose, exclude, or establish the severity of chronic pancreatitis found by endoscopic retrograde cholangiopancreatography. *Gastrointest Endosc* 1998;48:18–25.
 81. Robinson PJ, Sheridan MB. Pancreatitis: computed tomography and magnetic resonance imaging. *Eur Radiol* 2000;10:401–408.
 82. Jacobson DG, Curington C, Connery K, Toskes PP. Trypsin-like immunoreactivity as a test for pancreatic insufficiency. *N Engl J Med* 1984;310:1307–1309.
 83. DiMagno EP. A perspective on the use of the tubeless pancreatic function tests in diagnosis. *Gut* 1998;43:2–3.
 84. Forsmark CE. The diagnosis of chronic pancreatitis. *Gastrointest Endosc* 2000;52:293–298.
 85. Tham TC, Lichtenstein DR, Vandervoort J, Wong RC, Slivka A, Banks PA, Yim HB, Carr-Locke DL. Pancreatic duct stents for “obstructive type” pain in pancreatic malignancy. *Am J Gastroenterol* 2000;95:956–960.
 86. Vandervoort J, Soetikno RM, Montes H, Lichtenstein DR, Van Dam J, Ruymann FW, Cibas ES, Carr-Locke DL. Accuracy and

- complication rate of brush cytology from bile duct versus pancreatic duct. *Gastrointest Endosc* 1999;49:322-327.
87. Cremer M, Deviere J, Delhaye M, Baize M, Vandermeeren A. Stenting in severe chronic pancreatitis: results of a medium-term follow-up in seventy-six patients. *Endoscopy* 1991;23:171-176.
 88. Smits ME, Badiga SM, Rauws EAJ, Tytgat GNJ, Huibregtse K. Long-term results of pancreatic stents in chronic pancreatitis. *Gastrointest Endosc* 1995;42:461-467.
 89. Smith MT, Sherman S, Ikenberry SO, Hawes RH, Lehman GA. Alterations in pancreatic ductal morphology following polyethylene pancreatic stent therapy. *Gastrointest Endosc* 1996;44:268-275.
 90. Warshaw AL, Simeone JF, Schapiro RH, Flavin-Warshaw B. Evaluation and treatment of the dominant dorsal duct syndrome (pancreas divisum redefined). *Am J Surg* 1990;159:59-66.
 91. Rubin M, Pakula R, Konikoff FM. Microstructural analysis of bile: relevance to cholesterol gallstone pathogenesis. *Histol Histopathol* 2000;15:761-770.
 92. Marks JW, Bonorris G. Intermittency of cholesterol crystals in duodenal bile from gallstone patients. *Gastroenterology* 1984;87:622-627.
 93. Sherman S, Hawes RH, Troiano FP, Lehman GA. Pancreatitis following bile duct sphincter of Oddi manometry: utility of the aspirating catheter. *Gastrointest Endosc* 1992;38:347-350.
 94. Baillie J. Biliary sphincterotomy: less benign than once thought? *Curr Gastroenterol Rep* 1999;1:102-106.
 95. Somogyi L, Cintron M, Toskes PP. Synthetic porcine secretin is highly accurate in pancreatic function testing in individuals with chronic pancreatitis. *Pancreas* 2000;21:262-265.
 96. Uchida K, Okazaki K, Konishi Y, Ohana M, Takakuwa H, Hajiro K, Chiba T. Clinical analysis of autoimmune-related pancreatitis. *Am J Gastroenterol* 2000;95:2788-2794.

Received December 4, 2000. Accepted December 15, 2000.

Address requests for reprints to: Charles D. Ulrich II, M.D., Division of Digestive Diseases, Department of Internal Medicine, 231 Albert B. Sabin Way, Room 6555 MSB, ML 0595, Cincinnati, Ohio 45267-0595. e-mail: charles.ulrich@uc.edu; fax: (513) 558-1744.

Supported by the Division of Digestive Diseases, University of Cincinnati, and by National Institutes of Health grant CA74456 (to C.D.U.).

The authors thank the following members of the Midwest Multi-Center Pancreatic Study Group, who thoughtfully contributed to the algorithm facilitating stepwise identification and elimination of factors inciting recurrent acute pancreatitis: Stephen T. Amann, M.D. (Tupelo, MS), Frank R. Burton, M.D. (St. Louis, MO), Darwin L. Conwell, M.D. (Cleveland, OH), Mark T. DeMeo, M.D. (Chicago, IL), Babak Etemad, M.D. (Pittsburgh, PA), Christopher E. Forsmark (Gainesville, FL), Lawrence K. Gates, M.D. (Lexington, KY), Markus M. Lerch, M.D. (Munster, Germany), Albert B. Lowenfels (Valhalla, NY), Michael L. Kochman, M.D. (Philadelphia, PA), David C. Whitcomb, M.D., Ph.D. (Pittsburgh, PA), and Paul N. Yakshe (Minneapolis, MN).