Recurrent Acute Pancreatitis

International State-of-the-Science Conference With Recommendations

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Abstract: Recurrent acute pancreatitis (RAP) is a clinically significant problem globally. The etiology remains unclear in approximately 10% to 15% of patients despite a thorough workup. Data on natural history and efficacy of treatments are limited. We aimed to establish criteria for diagnosis, evaluate the causative factors, and arrive at a consensus on the appropriate workup and management of patients with RAP. The organizing committee was formed, and a set of questions was developed based on the current evidence, controversies, and topics that needed further research. After a vetting process, these topics were assigned to a group of experts from around the world with special interest in RAP. Data were presented as part of a workshop on RAP organized as a part of the annual meeting of the America Pancreatic Association. Pretest and Posttest questions were administered, and the responses were tabulated by the current Grades of Recommendation Assessment, Development and Evaluation system. The consensus guidelines were established in the format of a diagnostic algorithm. Several deficiencies were identified with respect to data on etiology, treatment efficacies, and areas that need immediate research.

Key Words: recurrent acute pancreatitis, etiology, diagnostic algorithm, treatment efficacies, workup

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Acute pancreatitis (AP) is a common clinical problem, with treatment costs exceeding $2.5 billion annually in the United States.[1] Approximately 10% to 30% of patients with AP develop recurrent attacks of pancreatitis.[2–4] There is a continuum between recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP).[5–7] A recent meta-analysis has shown that 10% of patients with a single episode of AP and 26% of those with RAP develop CP.[8]

Acute pancreatitis has many causes, of which alcohol and gallstones account for 70% in adults. In children, etiologies are broader and more variable.[9,10] The role of genetic variants in pancreatitis appears to be both important and complex, increasing susceptibility and modifying effects of environmental factors that play major roles in the onset, severity, and outcome of the pancreatic diseases.[11] If not corrected, any factor responsible for pancreatitis is capable of producing recurrent attacks of AP, and hence it is important to carefully evaluate the patient and address the underlying cause.[12] Furthermore, the etiology of pancreatitis is often multifactorial. Despite eliminating the reversible elements leading to pancreatitis, patients often remain susceptible to recurrent attacks. Etiology of RAP remains unidentified in at least 10% of patients despite a thorough workup including history, laboratory studies, and cross-sectional imaging. Such patients are often described as having idiopathic recurrent acute pancreatitis (IRAP). These patients often undergo expensive and sometimes invasive evaluations and treatments, some of which entail risk for significant complications, including further pancreatitis.[13]

At present, there is a lack of consensus on the etiologic factors, appropriate diagnostic workup, and most appropriate treatment options for patients with RAP. The ambiguity largely results from a paucity of data. In addition, terminology has not been standardized, thus limiting comparability of data among centers. The purposes of this conference were to address the current state of knowledge and assess the degree of consensus among experts in a spectrum of disciplines related to the pancreas.

AIM

The aim of this conference was to establish uniform definitions, diagnostic and treatment algorithms, and future research needs in diagnosis and management of RAP by international consensus.

MATERIALS AND METHODS

Leading international experts in various aspects of pancreatology, surgery, medical imaging, and interventional endoscopy were identified by the principal course directors based on publications and peer recognition and were invited to participate as moderators and/or speakers. Care was taken to represent as many leading centers and countries as possible. The focus of this meeting was on establishing criteria for diagnosis, evaluating the causative factors,

and arriving at a consensus on the appropriate workup and management of patients with RAP.

Prior to the conference, the planning committee (M.L.F., P.G., N.M.G., P.L.) developed questions applicable to current evidence and future research.

The proposed questions were vetted by the organizing committee and given to the invited speakers. Prior to the conference, a pretest was conducted, and after the presentation of evidence, audience response was obtained again to gather consensus based on the presented evidence. A series of lectures was prepared, each focusing on a specific question assigned by the meeting codirectors. After each session, a panel of experts reviewed the presentations and questions, and comments were taken from the audience. Responses to questions were based on the currently accepted Grades of Recommendation Assessment, Development and Evaluation system. (Supplemental Digital Content, Appendix, http://links.lww.com/MPA/A651). Audience responded to one of these 5 choices: definitely no, probably no, no specific recommendation, probably yes, and definitely yes.

Drafts of the manuscript were circulated to all the presenters for comments and editing on a repeated basis before publication. Important evidence that became available after the conference was incorporated into revision of the manuscript, and then conclusions were updated accordingly and approved by the coauthors. Participants in the consensus process who contributed substantially to preparation or editing of the manuscript are listed as principal coauthors.

Consensus Questions. Multiple questions about RAP (n = 37) were organized into 10 topics:

1. What is the definition of RAP?
2. Which patients with a sentinel episode of AP are at risk of recurrent attacks?
3. What is the role of genetic testing in RAP?
4. When to suspect microlithiasis as a possible cause for RAP?
5. Are pancreas divisum (PD) and sphincter of Oddi dysfunction (SOD) associated with RAP?
6. What is the diagnostic role of endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) in the management of RAP?
7. What is the role of endoscopic retrograde cholangiopancreatography (ERCP) in patients with RAP?
8. Does biliary and/or pancreatic sphincterotomy impact natural history of RAP?
9. Any role for medical therapies for RAP?
10. What are the problems with studying RAP?

DEFINING RAP

Acute pancreatitis is defined as presence of 2 of the 3 following criteria[14]: (*a*) abdominal pain suggestive of pancreatitis (epigastric pain often radiating to the back); (*b*) serum amylase or lipase levels 3 or more times normal; and (*c*) characteristic findings on computed tomogarphy (CT), magnetic resonance imaging (MRI), or transabdominal ultrasound studies.

Recurrent acute pancreatitis has been defined as 2 or more well-documented separate attacks of AP with complete resolution for more than 3 months between attacks.[15–17] It usually occurs in the setting of normal morphofunctional gland with self-limited edematous changes; however, evidence of underlying CP can be identified either at the time of the first attack or during follow-up attacks.

In contrast to RAP, CP is now defined mechanistically based on (*a*) its essence and (*b*) its characteristics, recognized in advanced stages.[18] The mechanistic definition defines the essence of CP as "a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress." In addition, "common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia," which define the characteristics of the disease.[18] Thus, RAP exists as a syndrome that is distinct from both AP and CP. However, without clear definitions and diagnostic criteria, RAP and CP have often been combined in electronic health records and administrative databases, such as under *International Classification of Diseases, Ninth Revision* code 577.1 which is applied to either condition.

New Mechanistic Definition of RAP

"Recurrent acute pancreatitis is a syndrome of multiple distinct acute inflammatory responses originating within the pancreas in individuals with genetic, environmental, traumatic, morphologic, metabolic, biologic, and/or other risk factors who experienced 2 or more episodes of documented AP, separated by at least 3 months."

This new definition follows the mechanistic definition of CP defining the essence (and inflammatory responses in subjects with risk factors) and characteristics (≥2 episodes of documented AP, separated by at least 3 months). Of note, the mechanistic definition of RAP does not include morphologic features, because morphology is not an essential or diagnostic component of RAP. Acute pancreatitis, RAP, and CP are linked by common etiologies (below). Thus, RAP can be diagnosed independent of CP, recognizing that the 2 syndromes can coexist or exist completely independent of each other (eg, RAP without CP, and CP without a history of RAP). However, in progressive, predictive disease models of CP, a distinction between a RAP phase and onset of established CP is appropriate because it allows organization of risk and protective factors that may accelerate or retard the expected rate of progression from RAP to early CP or established CP.

Multistate Conceptual Model

The 3 common forms of pancreatitis, AP, RAP, and CP share multiple risk factors and clinical features and typically occur sequentially as illustrated in the Sentinel Acute Pancreatitis Event model.[7,19,20] The first episode of AP is called the "sentinel event," as it is the first syndrome recognized by the clinician who then needs to consider future problems and the possibility of RAP and CP on the patient's medical horizon. This marks the transition from the "at risk" stage of the patient's life to becoming a pancreatitis patient. If the etiologic cause of AP is not eliminated, then RAP is likely to develop, making the process of determining the etiologies a top priority following the sentinel AP event.

In addition to the immediate damage and morbidity of AP, the sentinel AP event also results in long-lasting or permanent changes in the pancreatic gland that markedly increase susceptibility to further episodes of AP.[21] Although challenging to prove in humans, the changes in the pancreas linked to increased AP susceptibility likely involve microanatomic changes, epigenetic changes, and/or immunological changes such as populating the parenchyma widespread with tissue histiocytes (eg, macrophages, dendritic cell) following resolution of the acute phase of AP and the return to a grossly normal-appearing gland.[20] Thus, AP results in persistent changes that strongly predisposes to RAP.

Any condition causing a single episode of AP has the potential to cause recurrent episodes, unless the inciting factor has not been corrected. Current evidence suggests that overall risk of recurrent attacks after the sentinel episode is approximately 20% and varies according to etiology.[22–25] Treating the putative

underlying cause has the potential to reduce or eliminate recurrent attacks. Patients without identifiable cause and those with irreversible factors such as genetic abnormalities are at higher risk of subsequent attacks.[26] Taken together, RAP is a complex syndrome associated with multiple etiologies, clinical variables, complications, and outcomes.

In addition to the morbidity and cost of each episode of AP suffered by an RAP patient, RAP is the most important risk factor for progression to end-stage CP.[8,23] Therefore, the effort to effectively manage RAP, beginning with the sentinel AP event, becomes extremely important.

ETIOLOGY

Effective management of RAP requires identification of etiologic factors and pathogenic processes. Etiology of AP/RAP can be identified by first-line testing (history, blood work, standard imaging) in approximately 70% of patients with RAP.[27,28] In the remainder, etiology is not apparent; thus, the pancreatitis generally is termed as idiopathic. It is increasingly clear that pancreatitis may be the result of multiple contributing and possibly interacting factors including genetics, microlithiasis, potentially obstructive abnormalities such as PD, congenital anomalies such as annular pancreas, autoimmune pancreatitis (AIP), and occult malignant neoplasms. After exhaustive advanced evaluation, perhaps 10% of patients remain truly idiopathic and should be followed expectantly.

Excess alcohol consumption is responsible for 30% of adult cases of AP in the United States.[29] Although the natural history of RAP is incompletely understood, studies have shown that recurrent episodes of AP typically occur in those patients who continued to drink and in those with underlying chronic calcific pancreatitis.[30–32] Alcohol cessation decreases the risk of recurrence as well of progression after a first attack of AP.[33] Prevalence estimates for RAP in alcoholics are approximately 16.9% in men and 5.5% in women.[34] The North American Pancreatitis Study Group (NAPS2) has shown that after controlling for age, sex, smoking, and body mass index those subjects with heavy alcohol intake (>5 drinks per day) are at risk of RAP and CP.[35] Smoking is a newly recognized, independent, and dose-dependent risk factor for AP, RAP, and CP.[36–38] The effects of smoking are enhanced in the presence of alcohol consumption.[35] Risk for progression to CP in patients with AP and RAP are higher among smokers and alcoholics.[8] A recent retrospective study from Sweden showed that those patients with a first attack of AP who either had a severe attack, were smokers, or alcohol abusers are at increased risk of recurrences and subsequent CP.[25] Prospective analysis from a recent study showed that smoking is a risk factor for nongallstone AP, RAP, and CP; interestingly, moderate alcohol use may be protective against RAP and CP,[39] but use of alcohol in these subjects is not recommended. Therefore, it is important to elicit a complete social history and provide appropriate counseling.

Role of Genetics and Genetic Testing

Trypsin activates other pancreatic digestive enzymes from inactive to active states. Trypsin itself is synthesized in an inactive form, trypsinogen, which is normally activated by enterokinase after secretion into the duodenum. It is now generally accepted that premature activation of trypsin in the acinar cells or ducts initiates a digestive enzyme activation cascade within the pancreas, leading to AP. Genetic studies in hereditary pancreatitis (HP) kindred demonstrated unequivocally that genetic factors, such as the cationic trypsinogen gene (*PRSS1*) p.N29I and p.R122H variants (reported using a protein sequencing method as N21I[6] and R117H[7]), markedly increased the risk of AP, RAP, and CP, in that order. Multiple additional lines of evidence support a central role of trypsin in common forms of AP.[40–43] Multiple systems within the pancreas protect the organism from unregulated trypsin activity and AP, RAP, and eventually CP. Risk of RAP is unequivocally associated with multiple genetic variants in *PRSS1* with function variants in *PRSS1*, protective loss-of function in variants linked to the *PRSS1-PRSS2* locus[23] and the *PRSS2* gene[44] and copy number variants.[44] Increased risk is also associated with loss-of-function variants in at least 2 trypsin inhibitors, serine protease inhibitor Kazal type 1 (*SPINK1*)[44,45] and *CTRC*.[46–48] Furthermore, pathogenic variants in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) lead to RAP[49,50] by impairing bicarbonate secretion into the ducts and limiting the flushing of trypsinogen out of the pancreatic duct with loss of this protective mechanism.[51,52] Multiple sensors and other systems coordinate these processes, and genetic or environmental factors that modify these systems also modify risk. In some cases, strong genetic effects cause pancreatitis in utero or early infancy, such as cystic fibrosis (CF) caused by 2 severe *CFTR* variants.[53,54] But in most cases, the pancreatitis-associated gene variants appear to increase susceptibility to AP and RAP, triggered by any number of milder etiologic factors, so that the phenotype emerges early or later in life. These observations illustrate the importance of the trypsin pathway in pancreatitis.

The prevalence of pancreatitis susceptibility gene variants in representative populations is well documented. For example, in a Danish study, *PRSS1*, *SPINK1*, and *CFTR* mutations were present in up to 50% of patients with idiopathic CP.[55] Likewise, an American study identified *PRSS1*, *SPINK1*, *CFTR*, and/or *CTRC* variants in 58% of idiopathic RAP patients.[56] The prevalence of genetic variants in children is even greater (below). Thus, genetic variants are among the most important risk, etiologic, and prognostic factors in pancreatitis susceptibility, severity, and outcomes.

Genetic testing is indicated for all younger patients with RAP in whom biliary etiologies have previously been addressed with cholecystectomy or sphincterotomy and who are not "very heavy" alcohol drinkers (eg, >5 drinks per day) or binge drinkers. The purposes of genetic testing within the overall risk assessment and management decision tree include (1) identifying simple and complex etiologies, thus limiting the need for further etiologic testing; (2) defining pathogenic pathways; (3) anticipating complications; (4) developing etiology-based management plans; and (5) providing information to patients about their disease cause and prognosis. Most of the experience comes from testing 3 or 4 genes,[56,57] but many more pancreatitis-associated genes are known,[20,58–64] and more extensive panels, linked with environmental and other modifying factors and integrated with management plans to help minimize organ damage and slow progression to CP, must be developed to realize the full potential of precision medicine.[20,65]

Several genetic syndromes may be discovered through genetic testing that require special attention and management. These include HP and CFTR-associated disorders.

Hereditary pancreatitis is an autosomal dominant disorder caused by gain-of-function variants in the *PRSS1* gene, typically p.N29I and p.R122H[6,7] (although other variants, including copy number variants, are also seen).[66] Heredity pancreatitis typically begins with AP and RAP beginning at a median of approximately 10 years of age, with a distribution of onset, and approximately 80% penetrance.[67–69] As the diagnosis of HP has implications for both the patient and family members, genetic counseling should be available.[70,71] Risk factors such as alcohol and smoking should be avoided, because they increase the risk of all types of pancreatitis and because smoking is known to increase the risk of pancreatic cancer.[72] Early estimates of the risk of pancreatic cancers in HP include a standardized incidence ratio of 53, with 95% confidence interval of 23 to 105.[73] Furthermore, the estimated cumulative risk

of pancreatic cancer in patients with HP begins to rise after age 50 years and by age 70 years approached 40%, an estimate based on only 2 pancreatic cancer patients out of 5 HP patients older than 70 years.[73] Similar estimates were generated from Europe,[68,74] but more recent estimates from the United States, where a much larger number of HP subjects are now past age 70 years and the rate of smoking is much less, suggest the cumulative risk of pancreatic cancer is much lower (D.C.W., unpublished observations, May 2017).[75] One of the increasingly performed but irreversible treatments for HP is total pancreatectomy with islet autotransplantation (TPIAT). Although this procedure is effective in relieving disabling RAP and severe pain,[76,77] TPIAT should not be performed solely for fear of pancreatic cancer risk.[78]

Cystic fibrosis is an autosomal recessive disease that affects the respiratory, gastrointestinal, and reproductive systems and the sweat glands of the skin because of mutations in *CFTR*. More than 2000 *CFTR* variants have been identified, and they are classified by their effect on the pancreas (severe, mild),[79] mechanisms (classes I–VI),[80] and more complex criteria.[81] In addition to classic CF, there are multiple *CFTR*-related disorders, including atypical CF (milder phenotype in fewer organs than classic CF), with common phenotypes of RAP and CP.[54] Furthermore, *CFTR* variants are common in pancreatitis-only disorders that are not autosomal recessive (ie, 2 *CFTR* variants), but rather complex with 1 identifiable *CFTR* variant plus a pathogenic *SPINK1*, *CTRC*, *CASR*, or other variants or risk factors,[51,82,83] including PD.[84] Finally, LaRusch et al[52] recently identified a new syndrome linked to 9 *CFTR* variants, previously thought to be benign, which disrupt bicarbonate conductance but not chloride conductance and increase the risk of RAP, CP, male infertility, and chronic sinusitis.

Clinically significant *CFTR* variants are relatively common in the United States, being present in carrier frequencies in whites of 1/27 and African Americans of 1/79 using a 69-mutation panel in more than 100,000 people.[85] All of the common variants can affect the pancreas, but these estimates exclude less common variants, including most bicarbonate conductance-defective variants. For patient management, the full genotype (both CFTR alleles and possible complex genotypes with other genes) needs to be determined. Patients may benefit from genetic counseling, family planning, and/or referral to a CF center for CF or atypical CF diagnosis. Other risk factors, such as smoking and alcohol use, must be eliminated. Furthermore, new therapeutic agents are on the horizon that may be CFTR genotype dependent.[86,87]

SPINK1 codes for an acute phase protein, pancreatic secretory trypsin inhibitor (PSTI). Expression of SPINK1 is normally very low, but markedly increases in the setting of inflammation.[88] Although the prevalence of *SPINK1* mutations in most populations is greater than 1%, they are thought to be of no consequence unless there is inappropriate trypsin activation above an unknown threshold.[20] Thus, it is not surprising that pathogenic *SPINK1* variants are associated with RAP but less common with an initial/sentinel AP attack.[89] *SPINK1* variants are also associated with familial pancreatitis as an autosomal recessive disorder, or in combination with *CFTR* or other factors.[90] There is currently no specific treatment for patients with RAP and pathogenic *SPINK1* variants, but this information has important prognostic implications. General advice of avoidance of smoking and alcohol and maintaining a healthy lifestyle applies.

RAP IN CHILDREN

Once considered a rare disease, pancreatitis has become increasingly recognized in childhood, occurring from infancy to adolescence.[9,91–100] Most children with pancreatitis have a single acute episode that resolves without any complications. A subset of children with AP develop recurrent episodes. Pediatric RAP is defined as 2 distinct episodes of AP along with complete resolution of pain (≥1-month pain-free interval between episodes) or complete normalization of serum amylase and lipase, before the subsequent episode is diagnosed, along with complete resolution of pain symptoms, irrespective of a specific time interval between episodes.[101] Children with RAP or CP endure multiple hospital admissions and emergency room visits, and miss substantial amounts of school. During hospitalization, they may require intensive care unit admissions, multiple imaging studies, laboratory tests, procedures, and surgeries. The disease has a major impact on families as parents must take time off from their work, and siblings often have long periods where one or both parents are not at home. Pediatric pancreatitis imposes substantial health care costs and disease burden to society; the burden is much higher in children with CP compared with those with RAP.[102]

In children with RAP and CP, genetic risk factors are most common.[95,98–100,103,104] In the large multicenter INSPPIRE (International Study Group of Pediatric Pancreatitis: In search for a cuRE) cohort, approximately 50% of children with RAP and approximately 75% of children with CP had at least 1 mutation in pancreatitis-related genes, including *SPINK1*, *PRSS1*, *CFTR*, or *CTRC*.[98] Moreover, carboxypeptidase 1 (*CPA1*),[62] *PRSS1*, or *CTRC* variants[105] were associated with early onset pancreatitis in the pediatric population. Environmental risk factors (ie, alcohol, smoking, hypercalcemia) are uncommon causes of pediatric RAP or CP.[98,100] Obstructive factors and specifically PD are commonly seen in children with pediatric RAP or CP, but it is not known whether they are sufficient to cause pancreatitis. Autoimmune pancreatitis is rare and has a distinct presentation in children with features similar to type 2 in adults.[106] The pediatric guidelines for causal evaluation of RAP and CP have recently been published by the INSPPIRE group.[107]

MICROLITHIASIS: CAUSE AND ASSOCIATION

Microliths are small gallstones measuring less than 3 mm. A cutoff of 3 mm has been taken because abdominal ultrasound can detect stones of greater than 3 mm. They are predominantly composed of cholesterol. Microlithiasis and sludge are often used interchangeably. Sludge may regress spontaneously, but microlithiasis does not. Studies have shown that in patients with suspected microlithiasis there are often detectable gallstones on follow-up ultrasound.[108,109] Prevalence rates of microlithiasis as a cause for RAP have varied across studies.[27,108–110] A few studies have shown a high prevalence of microlithiasis (50%–73%) as the cause of IRAP.[108,109] On the other hand, many studies have shown a low prevalence of microlithiasis ranging from 6% to 16%.[27,111] In a prospective long-term follow-up study of 75 patients with IRAP, only 10 (13%) had microlithiasis, and 35 patients (47%) developed CP during the follow-up.[111] This variability was seen due to inconsistency, heterogeneity, short follow-up, and causality not well established in most studies.

Microlithiasis can be detected by either bile crystal analysis or by EUS. Bile microscopy has 65% to 95% sensitivity for detecting biliary crystals.[112] However, an important caveat is that bile microscopy detects biliary crystals and not microliths and is an indirect indicator of the presence of microliths. Microliths are best diagnosed on EUS, with a sensitivity of 96%.[113] Microliths may lead to pancreatitis by causing transient obstruction at the ampulla of Vater. Just as in gallstone pancreatitis, microliths should be suspected as the cause in the presence of abnormal liver function tests (LFT) within 24 to 48 hours of the onset of AP. If a biliary etiology is suspected, patients should undergo cholecystectomy if suitable, or ERCP with biliary sphincterotomy if not, to

prevent recurrent attacks.[114] If the gallbladder appears normal on EUS and liver chemistries are repeatedly within normal limits, empiric cholecystectomy can be avoided.

MEDICATIONS AND RAP

Although medications are commonly thought to cause pancreatitis, it is difficult to prove a causal association. Test-retest hypothesis is not applicable to drug-induced RAP. Although several drugs have been implicated as a cause of pancreatitis, most of the literature is limited to case reports or small case series. The latency period for drugs to cause pancreatitis when an individual is rechallenged with the same drug is also variable. Based on a recent systematic review of the literature and classification, only a few drugs have reliably caused recurrence of pancreatitis when other common etiological factors are ruled out. At this time, it is still recommended to rule out other common etiologies prior to labeling drugs as an etiological factor.[115]

AUTOIMMUNE PANCREATITIS AND RAP

Autoimmune pancreatitis (AIP) represents a combination of type 1 and type 2 disease. Type 1 includes pancreatic involvement by multisystem immunoglobulin G4 (IgG4) related disease, but usually presents as jaundice or a mass in older individuals and rarely causes acute pancreatitis. Type 2 AIP is often referred to as idiopathic duct centric pancreatitis, and more often presents as acute or recurrent acute pancreatitis especially in younger patients, and may be associated with inflammatory bowel disease. Type 2 AIP should be considered in the differential of recurrent acute pancreatitis.[116]

Pancreatic Ductal Outflow Obstruction: Cause or Effect (Pancreas Divisum and Sphincter of Oddi Dysfunction)

Potentially obstructive etiologies for RAP due to PD and even more to sphincter of Oddi dysfunction (SOD) have been subjects of significant controversy. In a large American cohort (NAPS2) including several thousands of patients with RAP or CP, PD was still considered as a potential cause per se.[117] The concept is that the minor papilla orifice is sometimes not sufficient to drain the majority of the pancreatic exocrine secretion, and thereby causes outflow obstruction to pancreatic outflow leading to upstream activation of pancreatic enzymes and pancreatitis.[118] The main argument for a causal relationship is presence of a dilated dorsal duct, evidence of CP localized only to the dorsal pancreas, and a putative increased frequency of PD in patients with idiopathic pancreatitis. Further evidence is case series reporting apparent efficacy of minor papillotomy in reducing or eliminating further attacks of pancreatitis.

Pancreas divisum is a common congenital anomaly of the pancreas which is present in 2.7%–22% (typically 7%) of Western populations; it is less common in Asians.[119,120] Pancreas divisum has been associated with RAP and CP, but why a few patients are affected, while the majority is spared, is unknown.[121,122] An older retrospective series found no correlation between PD and RAP.[123] A recent cross-sectional study using MRCP showed that pancreas divisum is not more common in patients with RAP than in controls, but that there is an increased prevalence of genetic abnormalities in patients with both PD and RAP - suggesting that PD is a cofactor rather than a cause per se.[124] Several studies have suggested that a heterozygous defect in the *CFTR* gene may predispose patients with PD to RAP.[84,124,125] Surgical series involving minor papilla sphincteroplasty or papillotomy have reported reduction in episodes of pancreatitis in more than 50% of patients followed for at least 2 years. These studies have been uncontrolled, and hence, do not provide robust evidence.[126] Current data suggest that endoscopic treatment might be beneficial in patients with relapsing acute pancreatitis.[127,128] Results of endoscopic series are no more convincing because they rely on uncontrolled retrospective series or databases, and do not report genetic status.[129,130] The pooled results of 16 studies evaluating endoscopic therapy success in the treatment of PD with RAP are shown in Table 1.[127,131–142] A total of 261 patients included in the studies were treated with minor papilla stenting or sphincterotomy, and 203 of them were considered treatment success, although definition of endpoints varied, and none included qualilty of life measures. Pancreas divisum associated with obvious CP or pain alone had lower treatment response rates from endoscopic therapy at 51.3% and 44.4%, respectively; such data are limited by confounding chronic pain with morphologic CP, which often do not correlate. A recent multicenter pilot study

TABLE 1. Endoscopic Therapy for PD Associated With RAP*

Reference	Patients	Follow-up, mo	Response, n (%)
Satterfield et al,[131] 1988	10	18	6 (60)
McCarthy et al,[132] 1988	19	14	17 (90)
Lans et al,†[133] 1992	10	28	10 (100)
Lehman et al,[134] 1993	17	20	13 (77)
Coleman et al,[135] 1994	9	23	7 (78)
Kozarek et al,[136] 1995	15	20	15 (100)
Jacob et al,[137] 1999	10	15	6 (60)
Ertan,[138] 2000	24	24	19 (79)
Heyries et al,[139] 2002	24	39	20 (83)
Kwan et al,[140] 2008	21	38	13 (62)
Borak et al,[127] 2009	62	44	44 (71)
Rustagi et al,[141] 2013	18	NA	17 (94)
Mariani et al,[142] 2014	22	60	16 (73.7)
Overall	261	16–60	203 (78)

*Retrospective, uncontrolled studies of efficacy of minor papilla therapy (papillotomy and/or stenting) for patients with recurrent acute pancreatitis.

†With exception of single prospective randomized controlled trial.

Definition of endpoints and outcome measures varied widely.

NA indicates not available.

(FRAMES) that evaluated the recurrence of AP after minor papilla sphincterotomy and temporary small-caliber stenting demonstrated substantially lower recurrence over 6 months following ERCP.[143] However, since none of the series includes an untreated control group, evidence for efficacy of any kind of minor papilla intervention in preventing recurrence of acute pancreatitis remains weak. A multicenter prospective, randomized and sham controlled trial is currently underway (Cote G, and Yadav D, personal communication).

SPHINCTER OF ODDI DYSFUNCTION

In patients with RAP, several studies have documented a high (30%–65%) prevalence of SOD, defined by sphincter of Oddi manometry as an elevation in basal biliary, pancreatic, or both sphincter pressures.[144–148] Among individuals with choledocholithiasis, those having concomitant RAP were found to have significantly higher basal sphincter pressure, along with higher gradients between the common bile duct and duodenum.[149] suggesting a possible role for SOD in causing pancreatitis.

While SOD may be associated with RAP, it remains unclear whether SOD represents an underlying cause, or is the result of a fibroinflammatory reaction in and around the papilla leading to stenosis. In a series of surgical sphincteroplasties primarily performed for SOD and without prior endoscopic therapy, "inflammation" and "fibrosis" were observed in 29% and 10% of ampullary biopsies, respectively; biopsies from the transampullary septum identified inflammation in 15% and fibrosis in 27% of all cases.[150] The "consequence" theory is further supported by observations that SOD occurs in the setting of CP[151] and that individuals with RAP and SOD have a more severe phenotype compared with those with RAP and normal sphincter manometry. Similar to PD, evidence for efficacy of endoscopic biliary plus minus pancreatic sphincterotomy in reducing or eliminating recurrent attacks of pancreatitis remains largely retrospective, uncontrolled, and with mixed endpoints.[152]

ROLE OF ENDOSCOPIC ULTRASOUND IN DIAGNOSIS AND MANAGEMENT OF RAP

Endoscopic ultrasound is a relatively accurate and safe diagnostic tool for the evaluation of unexplained pancreatitis and should be considered as a first-line examination in such patients.[153] Endoscopic ultrasound has been shown to be accurate in identifying microlithiasis or gallstones when standard imaging is negative.[154] Endoscopic ultrasound has been documented to have a sensitivity of 96% for diagnosing microlithiasis and has a negative predictive value of 95.4% for diagnosing common bile duct stones.[155] Endoscopic ultrasound is more accurate in diagnosing choledocholithiasis and especially small stones, than MRCP. A recent systematic review showed that the mean sensitivity of EUS and MRCP for detection of choledocholithiasis was 93.7 and 83.5, respectively; the specificity was 88.5 and 91.5, respectively.[156]

The yield of EUS in finding the putative etiology of pancreatitis is similar for patients with first attacks and those with repeated attacks.[156] Apart from EUS being the most sensitive test for gallbladder stones, it is highly accurate for the identification of PD, pancreatic intraductal papillary mucinous neoplasms, and small pancreatic and ampullary masses when performed by experienced operators. Endoscopic ultrasound is more sensitive in detecting smaller pancreatic tumors (<2 cm) compared with multi–detector-row computed tomography.[158–160] The frequency of the diagnosis of CP in patients with RAP on the basis of EUS criteria ranges from 10% to 30% but the accuracy of EUS for diagnosis of noncalcific chronic pancreatitis is questionable.[144,157,159] Because of the relatively high yield and low risks associated with the procedure, EUS should be considered as a part of the initial evaluation of RAP.

ROLE OF MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY IN RAP

Magnetic resonance cholangiopancreatography is a noninvasive test that permits evaluation of the parenchyma with T1- and T2-weighted images and allows 3-dimensional reconstruction of the modality to evaluate the biliary and pancreatic ductal anatomy. MRCP is complementary to EUS in the evaluation of RAP.[161] Administration of intravenous secretin in conjunction with magnetic resonance cholangiopancreatography (S-MRCP) allows the best noninvasive imaging technique for diagnosing congenital anomalies such as PD and choledoceles.[162]

Magnetic resonance cholangiopancreatography with secretin test permits indirect evaluation of sphincter of Oddi motility, as an alternative to more invasive tests such as sphincter of Oddi manometry.[163] Apart from ductal anatomy, MRI can also identify parenchymal abnormalities including cystic lesions and may be the best available test to diagnose non-calcific chronic pancreatitis.[164,4] Magnetic resonance cholangiopancreatography should be considered a key component in the evaluation of RAP.[164]

ERCP AND RAP: EMBRACE OR ABANDON?

In clinical practice, there is concern for indiscriminate and repeated use of ERCP with sphincterotomy and pancreatic stenting for patients with abdominal pain, PD, and pancreatitis. To a large extent, this practice stems from the notion that SOD and PD are established causes of not only RAP but also for functional abdominal pain. The distinction between functional abdominal pain and pancreatitis has been blurred in practice, and they are treated the same way partly because of the lack of standard definitions. The 30% to 40% placebo response due to sphincterotomies in patients with functional abdominal pain may be a reason to continue repeated sphincterotomies on these patients despite the return of symptoms. Although widely performed in the past, sphincter of Oddi manometry at ERCP has not been validated as a predictor of outcomes in SOD or RAP.[145] Manometrically, SOD is defined as basal biliary or pancreatic sphincter pressures greater than 40 mm Hg, which is greater than 3 standard deviations above normal.[165] In patients with well-documented RAP, in whom thorough evaluation has not demonstrated a cause, abnormal manometry is found in 15% to 72%. Sphincter of Oddi dysfunction has been classified under 3 subtypes on the basis of clinical and morphological parameters and manometric findings.[166] Based on the recent EPISOD study,[167] SOD type III does not exist as true pancreatobiliary disease, as it does not respond to biliary plus minus pancreatic sphincterotomy; as such these patients should be categorized as having functional abdominal pain,[168] rather than true pancreatobiliary disease. Unfortunately, abnormal findings on sphincter of Oddi manometry of biliary and/pancreatic sphincters do not necessarily predict consistent relief of symptoms from biliary and/or pancreatic sphincterotomy. As a result whether SOD causes RAP is very controversial. In one study, more than 80% of 5352 patients with upper abdominal pain had "abnormal" sphincter pressures, and of those with normal pressures, 60% had an abnormal reading on a repeat procedure.[169] These data suggest that abnormal sphincter of Oddi manometry may represent an epiphenomenon rather than a disease responsive to anatomic intervention.

Endoscopic retrograde cholangiopancreatography solely for the purpose of ductography in patients with PD should be avoided, and alternate imaging techniques should be used instead to establish the anatomy. Abdominal pain alone should not be an indication for minor papillotomy in PD. Minor papillotomy for patients with PD and RAP is controversial. As with all pancreatic sphincterotomies, minor papillotomy has high rates of post-ERCP pancreatitis, and of restenosis, occurring in 20% to 30% of patients, and leading to

a repetitive cycle of interventions to address an iatrogenic injury resulting from a procedure with unproven benefit.[170]

Endoscopic retrograde cholangiopancreatography has a definite role in RAP with anomalous pancreatobiliary junction, ampullary neoplasms, and choledochal cyst (especially type 3).[17,171,172]

Does Biliary and Pancreatic Sphincterotomy Impact the Natural History of RAP?

The role of biliary sphincterotomy in the setting of biliary pancreatitis is well defined; however, the benefit of empiric biliary sphincterotomy for RAP is unproven.[152]

Given the high prevalence of manometrically defined SOD in RAP, some endoscopists and surgeons have advocated for the therapeutic role of pancreatic sphincteroplasty or endoscopic pancreatic sphincterotomy for the treatment of RAP. Until recently, studies evaluating the therapeutic role of sphincterotomy or sphincteroplasty in the management of RAP have been hampered by variable definitions, limited duration of follow-up, and limited evaluation of outcomes including quality of life.[27,110,144,173–175] A randomized clinical trial of patients with RAP and pancreatic SOD compared biliary sphincterotomy (n = 33) with dual (biliary + pancreatic) sphincterotomy (n = 36).[152] The incidence of AP during follow-up was nearly identical between 2 groups, and there was a trend to higher recurrence rates during the first year of follow-up in patients randomized to dual sphincterotomies. Patients with pancreatic SOD, irrespective of their treatment allocation, had a 4-fold higher rate of AP during follow-up compared with individuals with normal pancreatic manometry. The majority of individuals who underwent a second ERCP during follow-up after at least 1 additional episode of AP had recurrent or persistent pancreatic SOD. This suggests that pancreatic sphincterotomy may have been inadequate in normalizing pancreatic sphincter pressures, or there are high rates of sphincter restenosis, or that SOD is an epiphenomenon that is not causal in RAP. Even in a surgical series that included measurement of sphincter of Oddi pressure following sphincteroplasty, basal pancreatic pressures decreased in 82% of patients but were not eliminated; basal pancreatic pressure decreased from 55 mm Hg to 26 mm Hg, whereas biliary/ampullary pressure decreased from 31 mm Hg to 0 mm Hg.[150] Data also suggest that there is poor response of pain to endoscopic treatment in patients with pathogenic *SPINK1* mutations.[176]

MEDICAL MANAGEMENT OF RAP

A number of medical therapies are effective for specific etiologies of relapsing pancreatitis. Abstinence from tobacco and alcohol has a substantial beneficial effect on patients with pancreatitis because of these toxins, reducing the progression of disease, reducing pain, and preventing both pancreatic and extrapancreatic complications. Similarly, the use of steroids and immunosupressants in patients with AIP and the control of serum triglyceride levels in those with hyperlipidemic pancreatitis can prevent relapses. The data on medical therapy for idiopathic pancreatitis are much less convincing. Several therapies have been assessed in these patients, including antioxidant supplementations, octreotide, ursodeoxycholic acid, and pancreatic enzymes.

Ursodeoxycholic acid has been studied in patients with presumed microlithiasis. Whether these patients can truly be classified as "idiopathic" is open to debate. Three studies have assessed the effectiveness of oral ursodeoxycholic acid in preventing relapse.[108,177,178] One study included 34 patients who were treated with ursodeoxycholic acid alone. Relapses occurred in 38% over approximately 1 year of follow-up, and many of these patients were subsequently found to have macroscopic gallstones.[177]

Octreotide has been studied as an agent to reduce the severity of AP, to prevent post-ERCP pancreatitis, to prevent postoperative pancreatic fistulas, and to reduce the pain of CP. Its effect on these outcomes is variable, but no data exist on preventing episodes of relapsing pancreatitis.

Pancreatic enzyme therapy has been studied both as a treatment for chronic pancreatic pain and as a therapy to prevent painful relapses in both AP and CP. Two small retrospective studies (abstract form only) assessed the role of enzymes in RAP. In 1 study, 29 patients with at least 3 episodes of AP but without imaging or functional features of CP were treated with pancreatic enzymes (mainly uncoated tablets) for a mean of 2.5 years (range, 1–10). Follow-up was obtained by telephone survey. One third of patients had no further attacks after starting enzymes, whereas 65% reported a decrease of at least 50% in the expected rate of their attacks. A second retrospective analysis in 22 patients with both AP and CP treated with conventional enzymes noted a reduction in number of attacks of more than 50% in 59% of patients, but the degree of reduction was much greater in the group with AP compared with CP. The retrospective nature and small numbers of patients make these studies less than convincing.

Antioxidants have primarily been studied in patients with CP. One very small older study[179] included 5 patients with RAP and noted 1 attack of pancreatitis while on placebo and none on antioxidants.

Of these therapies, only antioxidants have been studied in a randomized controlled trial in patients with CP, but not in RAP. These data do not provide support for the clinical use of antioxidants to prevent relapse. Despite the lack of supporting data, these agents are used in clinical practice, perhaps justified by the overlap between RAP, chronic pancreatitis, with associated chronic pain and exocrine pancreatic insufficiency.

In summary, high-quality or convincing data supporting the use of medical therapy for RAP are lacking. The data are strongest for the use of antioxidants and pancreatic enzymes, and the use of these relatively safe agents may be considered.

QUALITY OF LIFE IN RAP

Quality of life is impaired in patients with recurrent pancreatitis. Data suggest that patients followed over 14 months after AP had significantly impaired physical health–related quality of life.[180] In that study, etiology, severity, and endoscopic intervention did not affect health-related quality of life. Data from NAPS2 have shown that the quality of life is impaired in patients with CP. The NAPS2 cohort with RAP showed that quality of life was lower than in controls, but higher than in those with CP. Constant pain and pain-related disability seem to adversely affect the quality of life.[181] There are no validated tools to measure quality of life in RAP, and the natural history of pain and pain-related disability are variable. Data from the pediatric population show that quality of life is significantly impaired (see RAP IN CHILDREN). Total pancreatectomy with islet cell autotransplantation has been shown to improve quality of life in patients with RAP, although TPIAT has not become a widely accepted treatment for RAP.[182] Disease-specific quality-of-life instruments are needed to study the impact of RAP on quality of life.

PROBLEMS WITH CURRENT DATA AND NEED FOR RESEARCH

- Lack of randomized controlled trials and long term follow-up
- Effects of variables and cointerventions on outcomes

- Interplay between multiple potential etiologies such as genetics and environmental factors
-Validated and standardized outcome measures

It is not clear that correction of structural factors without altering genetics/environmental factors will alter outcomes. Interventions such as ERCP are prone to causing post-ERCP pancreatitis and ductal and parenchymal injuries from stents. Recurrences may result from natural history or interventions, and at variable times after initial investigation.[16] Focus should now shift towards well-designed randomized controlled studies including recurrences and frequencies of attacks and quality of life, pain between attacks, and progression to chronic pancreatitis.

SUMMARY OF RECOMMENDATIONS

Definitions:

(1) **Acute pancreatitis** is defined as a clinical syndrome of an episode of acute inflammation originating in the pancreas diagnosed according to the Revised Atlanta Criteria.[14]
(2) **Recurrent acute pancreatitis** is defined as a syndrome of multiple distinct acute inflammatory responses originating from the pancreas in individuals with 2 or more episodes of documented AP, separated by at least 3 months.
(3) **Chronic pancreatitis** is defined using a 2-part mechanistic definition.[18] CP is defined as "a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress"; "common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia."
(4)The diagnosis of CP does not preclude the later diagnosis of AP or RAP.

(A) **Identification of Patients with IRAP**
(1) The diagnosis of acute pancreatitis is based on 2 of the 3 following criteria: (*a*) clinical (upper abdominal pain), (*b*) laboratory (serum amylase or lipase ≥3 times upper limit of normal), and/or (*c*) imaging suggestive of inflammation (CT scan, MRI, ultrasonography). Idiopathic recurrent acute pancreatitis is defined as RAP after exclusion of readily apparent causes by history, routine laboratory tests, and conventional imaging, not necessarily including EUS, MRCP, ERCP with or without manometry, or genetic testing (grade 1B, 75% probably or definitely agree with the definition).
(B) **Etiology of RAP**
(2) More than one potential etiology of RAP may be detected in the same patient (ie, gallstones, hyperlipidemia, alcohol, PD, gene mutations), consistent with a "multihit" hypothesis (grade 2B, >60% probably or definitely agree with multihit hypothesis).
(3) Although uncommon, there should be a high index of suspicion for medications as a cause of RAP (grade 1B, >50% probably or definitely agree).
(4) Pancreas divisum is not a clearly established etiology of RAP (grade 1B, 75% probably or definitely agree).
(5) Genetic mutations/polymorphisms play a significant cofactor role in causing pancreatitis in patients with PD (grade 2B, 60% probably or definitely agree).
(6) Etiologies of RAP in children are different than those in adults (grade 2B, 70% probably or definitely agree).
(7) Evaluation for RAP should include careful assessment of unusual causes of RAP including ampullary neoplasms, anatomic variants such as type III choledochal cyst, and anomalous pancreaticobiliary junction (grade 2C, 82% probably or definitely agree).
(C) **RAP as a Continuum for CP**
(8) The pathway for acinar cell injury in RAP is different than that of an isolated episode of AP (grade 2C, <30% probably or definitely agree).
(9) A significant number of patients with RAP progress to clinical and morphological evidence of CP over time (grade 1A, >75% probably or definitely agree).
(10) There is often poor correlation between clinical symptoms (i.e., pain or RAP) and morphologic evidence of CP (grade 1B, >80% probably or definitely agree).
(D) **RAP and Genetics**
(11) RAP is likely to be multifactorial syndrome with interaction of genetic, anatomic, and environmental factors (grade 1A, 90% probably or definitely agree).
(12) Genetic testing (mutations in *CFTR, SPINK1, PRSS1, CTRC*, and other genes) is indicated in most younger (<35 years old) patients with RAP (grade 2B, 70% probably or definitely agree).
(E) **EUS in IRAP**
(13) Endoscopic ultrasound is the most sensitive test for occult gallstones or microlithiasis (grade 2B, 80% probably or definitely agree).
(14) Endoscopic ultrasound is the most sensitive test for small or occult tumors associated with RAP (grade 1B, 80% probably or definitely agree).
(15) After conventional imaging (CT, ultrasound), EUS should be a first line test in evaluating patients with RAP (grade 1B, 60% probably or definitely agree).
(F) **Cross-sectional Imaging**
(16) Contrast-enhanced CT is the first-line cross-sectional imaging test evaluation of RAP (grade 1B, >60% probably or definitely agree).
(17) Magnetic resonance imaging/MRCP is the most accurate cross-sectional imaging test in detecting pancreatic ductal abnormalities that may contribute to or result from RAP (grade 1A, >90% probably or definitely agree).
(18) Addition of secretin stimulation to MRI/MRCP significantly enhances the diagnostic yield of intraductal abnormalities that might contribute to or result from RAP (grade 2C, >50% probably or definitely agree).
(G) **RAP and PD**
(19) Endoscopic minor papillotomy is a reasonable option for patients with RAP and PD without interval symptoms or evidence of CP (grade 2C, <50% probably or definitely agree).
(20) Endoscopic minor papillotomy is a reasonable option for patients with RAP and PD and who also have chronic pain and/or evident CP (grade 2C, approximately 30% probably or definitely agree).
(21) Genetic testing should routinely be performed in patients with PD and RAP (grade 2C, <50% probably or definitely agree).
(H) **AIP and RAP**
(22) Autoimmune pancreatitis is a rare (<5%) cause of IRAP (grade 1A, >90% probably or definitely agree).
(23) Type II AIP (idiopathic duct centric pancreatitis) is significantly more likely to present with RAP than the classic type 1 (IgG4 related) AIP (grade 2B, >60% probably or definitely agree).
(24) Routine serological testing for IgG4 should not be done in patients with RAP in the absence of imaging features suggestive of AIP (grade 1B, >60% probably or definitely agree).
(25) Empiric trials of steroids should not be done for IRAP in the absence of compelling evidence of AIP (grade 1B, >90% probably or definitely agree).
(I) **Microlithiasis and IRAP**

(26) Microlithiasis is a potential cause for IRAP (grade 1A, 80% probably or definitely agree).
(27) Microlithiasis is an uncommon cause of IRAP (grade 1B, approximately 50% probably or definitely agree).
(28) Bile crystal analysis is not an accurate test of microlithiasis as a cause for IRAP (grade 1B, >60% probably or definitely agree).
(29) Cholecystectomy is a reasonable option in patients with IRAP who have transiently abnormal LFTs within 1 to 2 days after an attack of pancreatitis and no other etiology on advanced imaging (grade 2C, >60% probably or definitely agree).
(30) Empiric cholecystectomy is not advised in patients with no evidence of gallbladder disease by either EUS or other imaging and who have normal LFTs (grade 1C, >80% probably or definitely agree).

(J) **SOD and RAP**

(31) In patients with RAP and absence of any morphologic abnormalities, ERCP with sphincter of Oddi manometry and biliary plus minus pancreatic sphincterotomy is a reasonable option (grade 2C, <40% probably or definitely agree).
(32) Pancreatic sphincterotomy provides no added benefit to biliary sphincterotomy in prevention of RAP in patients with abnormal pancreatic sphincter manometry and should not be performed (grade 2B, >70% probably or definitely agree).
(33) Empiric biliary sphincterotomy is not advised in patients with RAP (grade 1C, >70% probably or definitely agree).

(K) **Therapy in RAP**

(34) If performed for RAP, ERCP should be done at specialized centers by physicians with advanced expertise in pancreatic ERCP. Patients with RAP are at a high risk of complications, especially post-ERCP pancreatitis. As such, endoscopists must consistently be able to place protective small-caliber pancreatic stents in small or tortuous pancreatic ducts and/or in the minor papilla to reduce risks associated with ERCP (grade 1A, >80% probably or definitely agree).
(33) There is a role for endoscopic therapy for unusual causes of RAP including ampullary neoplasms, anatomic variants such as type III choledochal cyst, and anomalous pancreatobiliary junction (grade 2C, >70% probably or definitely agree).
(35) There is no proven role for medical therapy in RAP (grade 1B, >60% probably or definitely agree).
(36) A substantial portion of patients with RAP have chronic pain and disability including impaired emotional and social functioning between overt attacks of AP (grade 1B, >70% probably or definitely agree).
(37) Endoscopic interventions help patients with RAP and slow progression of disease (grade 2C, approximately 20% probably or definitely agree).
(38) Total pancreatectomy with islet autotransplantation may be a viable option for patients with RAP who evolve to intractable disabling pain between episodes of overt pancreatitis, with or without overt evidence of CP (grade 2C, <25% probably or definitely agree).

SUMMARY

The current guidelines on management of RAP are the result of an international, multidisciplinary, and evidence-based approach. These guidelines provide recommendations to key aspects of medical, endoscopic, radiological, and surgical evaluation and management of RAP combined with remarks based on the available literature and the opinion of leading international experts from multiple disciplines. The consensus paper highlights the lack of universally accepted definitions and the need for well-controlled studies that take into consideration the multifactorial nature of the disease, quality of life measures, and refines the instruments used for measurement of outcomes. The consensus members agreed that there is an urgent need for study of RAP especially in the following areas:

- a randomized controlled trial of sham versus minor papillotomy for RAP with PD (just such a multicenter study has been funded by the NIDDK and is expected to start enrolling in 2018, Cote G and Yadav D, personal communication);
- a randomized controlled trial of sham versus biliary/pancreatic sphincterotomy for SOD;
- a prospective observational study of cholecystectomy for IRAP;
- the association of genetic abnormalities with or without anatomic anomalies in IRAP;
- the role of cofactors in IRAP;
- prospective observational cohort studies in broad populations with RAP evaluating the natural course and progression to CP; including both the clinical course and morphological changes over time;
- the role of oxidative stress in RAP;
- and the prevalence of occult of intraductal papillary mucinous neoplasia in patients with IRAP.

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