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REVIEW ARTICLE

Endoscopic Ultrasound for Routine Assessment in Idiopathic Acute Pancreatitis

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Abstract

Background Acute pancreatitis (AP) is one of the most common general acute surgical presentations. Current recommendations are that idiopathic acute pancreatitis (IAP) should account for no more than 20% of AP cases. Some studies suggest gallbladder microlithiasis is the aetiology in up to 75% of IAP patients. Endoscopic ultrasound (EUS) has been reported to be effective in the detection of microlithiasis and choledocholithiasis as well as pancreatic parenchymal, ductal and ampullary disorders. The aims of this study were to evaluate the usefulness of EUS in establishing aetiology in IAP patients and to assess if there is a role for EUS in the selection criteria for laparoscopic cholecystectomy to treat a potential biliary cause in IAP patients.

Methods A systematic review following PRISMA guideline was performed to gather data on patients with IAP undergoing EUS for further investigation. Three databases (MEDLINE, PubMed, and EMBASE) were searched to 28 July 2018.

Results Our systematic review included 28 studies, comprising 1850 patients with an initial diagnosis of IAP prior to having EUS. Diagnosis of a potential aetiology or associated pancreatic pathology was established in 1095 (62%, $p < 0.001$) of cases. A biliary aetiology (microlithiasis or choledocholithiasis) was found in 37%. Chronic pancreatitis and associated pancreatic findings (dilated pancreatic duct, pancreatic duct stricture or stone) were found in 21%. Pancreatic neoplasms were found in 6%. Of the patients who had identifiable biliary pathology on EUS that proceeded to cholecystectomy, 2% had a recurrence of AP during a mean follow-up period of 20.5 months.

Conclusions There is a likely role for the routine use of EUS in the assessment of patients with IAP. The routine use of EUS may decrease the proportion of cases with a diagnosis of IAP. EUS may provide better selection criteria for laparoscopic cholecystectomy in patients with an initial diagnosis of IAP.

Keywords Endoscopic ultrasound · EUS · Idiopathic pancreatitis

Introduction

Acute pancreatitis (AP) is one of the most common acute general surgical presentations requiring hospital admission.[1–4] Worldwide, the incidence of AP varies between 4.9 and 73.4 cases per 100,000 and is noted to be increasing.[1,3,4] This is particularly concerning given AP is associated with significant morbidity and mortality as well as the financial burden of AP treatment.[5,6]

The diagnosis of AP requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis; (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on contrast-enhanced

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computed tomography, magnetic resonance imaging (MRI) or transabdominal ultrasonography (US).[1,2,7]

Once the diagnosis is established, early management is guided by severity assessment, identification of the aetiology and early interventions for specific indications.[1,2] The two most common causes of AP are gallstones (40–70%) followed by alcohol (25–35%).[1,2,8,9] Worldwide, the cause of AP differs according to the area studied and is primarily influenced by regional variation in alcohol consumption.[9–13] The aetiology of AP should be determined by a thorough history (personal and family) and systematic investigation (laboratory and imaging) on admission. It is generally accepted that after careful assessment, where no aetiology can be determined, the cause is defined as idiopathic acute pancreatitis (IAP).[1,2,8,14] The reported incidence of IAP varies from 8 to 27%.[5,8,10,12,15] Current recommendations state that IAP should account for no more than 20% of AP cases in a given population.[1,2,16]

The presence of microlithiasis as a likely cause of IAP has been known since the 1980s.[17–20] Some studies suggest that gallbladder microlithiasis or sludge is the aetiology in up to 75% of patients with IAP.[17,21] The possibility of undetected microlithiasis has led some groups to offer either endoscopic retrograde cholangiopancreatography (ERCP) (± endoscopic sphincterotomy) or empiric laparoscopic cholecystectomy (LC) for all patients with IAP despite no clear demonstration of a biliary aetiology.[21–25] This is a practical solution reducing the risk of recurrent episodes of AP in those that do have a biliary aetiology. In addition to detecting occult microlithiasis, endoscopic ultrasonography (EUS) can be used to assess for pancreatic neoplasms, chronic pancreatitis and other pancreatic parenchymal, ductal and ampullary disorders that may be contributing to the IAP.[2] The recent IAP/APA guidelines recommend patients considered to have IAP should have EUS. This was a grade 2 recommendation with only weak agreement[2], whereas the ACG guidelines did not recommend the use of EUS in IAP.[1]

The aim of this study was to evaluate the evidence for the use of routine EUS in patients with IAP.

Methods

Data Sources and Searches

A search to identify patients with a presumed diagnosis of IAP having EUS after the initial or recurrent episodes of IAP was performed. This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[26] Studies were identified by searching three electronic databases (MEDLINE from 1946, PubMed from 1946, and EMBASE from 1949) to 28 July 2018, performing a Google Scholar search and scanning reference lists of articles. Keywords used in the search were Endoscopic Ultras*, EUS, Echo-endoscopy, Echo Endoscopy, Idiopathic, Agnogenic, Cryptogenic, Primary, Spontaneous, Pancreatitis, Pancreatic Inflammation, IRAP. Inclusion criteria included case series and studies after either a single or recurrent episode of IAP reporting the results of EUS. Exclusion criteria included pathology found on routine transabdominal ultrasound, no clear definition of IAP, the uncertainty of the specific EUS imaging to establish the diagnosis, studies in children, intraductal ultrasound and EUS to evaluate known chronic pancreatitis. Where studies from the same centre had data collection periods that overlapped, only the most recent study was included.

Data Extraction

Two reviewers (RP and GE) screened independently the titles identified by the literature search, extracted the data and analysed the results. Studies included full manuscripts and published abstracts. Data extracted included the year of publication, country of origin, sample size, mean age, gender distribution, initial AP episodes, recurrent AP episodes, preceding imaging, pathology identified by EUS and negative EUS results. Additionally, in patients who underwent cholecystectomy after EUS, AP recurrence and follow-up duration were recorded. Data was collected in a standard excel spreadsheet.

Data Synthesis and Analysis

From the data obtained, a mean event rate and confidence interval were obtained for the various aetiologies identified by EUS. Mean event rate and confidence interval for gender distribution, initial AP episode, recurrent AP episode, preceding imaging, total positive EUS, total negative EUS, cholecystectomy, post cholecystectomy AP and follow-up duration were also calculated. Statistical analysis was conducted using Comprehensive Meta-Analysis software (version 2.2.057), Biostat Inc., Englewood, NJ. Heterogeneity was tested using I^2 statistics and p values produced from Cochran's Q test.

Results

The initial search for EUS data identified 1486 papers. After studies were reviewed and excluded, there were 28 studies, compromising 1850 patients having an EUS to assess for possible causes of IAP (Fig. 1, Table 1).[21,27–45,47–53] Gender distribution was reported in 17 (58.6%) studies with 49% male (Table 1).

The number of AP attacks before EUS was performed was reported for 1002 patients (54.2%) by 12 studies (Table 1). In this group of cases, EUS was performed after the initial episode in 53% ($n = 518$) of patients and after a recurrent episode (2 or more episodes) in 47% ($n = 484$) of patients (Table 1).

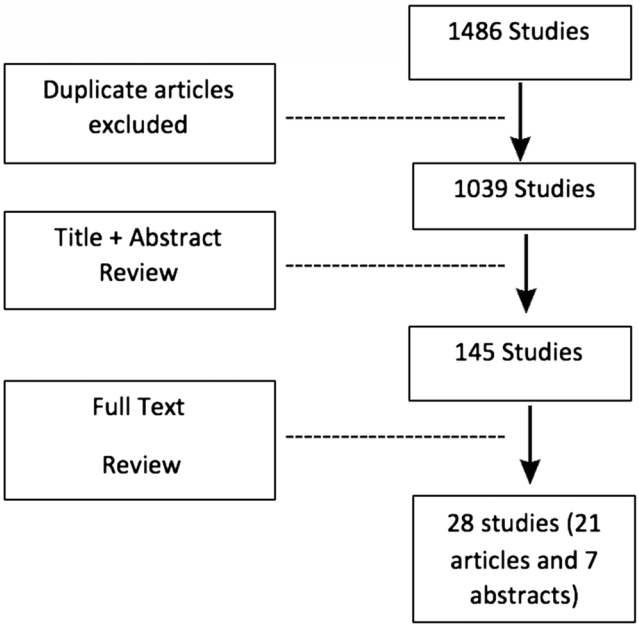

Fig. 1 PRISMA flow diagram showing the systematic search results

The majority of the studies ($n = 27$) had performed a transabdominal US prior to the EUS. These were normal in all 1565 (84.6%) patients studied. A CT abdomen preceding EUS was performed in 697 patients (37.7%) in 16 studies. No abnormal CT findings pertaining to AP aetiology could be identified in any of these patients. Magnetic resonance cholangiopancreatography (MRCP) preceding EUS was performed in only 262 patients (14.2%) in six studies. No abnormal MRCP findings pertaining to AP aetiology could be identified in these patients.

A potential AP aetiology or associated pancreatic pathology was established at EUS in 1095 (62%) patients (CI = 0.56–0.68, $p < 0.001$) (Table 2). A biliary aetiology (37%), either microlithiasis (32%) or common bile duct stones (5%), was the most frequent aetiology. Chronic pancreatitis and associated pancreatic duct (PD) abnormalities (dilated PD, PD stricture or PD stone) were the next most frequent findings in 21% of cases. There were several forms of pancreatic neoplasm found, accounting for 6% of cases. Finally, there were several miscellaneous findings (Table 2). No biliary or pancreatic abnormality was detected in 38% of patients.

LC was reported to be performed in 168 (28.4%) patients with microlithiasis demonstrated on EUS. Of these, 98 (58%) patients were followed up for a mean of 20.5 months after the LC with only 2 (2%) having a recurrent episode of AP.

Discussion

Previous studies have reported up to 30% of patients with AP being labelled as having idiopathic disease.[5,8,54] Our systematic review demonstrates that with the use of EUS, a potential biliary aetiology can be established in 37% of patients previously labelled as having IAP. Treatment of EUS detected microlithiasis was associated with a 2% incidence of recurrent AP over a 20.5-month follow-up.

Given AP is a frequent presentation to the emergency department as well as a major contributor to surgical admissions, a large number of patients will potentially benefit from the use of EUS to investigate IAP.[1–4,55] While gallstones are a well-established cause of AP, biliary sludge and microlithiasis as causative agents for AP have been increasingly recognised since the 1980s.[17–20,56,57] Microlithiasis is defined as tiny stones (< 3 mm) that are often missed on routine transabdominal US. Biliary sludge is a collection of crystals (seen only by microscopic exam), glycoproteins, protein, cellular debris and mucin. In practice, since biliary sludge may contain microlithiasis, these two terms are often used interchangeably.[58] The current study demonstrated a biliary aetiology (microlithiasis or common bile duct stones) as the most frequent aetiology (37.3%) established by EUS in patients with IAP. This incidence of a biliary aetiology is much lower than the 75% incidence in other studies.[17,21] The identification of a biliary aetiology should lead to LC and intraoperative cholangiography (IOC) (or ERCP where cholecystectomy has been performed prior) to prevent recurrent episodes of AP.[1]

In this study, the recurrence rate for AP after LC for EUS detected microlithiasis was only 2%. Although a potential aetiology is established, cholecystectomy may not prevent recurrence of AP. Following a LC for biliary pancreatitis from proven gallstones, the incidence of recurrent AP is between 3 and 5%.[59,60] The recurrence rate of AP after LC for a biliary cause found at EUS needs to be balanced against the natural history of recurrent attacks of IAP. Despite being a common cause of AP (8 to 27%), the natural history of IAP is not well evaluated.[8,10,12,15] Studies report IAP recurrence rates of 19–20% with variable interval timing after the initial IAP attack.[2,9,51] In one study where EUS was used in all patients with IAP, those having a single attack had a 19% recurrence rate (median recurrence time 12 months, range 1–81 months). Those with recurrent attacks of IAP had a 40% recurrence rate (median time to recurrence 13.5 months, range 1 to 90 months).[51] Of note, if no abnormality was found on EUS, the recurrence rate was 35% after a single attack of IAP and 52% in the recurrent group.[51] These results suggest that when a biliary aetiology is found, LC and IOC are likely to reduce the recurrence rate of AP.

Some centres have recommended empiric laparoscopic cholecystectomy (LC) in patients following either a single or a recurrent attack of IAP based on possible occult biliary disease being present.[22–25,61] An empiric LC and IOC are low risk, practical approaches to manage patients presenting with IAP. There are three studies reporting long-term follow-up of patients who underwent empiric LC for IAP with an AP

Table 1 Study demographics

Author	Year	Country	Pt no.	Initial AP episode	Recurrent AP episode	Male gender
Ardengh[27]	2010	Brazil	36	13	23	15
Berzosa[28]	2013	USA	7	NR	NR	NR
Bianchi[29]	2013	Italy	42	NR	NR	18
Bolado[30]	2015	Spain	34	NR	NR	NR
Boulay[31]	2009	USA	110	39	71	41
Canadas[32]	2013	Columbia	21	10	5	9
Choudhary[33]	2016	India	135	74	61	NR
Dahan[34]	1996	France	25	NR	NR	11
Govil[35]	2014	India	51	51	0	35
Hwang[36]	2017	Argentina	32	NR	NR	11
Kundu[37]	2009	USA	222	NR	NR	NR
Liu[38]	2000	Hong Kong	18	NR	NR	9
Mariani[39]	2009	Italy	44	NR	NR	20
Morris-Stiff[40]	2009	UK	42	NR	NR	25
Norton[41]	2000	UK	43	NR	NR	20
Ortega[21]	2011	Spain	49	33	16	24
Poves[42]	2010	Spain	32	NR	NR	NR
Queneau[43]	2002	France	17	NR	NR	NR
Rana[44]	2012	India	40	23	17	26
Saleem[45]	2015	UK	44	11	33	32
Somani[46]	2017	India	158	NR	NR	NR
Tandon[47]	2001	USA	31	14	17	12
Thevenot[48]	2013	USA	38	30	8	NR
Vila[49]	2010	Spain	44	NR	NR	NR
Vila[50]	2012	Spain	15	NR	NR	NR
Wilcox[51]	2016	USA	201	80	121	95
Yusoff[52]	2004	Canada	246	134	112	NR
Zhan[53]	2011	China	33	NR	NR	13

NR, not reported

recurrence rate of 23% over a mean follow-up period of 55 months.[22–24] One of these studies was a randomised controlled trial (RCT) that demonstrated much better outcomes for empiric LC compared with a control group of active observation.[22] This needs to be balanced against the natural history of IAP, as well as using EUS to select patients with a potential biliary cause. Although the present study suggests that using EUS to select patients for LC may be beneficial, there are several potential confounders. Unfortunately, not all cases found to have microlithiasis on EUS had the results of subsequent LC reported. Of the 28.4% having an LC reported, only half had any follow-up data that was less than 2 years. Another potential confounder is a false negative result for the EUS. Unfortunately, the false negative rate for a biliary aetiology for IAP at EUS is unknown. Therefore, in addition to more long-term prospective studies on the natural history of IAP, an RCT comparing empiric LC with EUS directed LC, with a long-term (up to 10 years) follow-up required to assess

Table 2 EUS Findings for IAP

Aetiology	Dx. yield (%)	CI (95%)	*p*	I^2	*n*
Cholelithiasis/microlithiasis	32	0.26–0.39	< 0.001	86.63	542
Chronic pancreatitis	17	0.13–0.22	< 0.001	75.41	351
Choledocholithiasis	5	0.03–0.08	< 0.001	53.21	65
Pancreatic divisum	3	0.02–0.06	< 0.001	70.37	82
Pancreatic neoplasm	2	0.01–0.04	0.002	49.27	51
Cystic neoplasms	2	0.01–0.03	0.01	41.07	13
IPMN	2	0.02–0.04	0.08	28.84	20
Dilated CBD/PD	2	0.01–0.03	0.98	0.00	6
Anatomic abnormality	2	0.01–0.02	0.99	0.00	9
Pancreatic duct stones	1	0.01–0.03	< 0.001	55.93	12
Pancreatic duct stricture	1	0.01–0.03	< 0.001	73.47	19
Cholesterosis	1	0.01–0.02	0.99	0.00	2
Unknown	36	0.30–0.42	< 0.001	80.68	722

Note that in six studies, more than one aetiology was identified within the same patient. As a result, the mean event rate of individual aetiologies (including unknown) does not total 100%. Consequently, the results are presented in tabulated form as opposed to a distributive graph

if the EUS selection for LC has a benefit over the empiric approach. An alternate prospective, non-randomised study would be to perform EUS on all patients with IAP prior to performing an empiric LC and IOC with a long-term prospective follow-up comparing those with a biliary aetiology with those with no biliary aetiology defined. This would define the false negative rate for a biliary aetiology for EUS and define the benefit of EUS and if empiric LC has a benefit irrespective of the result of the EUS.

One-third of patients had evidence of associated pancreatic disease not detected on previous imaging modalities. The most frequent finding was evidence of chronic pancreatitis, which itself is not aetiology, but it demonstrates chronic disease and may reflect the end organ damage from recurrent episodes of IAP.[62,63] Some of those patients with a dilated PD, a PD stricture or PD stones may benefit from endoscopic or surgical pancreatic duct drainage procedures to manage these changes associated with chronic pancreatitis that result in recurrent episodes of AP or chronic pain.[62,63] Performing an empiric LC and IOC would potentially overlook the pancreatic abnormalities that could be managed with alternate therapeutic procedures where indicated.

The finding of a pancreatic divisum may lead to therapeutic intervention with a reduction or cessation of episodes of AP.[64] Although EUS detected these findings, many of them may have been detected by performing pancreatic-specific CT and/or MRCP. As only just over one-third had a CT and 15% an MRCP, the findings related to chronic pancreatitis may have been overlooked. Therefore, the routine use of pancreatic-specific CT and/or MRCP may have selected out patients with pancreatic parenchymal abnormalities. Nonetheless, as neither CT nor MRCP can detect microlithiasis, there remains a role for EUS in these patients.

A smaller but significant number of pancreatic neoplasms (6%) were detected by EUS. Once again, the routine use of pancreatic-specific CT scanning and/or MRCP may have detected these lesions. Nonetheless, defining these lesions alters the subsequent treatment of this small subset of patients presenting with IAP.

The UK Working Party on Acute Pancreatitis determined that no more than 20% of patients should be labelled as idiopathic.[16] The results of the present study suggest that if patients initially labelled as IAP undergo EUS, the expected incidence of IAP in a given population could be reduced by approximately 50%.

Although EUS is associated with less morbidity than ERCP, it is still an invasive procedure with higher morbidity than an MRCP.[65–67] MRCP as a primary imaging modality may detect most of the pancreatic duct abnormalities seen with EUS; however, MRCP does not accurately identify microlithiasis.[68] The higher rate of biliary aetiology[1,2] in this study compared with pancreatic pathology would favour using EUS as the initial imaging investigation in IAP. This finding supports the IAP/APA guidelines that suggest that EUS be the initial investigation in IAP and when negative to proceed with an MRI.[2] These guidelines had a grade 2 recommendation based on weak evidence with only a weak agreement by the working party.[2] The current results provide some additional support for this recommendation with data provided from an additional 13 studies comprising 843 patients since October 2012 when the guidelines were developed.[28–30,32,33,35,36,44–46,48,50,51] Our results provide support for the routine use of EUS, when available, to investigate patients with apparent IAP after the initial episode of AP and proceeding to an LC and IOC when a biliary cause is detected.

Where EUS is not available, pancreatic-specific CT and/or MRCP should be performed to exclude chronic pancreatitis or pancreatic neoplasms. In the absence of any abnormalities on CT or MRCP, consideration then needs to be given to performing an empiric LC and IOC. As previously stated, more comprehensive data is required to understand the natural history of IAP and to address the best management for patients with a potential biliary aetiology. A large RCT comparing routine EUS and empiric LC or EUS prior to an empiric LC and IOC with long-term (minimum of 10 years) follow-up is required to provide a definitive answer to this question.

Author Contribution Statement Ryan Pereira: Established the initial concept of the study; data acquisition, analysis and interpretation; prepared the initial draft of the manuscript; provided approval of the final manuscript; stands accountable for the accuracy and integrity of the manuscript

Guy Eslick: Data analysis and interpretation; reviewed various drafts of the manuscript; provided approval of the final manuscript; stands accountable for the accuracy and integrity of the manuscript

Michael Cox: Developed the concept and study design; data analysis and interpretation; revisions of subsequent drafts of the manuscript; provided approval of the final manuscript; stands accountable for the accuracy and integrity of the manuscript

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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