

WJG 20<sup>th</sup> Anniversary Special Issues (18): Pancreatitis**Imaging tests for accurate diagnosis of acute biliary pancreatitis**

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**Abstract**

Gallstones represent the most frequent aetiology of acute pancreatitis in many statistics all over the world, estimated between 40%-60%. Accurate diagnosis of acute biliary pancreatitis (ABP) is of utmost importance because clearance of lithiasis [gallbladder and common bile duct (CBD)] rules out recurrences. Confirmation of biliary lithiasis is done by imaging. The sensitivity of the ultrasonography (US) in the detection of gallstones is over 95% in uncomplicated cases, but in ABP, sensitivity for gallstone detection is lower, being less than 80% due to the ileus and bowel distension. Sensitivity of transabdominal ultrasonography (TUS) for choledocholithiasis varies between 50%-80%, but the specificity is high, reaching 95%. Diameter of the bile duct may be orientative for diagnosis. Endoscopic ultrasonography (EUS) seems to be a more effective

tool to diagnose ABP rather than endoscopic retrograde cholangiopancreatography (ERCP), which should be performed only for therapeutic purposes. As the sensitivity and specificity of computerized tomography are lower as compared to state-of-the-art magnetic resonance cholangiopancreatography (MRCP) or EUS, especially for small stones and small diameter of CBD, the later techniques are nowadays preferred for the evaluation of ABP patients. ERCP has the highest accuracy for the diagnosis of choledocholithiasis and is used as a reference standard in many studies, especially after sphincterotomy and balloon extraction of CBD stones. Laparoscopic ultrasonography is a useful tool for the intraoperative diagnosis of choledocholithiasis. Routine exploration of the CBD in cases of patients scheduled for cholecystectomy after an attack of ABP was not proven useful. A significant rate of the so-called idiopathic pancreatitis is actually caused by microlithiasis and/or biliary sludge. In conclusion, the general algorithm for CBD stone detection starts with anamnesis, serum biochemistry and then TUS, followed by EUS or MRCP. In the end, bile duct microscopic analysis may be performed by bile harvested during ERCP in case of recurrent attacks of ABP and these should be followed by laparoscopic cholecystectomy.

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**Key words:** Biliary; Pancreatitis; Lithiasis; Endoscopic ultrasonography; Magnetic resonance cholangiopancreatography; Endoscopic retrograde cholangiopancreatography

**Core tip:** Gallstones represent the most frequent aetiology of acute pancreatitis estimated between 40%-60%. Clearance of lithiasis (gallbladder and common bile duct, CBD) rules out recurrences. Confirmation of biliary lithiasis is done by imaging. Endoscopic ultrasonography (EUS) seems to be a more effective tool to diagnose acute biliary pancreatitis rather than endoscopic

retrograde cholangiopancreatography, which should be performed only for therapeutic purposes. As the sensitivity and specificity of computerized tomography are lower as compared to state-of-the-art magnetic resonance cholangiopancreatography or EUS, especially for small stones and small diameter of CBD, the later techniques are preferred nowadays.

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## INTRODUCTION

Gallstones represent the most frequent aetiology of acute pancreatitis in many statistics all over the world. The proportion from the total number of acute pancreatitis cases is estimated between 40%-60%, with variations due especially to diagnostic efforts and availability of imaging tests<sup>[1]</sup>. Accurate diagnosis of acute biliary pancreatitis (ABP) is of outmost importance because clearance of lithiasis (gallbladder and common bile duct, CBD) rules out recurrences, very frequent otherwise, with 30% to 50% of the patients developing recurrent acute pancreatitis relatively soon after discharge (average time 108 d), some of them maybe more severe than the previous episode<sup>[2]</sup>.

Once the diagnosis of acute pancreatitis is made, grounded on generally acknowledged criteria of abdominal pain and three times more than normal hyperamylasemia/hyperlipidemia and/or intravenous (*iv*) contrast-enhanced helical computerized tomography (CT) scan/magnetic resonance imaging (MRI)/transabdominal ultrasonography (TUS), the biliary aetiology is suspected if jaundice, elevated alanine aminotransferase (ALT) (three times more than normal) or a dilated CBD are present<sup>[3]</sup>. To those criteria we might add statistical data of a higher incidence in women, between 50 and 70 years of age<sup>[1]</sup>.

Confirmation of biliary lithiasis is done by imaging. Clearance of biliary lithiasis implies a cholecystectomy and the removal of CBD stones. The minimal invasive approach is preferred nowadays, either by combined approach of laparoscopic cholecystectomy and endoscopic extraction of CBD stones, or total laparoscopic approach (cholecystectomy and CBD exploration and calculi extraction). Thus, once a diagnosis of gallbladder lithiasis is made, especially for microlithiasis, the most important thing is to establish whether there is also a CBD stone. Over 90% of the CBD stones come from the gallbladder through the cystic duct. Primary stones arising in the CBD are rarer and usually due to conditions that alter the normal flow of the bile and create conditions for bile stasis. "Silent stones" in the CBD may be present in up to 15% in patients younger than 60 years undergoing cho-

lecystectomy, and even more frequent in older patients<sup>[4]</sup>. However, the incidence of ABP in choledocholithiasis is only 3%-8%<sup>[1]</sup>. Even more important, after triggering the acute pancreatitis, most of stones pass through the papilla into the duodenum<sup>[5]</sup>. Thus, the percentage of CBD stones in ABP decreases from 28.6% in the first 4 h to 8% at 1 wk<sup>[6,7]</sup>.

## IMAGING TESTS

### Transabdominal US

The first, and the most available and commonly performed is TUS. It seeks for lithiasis in the gallbladder, CBD or indirect signs of biliary obstruction, *e.g.*, dilation of the CBD. The sensitivity of the US in the detection of gallstones is over 95% in uncomplicated cases, but in ABP, sensitivity for gallstone detection is lower, being only 67%-78% due to the ileus and bowel distension<sup>[8]</sup>. Sensitivity of TUS for choledocholithiasis varies between 50%-80%, but the specificity is high, reaching 95%<sup>[9]</sup>.

Diameter of the bile duct may be orientative for diagnosis. In a prospective study, the diameter of the CBD was measured before cholecystectomy and it was compared afterwards with finding stones at the surgical intervention. There were no stones in the CBD if the diameter was less or equal to 3 mm, while 7.7% of patients with the ducts measuring 4 mm or more had stones. If the size increased, the probability of having stones also increased, nearly all ducts of 9 mm or more had stones<sup>[10]</sup> (Figure 1).

### Endoscopic US

Endoscopic US is more accurate than transcutaneous US, with a sensitivity of over 90% and an even higher specificity<sup>[11,12]</sup>. Nevertheless, the technique is more expensive and it requires a longer learning curve. EUS seems to be a more effective tool to diagnose ABP rather than ERCP, which should be performed only for therapeutic purposes. In a systematic review of clinical trials from 1994 to 2010, comparing EUS and ERCP in ABP, it was found that EUS avoided ERCP in 71.2% of cases, had no related complication, while ERCP was complicated in over 20% of cases. The clinical course of ABP was not influenced by either of those explorations<sup>[13]</sup>. A meta-analysis performed on 36 studies with 3532 patients revealed a sensitivity of 89% and a specificity of 94% for choledocholithiasis<sup>[14]</sup>, with another meta-analysis performed on 2673 patients showing even higher numbers of 94% sensitivity and 95% specificity<sup>[15]</sup>. Consequently, EUS is an important diagnostic tool for the presence of CBD stones, as it accurately visualizes the CBD without the need of instrumentation<sup>[16]</sup>. There is now enough evidence to support the use of EUS before ERCP, even for smaller stones (less than 4 mm), as it can spare at least two thirds of ERCPs<sup>[17]</sup>. Moreover, as compared to MRCP, EUS has the same sensitivity, specificity and accuracy, although the sensitivity of MRCP seems to diminish in small (less than 6 mm) CBD stones. Thus,



Figure 1 Large, conglomerated stones into a dilated common bile duct (over 12 mm).

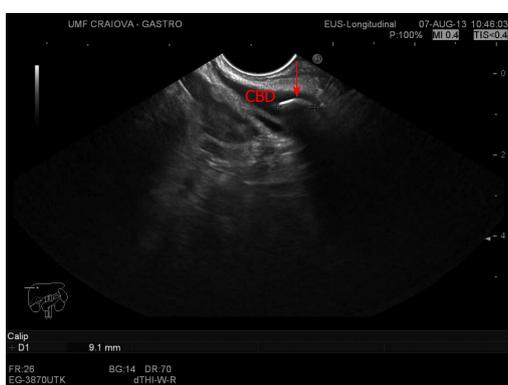


Figure 2 A 9 mm stone, within a slightly dilated, elongated common bile duct.

EUS has a significant impact for surgical decision making, especially in the patients with suspected ABP<sup>[18]</sup> (Figure 2).

### CT

Unenhanced helical CT scan has a variable accuracy for the detection of choledocholithiasis, with a sensitivity of 60%-87% and a specificity of 97%-100%<sup>[19,20]</sup>. CT-choangiography has a higher performance for the diagnosis of choledocholithiasis with a sensitivity of 85%-96% and a specificity of 88%-98%<sup>[19,21]</sup>. As the sensitivity and specificity of CT are lower as compared to state-of-the-art MRCP or EUS, especially for small stones and small diameter of CBD, the later techniques are nowadays preferred for the evaluation of ABP patients.

### MRCP

MRCP has a high reported accuracy in the diagnosis of choledocholithiasis. Meta-analyses report pooled sensitivities of 92%-94%<sup>[7,22]</sup> and a specificity of 99%. There are still controversies regarding the optimal imaging method in the preoperative assessment of patients with ABP, but MRCP has the advantage of a non-invasive method that could properly detect CBD lithiasis. The efficacy of MRCP in detecting CBD stones and to assess the time of choledochal passage of calculi was also compared to

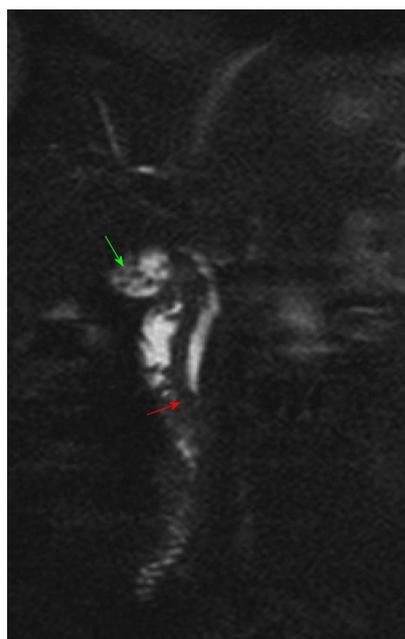


Figure 3 Multiple gallstones in T2 hyposignal less than 5 mm diameter (green arrow), diameter of the common bile duct 6 mm, with a 4 mm migrated stone (red arrow).

ERCP. Overall, MRCP had a positive predictive value 90.5%, negative predictive value 95.2%, sensitivity 82.6%, specificity 97.5% and overall accuracy 94.2%. Moreover, MRCP diagnoses anatomical variants of cystic duct and acute cholecystitis<sup>[6,7]</sup>. A prospective study compared the efficacy of EUS compared to MRCP and ERCP in the same patients with suspected extrahepatic biliary disease, taking into account also the economic aspect. Results regarding choledocholithiasis were that EUS was more sensitive than MRCP in the detection of choledocholithiasis (80% *vs* 40%), with similar specificity. Rate of acute pancreatitis after ERCP was 6.6%. EUS strategy had the greatest cost-utility by avoiding unnecessary ERCP examinations<sup>[23]</sup>. Nevertheless, a systematic review showed a similar diagnostic value for prospective studies that compared MRCP and EUS for the detection of CBD stones<sup>[24]</sup> (Figure 3).

### ERCP

ERCP has the highest accuracy for the diagnosis of choledocholithiasis and is used as a reference standard in many studies, especially after sphincterotomy and balloon extraction of CBD stones. Diagnostic ERCP does not, however, detect all stones and in one study its sensitivity was 89% in comparison with EUS, especially for small stones hidden by contrast injection<sup>[12]</sup>. EUS has been compared to ERCP in a prospective randomized fashion in cases of acute pancreatitis suspected to have a biliary cause. The patients had EUS or ERCP examinations within 24 h from admission. If EUS detected choledocholithiasis, therapeutic ERCP was performed immediately. EUS was successful in all patients, but ERCP failed in 10%, the difference being significant. Also ERCP

failed to identify stones in 8.5%. Morbidity, hospital stays and mortality was similar in both groups<sup>[25]</sup>. The preferred approach for concomitant gallbladder and CBD stones in the laparoscopic era is sequential preoperative ERCP followed by laparoscopic cholecystectomy, although this has been found to have similar efficacy, maybe with a shorter hospital stay with laparoscopic CBD exploration during cholecystectomy<sup>[26]</sup>. The same conclusion was also reached by a Cochrane systemic review comparing the endoscopic versus surgical treatment of CBD stones, with laparoscopic CBD clearance being as effective as pre- or post-operative ERCP<sup>[27]</sup>.

### Laparoscopic ultrasonography

Laparoscopic ultrasonography (LUS) is a useful tool for the intraoperative diagnosis of choledocholithiasis. Thus, LUS was compared to laparoscopic cholangiography with the same specificity (100%) and positive predictive value (100%), and a sensitivity of 93%<sup>[28]</sup>. Nevertheless, laparoscopic exploration of the bile duct is as safe and effective as postoperative ERCP in clearing stones from the common duct<sup>[29]</sup>. The benefit of routine intraoperative cholangiography at the time of cholecystectomy in patients with ABP submitted to laparoscopic cholecystectomy was also questioned. Thus, patients with ABP submitted to cholecystectomy with or without intraoperative cholangiography and CBD exploration were compared in terms of outcome. At 3.8 years of follow up there was no significant difference regarding the rate of recurrent pancreatitis or biliary complications, suggesting that intraoperative cholangiography does not improve outcome after cholecystectomy for gallstone pancreatitis<sup>[30]</sup>. Another study showed that laparoscopic cholecystectomy (LC) can be performed safely without intraoperative cholangiography (IOC). Thus, from the patients with symptomatic gallstone disease, about 9.2% were selected for preoperative ERCP based upon preoperative clinical, laboratory and ultrasound criteria. In those patients, 58% were found with choledocholithiasis, and stone clearance was achieved in all cases. The other patients were submitted to laparoscopic cholecystectomy with no injury of CBD, no mortality and a rate of retained CBD stones of 1.5% at 2 years follow-up<sup>[31]</sup>.

The necessity of routine exploration of the CBD in cases of patients scheduled for cholecystectomy after an attack of ABP was submitted to question. Ito *et al*<sup>[32]</sup> investigated this in cases of low risk for choledocholithiasis. The authors included 148 patients without preoperative ERCP, normal and decreasing liver function tests, and normal CBD diameter. They were divided into 2 groups - with or without intraoperative cholangiography. Follow-up didn't find any significant differences between the 2 groups regarding postoperative episodes of acute pancreatitis, cholangitis or changes in liver function tests. Authors concluded that direct CBD exploration could be safely avoided in selected cases of ABP, with low-risk for choledocholithiasis.

## ETIOLOGY

Some of the acute pancreatitis cases remain idiopathic even after complete serum biochemistry, ultrasound and CT evaluations. Nevertheless, the aetiology of acute pancreatitis should be determined in at least 80% of cases and no more than 20% should be classified as idiopathic (recommendation grade B)<sup>[33]</sup>. These represent between 10% and 30% in different series. Some studies suggested that more accurate imaging tests for biliary lithiasis detection may reveal the biliary cause in those cases. In our experience, it also happened that once we introduced in our hospital EUS and ERCP there was a shift between the leading causes for acute pancreatitis between the alcoholic and biliary causes, many of idiopathic pancreatitis being actually biliary ones. Recently, some studies showed that a significant rate of the so-called idiopathic pancreatitis are actually caused by microlithiasis and/or biliary sludge, identified by the presence of cholesterol monohydrate and/or calcium bilirubinate microcrystals in the biliary sediment.

### Microlithiasis

Microlithiasis is a viscous precipitate containing mucin, cholesterol and calcium bilirubinate which can obstruct the pancreatic duct. US has a sensitivity of only about 55% in detecting microlithiasis and does not allow for analysis of the chemical composition of bile<sup>[34]</sup>. This is an important cause of recurrent acute pancreatitis. Though a EUS procedure is diagnostic, with a high sensitivity and specificity<sup>[35]</sup> a duodenal aspirate or a bile duct aspirate for the microliths<sup>[36]</sup> at ERCP is confirmatory. In a series of 86 patients<sup>[37]</sup> with acute pancreatitis, 21 patients had microlithiasis. Six patients were subjected to cholecystectomy and 4 patients to endoscopic sphincterotomy. Fewer recurrences were noted in patients receiving either of the two treatment modalities compared to the group managed conservatively. The treatment protocol would warrant a cholecystectomy in all patients unless contraindicated. In those with a high operative risk, endoscopic biliary sphincterotomy is a safe and viable option<sup>[38]</sup>. Ursodeoxycholic acid is an alternative in those with bleeding tendencies<sup>[39]</sup>. Thus, microlithiasis or biliary sludge as a causative aetiology for acute pancreatitis remains controversial and not well understood. Several studies have demonstrated the presence of biliary sludge in as many as 75% of patients with unexplained acute pancreatitis<sup>[37]</sup>. Bile analysis with microscopic examination is considered the gold standard for diagnosis. Bile can be obtained directly while cannulating the bile duct during ERCP or following CCK stimulation on EGD. ERCP with bile aspiration from the CBD has a reported sensitivity of 83% in detecting microlithiasis<sup>[40]</sup>.

In patients considered to have idiopathic acute pancreatitis, after negative routine work-up for biliary etiology, EUS is recommended as the first step to assess for occult microlithiasis, neoplasms and chronic pancreatitis.

If EUS is negative, rare and uncommon causes should be looked for. MRCP (secretin-stimulated) is advised to identify or rule out rare morphologic abnormalities. If aetiology still remains unidentified, genetic counselling (not necessarily genetic testing) should be considered in order to search for hereditary or other genetic causes<sup>[3]</sup>.

In conclusion, the general algorithm for CBD stone detection starts with anamnesis, serum biochemistry and then TUS, followed by EUS or MRCP. In the end, bile duct microscopic analysis may be performed by bile harvested during ERCP in case of recurrent attacks of ABP and these should be followed by laparoscopic cholecystectomy.

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