



Indications for endoscopic retrograde cholangiopancreatography and cholecystectomy in biliary pancreatitis

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Acute pancreatitis is the second most common cause of hospital admission of all gastrointestinal disorders and is associated with an overall mortality rate of 0.5 per cent¹. Some 351 526 patients were diagnosed with acute pancreatitis in 2014 in the USA.

First reported in 1901, acute biliary pancreatitis (ABP) is the second most common cause of acute pancreatitis in the Western world and accounts for 40–56 per cent of all cases^{1–3}. ABP is caused by passage of gallstones leading to obstruction of the pancreatic duct, blockage of pancreatic secretion and increased duct pressure, resulting in autodigestion followed by a systemic inflammatory response.

Gallstones occur in up to 20 per cent of the population and the lifetime risk for ABP in these individuals is 2–8 per cent. The prevalence of gallstones in patients with acute pancreatitis is 85–95 per cent. Cholecystectomy in gallstone carriers lowers the risk of a first episode of acute pancreatitis to that of the general population. Management of ABP only differs from that of pancreatitis of other aetiologies when it comes to the question of early endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy to restore pancreatic secretion, and the timing of cholecystectomy.

Reliably diagnosing biliary obstruction has a major impact on further clinical management. Transabdominal ultrasonography has a sensitivity and specificity of 95–98 per cent for gallbladder stones, but its sensitivity for detecting common bile duct

stones is significantly lower. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound imaging both have high accuracy for the diagnosis of stones in the common bile duct in combination with a high negative predictive value (*Table S1*, supporting information). Exclusion of persistent biliary obstruction does not disprove a biliary aetiology for acute pancreatitis. A typical biochemical profile in combination with the presence of gallstones suggests a biliary cause of pancreatitis with probable stone passage. However, conflicting results have been reported with respect to the ability of increased liver enzyme levels to discriminate between a biliary and non-biliary origin of acute pancreatitis; an increase in alanine aminotransferase level of at least three times the upper limit of normal is known to predict ABP with a positive predictive value of 95 per cent, whereas aspartate aminotransferase, alkaline phosphatase and bilirubin have less predictive value (*Table S2*, supporting information).

The role of endoscopic interventions as a therapeutic approach to biliary pancreatitis has been under debate for decades. The American Pancreatic Association/International Association of Pancreatology (APA/IAP) guidelines³ as well as the British Society of Gastroenterology guidelines⁴ recommend the following evidence-based clinical indications for ERCP in ABP: early ERCP is not indicated in patients with predicted mild biliary pancreatitis (strong recommendation,

high-quality evidence, grade 1A); patients with pancreatitis who have associated cholangitis or persistent biliary obstruction should undergo ERCP (strong recommendation, high-quality evidence, grade 1B); co-existing biliary obstruction is a probable indication for early ERCP (strong recommendation, low-quality evidence, grade 1C); and early ERCP seems to have no benefit in patients with predicted severe biliary pancreatitis (strong recommendation, moderate-quality evidence, grade 1B).

Historically, ERCP with sphincterotomy in biliary pancreatitis was believed to improve prognosis by removing remaining common bile duct stones. A recent meta-analysis of seven RCTs including 757 patients found no evidence that early routine ERCP significantly affects mortality or local/systemic complications, regardless of the predicted severity of biliary pancreatitis⁵. More recent RCTs reported relevant confounders for the efficacy of early ERCP in biliary pancreatitis. RCTs^{6–8} in patients without acute cholangitis did not demonstrate any benefit of early ERCP with or without sphincterotomy in patients with mild or severe ABP. Against the background of spontaneous passage of the majority of common bile duct stones within 24–48 h, the use of endoscopic ultrasound imaging or MRCP before ERCP supersedes the invasive procedure of ERCP in more than two-thirds of patients⁹. Nevertheless, the individual trials, and even the pooled

data in meta-analyses, did not include enough patients with 'predicted severe biliary pancreatitis without cholangitis' to study hard clinical endpoints such as mortality (possible type II statistical error). Therefore, the Dutch Pancreatitis Study Group¹⁰ initiated the APEC trial to clarify the role of early ERCP in patients with predicted severe biliary pancreatitis in the absence of cholangitis. Data were presented to United European Gastroenterology 2018. In 230 patients with predicted severe ABP, early ERCP with sphincterotomy (less than 24 h after presentation, within 72 h of symptom onset) was compared with medical management without endoscopic intervention. The combined primary endpoint was death or severe complications. There was no statistically significant difference between groups with regard to the composite primary endpoint, but a significant increase was found in the rate of cholangitis in the medically managed group. This finding was counterbalanced by an increased number of patients being transferred to ICU and a significantly increased number of patients with new-onset respiratory failure in the ERCP group. The authors concluded that, in patients with predicted severe ABP without cholangitis, the superiority of early ERCP with sphincterotomy compared with conservative treatment could not be proved and so early ERCP cannot be recommended in this group¹¹.

The question of timing of cholecystectomy in mild APB to prevent recurrence was addressed in the PONCHO (Pancreatitis of biliary origin: Optimal timing of CHolecystectomy) trial¹². Based on this trial, cholecystectomy is recommended during the index admission in patients with mild ABP. Failure to remove the gallbladder on index admission resulted in an increase in gallstone-related complications

such as pancreatitis, biliary colic and readmissions, as confirmed in a meta-analysis¹³. With respect to conversion rates from laparoscopy to laparotomy or surgical complexity, no differences between groups were detected. Recommendations for the timing of cholecystectomy in severe biliary pancreatitis stem from the IAP/APA guidelines. Cholecystectomy should be delayed in patients with an episode of moderate-to-severe ABP with peripancreatic fluid collections, walled-off pancreatic necrosis or pseudocysts until collections have been resolved or persist beyond 6 weeks. Unfortunately, the recommendation is derived from only two retrospective analyses and so the level of evidence is low¹⁴.

The following recommendations can be made for management of ABP. Early ERCP is not indicated in patients with predicted mild ABP and has no clinical benefit in those with predicted severe ABP. Only co-existing cholangitis is an indication for early ERCP as co-existing biliary obstruction is a probable indication for early ERCP. Cholecystectomy in patients with mild ABP should be performed on index admission and delayed in those with severe ABP, but sphincterotomy can also be regarded as definitive treatment only in patients unfit for cholecystectomy.

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References

- 1 Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL

et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. *Gastroenterology* 2019; **156**: 254.e11–272.e11.

- 2 Giljaca V, Gurusamy KS, Takwoingi Y, Higgie D, Poropat G, Štimac D *et al.* Endoscopic ultrasound *versus* magnetic resonance cholangiopancreatography for common bile duct stones. *Cochrane Database Syst Rev* 2015; (2)CD011549.
- 3 Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; **13**(Suppl 2): e1–e15.
- 4 Williams E, Beckingham I, El Sayed G, Gurusamy K, Sturges R, Webster G *et al.* Updated guideline on the management of common bile duct stones (CBDS). *Gut* 2017; **66**: 765–782.
- 5 Coutinho LMA, Bernardo WM, Rocha RS, Marinho FR, Delgado A, Moura ETH *et al.* Early endoscopic retrograde cholangiopancreatography *versus* conservative treatment in patients with acute biliary pancreatitis: systematic review and meta-analysis of randomized controlled trials. *Pancreas* 2018; **47**: 444–453.
- 6 Petrov MS, van Santvoort HC, Besselink MG, van der Heijden GJ, van Erpecum KJ, Gooszen HG. Early endoscopic retrograde cholangiopancreatography *versus* conservative management in acute biliary pancreatitis without cholangitis: a meta-analysis of randomized trials. *Ann Surg* 2008; **247**: 250–257.
- 7 Oria A, Cimmino D, Ocampo C, Silva W, Kohan G, Zandalazini H *et al.* Early endoscopic intervention *versus* early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: a randomized clinical trial. *Ann Surg* 2007; **245**: 10–17.
- 8 Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent

- endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy *versus* conservative treatment for acute pancreatitis due to gallstones. *Lancet* 1988; **2**: 979–983.
- 9 Liu CL, Fan ST, Lo CM, Tso WK, Wong Y, Poon RT *et al*. Comparison of early endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in the management of acute biliary pancreatitis: a prospective randomized study. *Clin Gastroenterol Hepatol* 2005; **3**: 1238–1244.
- 10 Schepers NJ, Bakker OJ, Besselink MG, Bollen TL, Dijkgraaf MG, van Eijck CH *et al*. Early biliary decompression *versus* conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial. *Trials* 2016; **17**: 5.
- 11 Schepers NJ, Hallensleben ND, Besselink M, Anten MP, Bollen T, van Delft F *et al*. Early endoscopic retrograde cholangiography with biliary sphincterotomy or conservative treatment in predicted severe acute biliary pancreatitis (APEC): a multicenter randomized controlled trial. *Gastroenterology* 2019; **156**: S112–S112. Meeting Abstract: 570.
- 12 da Costa DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S *et al*. Same-admission *versus* interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet* 2015; **386**: 1261–1268.
- 13 Moody N, Adiamah A, Yanni F, Gomez D. Meta-analysis of randomized clinical trials of early *versus* delayed cholecystectomy for mild gallstone pancreatitis. *BJS* 2019; **106**: 1442–1451.
- 14 Yang DJ, Lu HM, Guo Q, Lu S, Zhang L, Hu WM. Timing of laparoscopic cholecystectomy after mild biliary pancreatitis: a systematic review and meta-analysis. *J Laparoendosc Adv Surg Tech A* 2018; **28**: 379–388.

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