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Endoscopic assessment and treatment of biliary pancreatitis

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1. Introduction

Acute pancreatitis is the most common gastro-intestinal cause for acute hospital admission in the United States and associated with substantial costs (20). The reported incidence varies from 5 to 73 per 100.000 persons in different populations (8, 37). The overall mortality rate is 4 to 8%, which increases to 33% in patients with infected necrosis (4, 12, 20, 32). As the incidence of acute pancreatitis is rising, the burden for patients and society will further increase (23, 37). An ageing population and abdominal obesity, with a concomitant increased risk of gallstone formation, is likely to play an important role (23, 27, 37).

'Sludge' or gallstones, particularly small common bile duct stones, are the cause of acute pancreatitis in approximately 32 to 40% of cases (9, 26, 33, 36). Although the pathogenesis of acute biliary pancreatitis is not fully understood, transient or persistent obstruction of the ampulla, compromising the outflow of pancreatic juices and bile, is thought to be the initiating event (1). Either an obstructing stone or mucosal edema after spontaneous gallstone passage can result in ampullary obstruction. The etiology of acute pancreatitis should be determined on admission, as biliary obstruction may require duct clearance in the early phase. This chapter gives an overview of the available diagnostic tests and imaging modalities. Subsequently, the role of endoscopic retrograde cholangiography (ERC) will be discussed.

2. Establishing a Biliary Etiology

Acute pancreatitis is diagnosed when two of the following three criteria are fulfilled: 1. typical abdominal pain, 2. more than three times elevated serum amylase/lipase and 3. signs of acute pancreatitis on imaging. Determination of the etiology is important for clinical decision-making. A history of gallstone disease or biliary colics points towards biliary etiology. In the early disease phase, biochemical markers can be helpful. In the absence of alcohol abuse, an alanine transaminase (ALAT) >150 IU/L has a predictive value of 88 to 100% in establishing biliary etiology (15, 17, 25). Other elevated biochemical markers, such as serum alkaline phosphatase, bilirubin, gammaglutamyl-transferase and aspartate aminotransferase are also suggestive of a biliary origin. However, 15 to 20% of patients with acute biliary pancreatitis

have normal liver function tests at presentation (7).

Recent guidelines advocate abdominal ultrasonography on admission, to identify cholelithiasis, because of its high sensitivity of 92 to 95% (24, 35). However, in patients with acute pancreatitis, sensitivity is lower (67 to 87%), due to bowel distension, and in obese patients it decreases even further (11, 19). Nevertheless, the combination of cholelithiasis on abdominal ultrasonography and elevated liver biochemistry has a positive predictive value of 100% for biliary pancreatitis (2, 19). Predicting the severity of the disease course is desirable to determine whether intensive monitoring or early interventions are needed. Although several scoring systems exist, they lack accuracy and are generally cumbersome to use (18). Due to the simplicity, familiarity and comparable performance, recent IAP/APA guidelines recommend using persistent (lasting for more than 48hours) systemic inflammatory response syndrome (SIRS) as a predictor for disease severity (35).

3. Endoscopic Ultrasonography (EUS) or Magnetic Resonance Cholangiopancreatography (MRCP)?

If the etiology of pancreatitis remains unclear, EUS or MRCP are the next step in the diagnostic pathway **(Figure 1)**. Both modalities have a higher accuracy in detecting common bile duct (CBD) stones, compared to laboratory tests and transabdominal ultrasound (31).

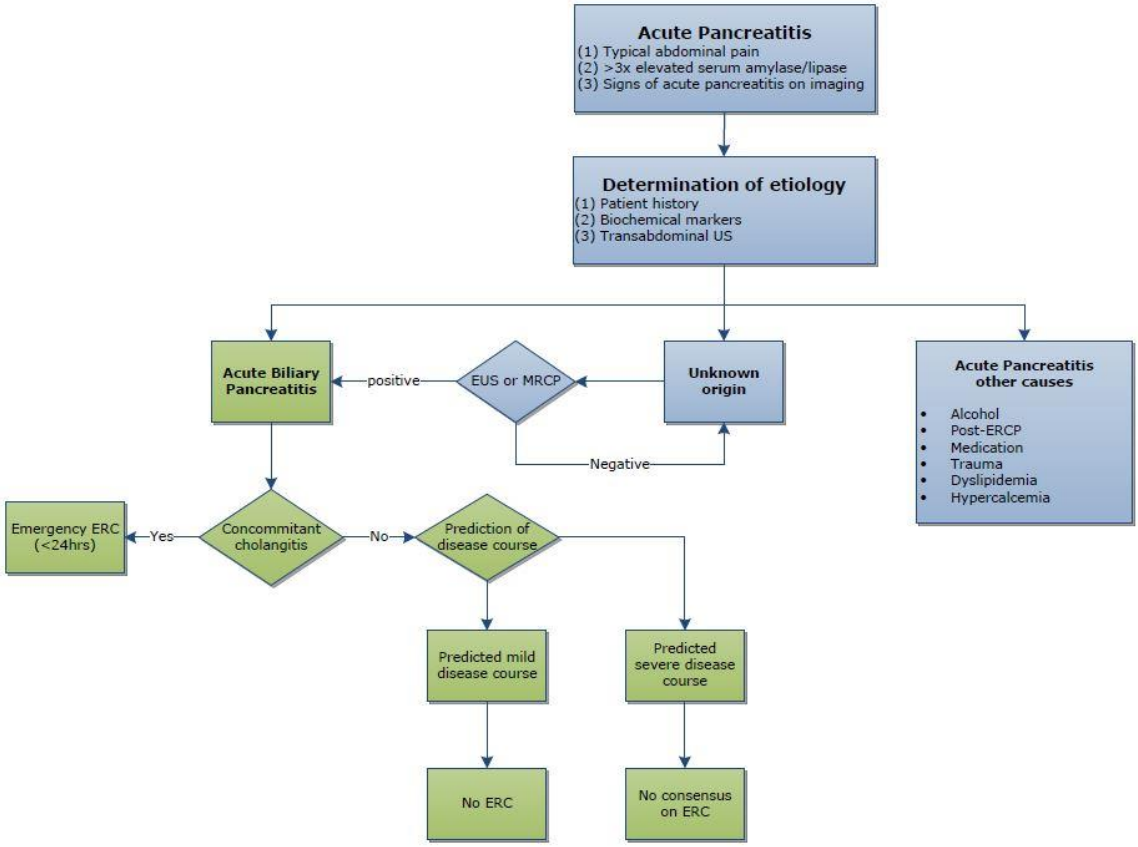

Fig 1. Diagnosis and management in the early phase of acute (biliary) pancreatitis.

For EUS, a recent meta-analysis showed a sensitivity and specificity for detecting choledocholithiasis of 0.95 (95% CI 0.91 - 0.97) and 0.97 (95% CI 0.94 - 0.99), respectively (10). In patients with pancreatitis, data are limited, but the accuracy of EUS does not seem to drop, with a reported sensitivity of 91 to 100% and specificity of 85 to 100% (14).

An advantage of EUS over MRCP is the possibility of conversion to ERC, in case common bile duct (CBD) stones are detected, provided the procedures are done in the same setting and by investigations trained in both techniques. Thus, in the hands of a trained physician with access to the appropriate equipment, diagnosis and treatment can be combined into a single procedure, with minimal additional burden for the patient. In patients with a contraindication for MRCP (e.g. claustrophobia, metal implants or cardiac pacemaker), EUS is the only semi-invasive technique available, before intraoperative cholangiography or ERC.

The advantage of the MRCP over EUS is that it is not operator dependent and is non-invasive. Although small gallstones (<5mm) and sludge may be missed, the sensitivity and specificity of MRCP were 0.93 (95% CI 0.87 - 0.96) and 0.96 (95% CI 0.89 – 0.98), in a meta-analysis (10, 13, 21). Data regarding the accuracy of MRCP in the acute phase of pancreatitis are lacking.

In conclusion, the diagnostic accuracy of both EUS and MRCP is excellent and these modalities can prevent unnecessary invasive procedures, by preselecting patients for ERC (16). In clinical practice, factors such as availability, costs and experience will determine the choice between these two modalities (34).

4. Endoscopic Retrograde Cholangiography (ERC)

In biliary pancreatitis, ampullary obstruction results in pancreatic inflammation and complications. Accordingly, early biliary decompression, using endoscopic sphincterotomy and, if necessary, stone extraction, may ameliorate disease severity and prevent complications. On the other hand, CBD stones pass spontaneously in up to 80% of cases, in which case ERC might be redundant and even unhelpful (28). This is important, as ERC is associated with a complication rate of around 10% and a resultant mortality of 0.3 to 1% (3, 6). The most common complications are perforation and bleeding. Furthermore, contrast injection or cannulation of the pancreatic duct, may aggravate the disease course (30).

Recent guidelines state that in patients with acute biliary pancreatitis and concomitant cholangitis, emergency ERC is warranted (24, 35). Urgent biliary decompression has been proven to reduce mortality and complications (29). However, diagnosing cholangitis can be challenging in this group, as the clinical signs of cholangitis are often not easily differentiated from a SIRS reaction due to pancreatitis. Evidence based diagnostic criteria for cholangitis in patients with acute pancreatitis are currently not available.

In patients with predicted mild disease, the potential benefits of ERC do not outweigh the risks for complications. Therefore, ERC is not advocated in this group (24, 35). The indication for ERC in patients with an acute biliary pancreatitis and a predicted severe disease course is controversial. Recent international guidelines state that early ERC with sphincterotomy may be beneficial, but acknowledge the limited evidence (24, 35). A recent systematic review draws a similar conclusion; despite publication of multiple

randomized trials and systematic reviews on this subject, there is no consensus on the use of ERC in this group of patients (5). Heterogeneity of the studies is a possible source of contradiction. Some studies included patients with predicted mild disease or non-biliary etiology and different scoring systems for identifying patients at high risk for complications were used. Also, patients with cholangitis or signs of biliary obstruction were not analyzed separately in all studies. Furthermore, the pooled sample size of patients with a predicted severe disease course was too small and statistically underpowered to draw conclusions. Finally, the definition of 'early' ERC differed between trials and varied between 24 to 72 hours after onset of symptoms or after hospital admission. Timing may be important, as the duration of biliary obstruction seems to correlate with disease severity. Therefore, some suggest that ERC should be performed as early as possible (22).

Currently, an adequately powered, randomized multicenter superiority trial is being conducted by the Dutch Pancreatitis Study Group to study the role of early ERC with sphincterotomy in patients with predicted severe biliary pancreatitis without cholangitis. (APEC trial, Current Controlled Trials number, ISRCTN97372133).

5. Conclusion

Acute pancreatitis is a common and potentially fatal disease. Establishing it's etiology on admission is paramount for adequate treatment. In about half of the cases, acute pancreatitis is caused by gallstones or 'sludge'. The first steps in establishing a biliary origin is a detailed history, laboratory tests and an transabdominal ultrasound. In the acute phase, an elevated ALAT (>150 IU/L) is the most sensitive biomechanical marker. MRCP and EUS both have an excellent diagnostic accuracy in detecting choledocholithiasis and can be used as second line diagnostic tools. Early ERC, is only indicated in patients with proven biliary pancreatitis and concomitant cholangitis. It is not indicated in patients with a predicted mild disease course and in patients with with a predicted severe disease course, the role of ERC is currently under investigation. A flow sheet on diagnosis and management of acute biliary pancreatitis is provided in **Figure 1**.

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6. References

1. **Acosta JM and Ledesma CL.** Gallstone migration as a cause of acute pancreatitis. *N Engl J Med* 290: 484-487, 1974. PMID: 4810815.
2. **Ammori BJ, Boreham B, Lewis P, and Roberts SA.** The biochemical detection of biliary etiology of acute pancreatitis on admission: a revisit in the modern era of biliary imaging. *Pancreas* 26: e32-35, 2003. PMID: 12604925.
3. **Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, et al.** Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 102: 1781-1788, 2007. PMID: 17509029.
4. **Banks PA and Freeman ML.** Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 101: 2379-2400, 2006. PMID: 17032204.
5. **Burstow MJ, Yunus RM, Hossain MB, Khan S, Memon B, and Memon MA.** Meta-Analysis of Early Endoscopic Retrograde Cholangiopancreatography (ERCP) +/- Endoscopic Sphincterotomy (ES) Versus

Conservative Management for Gallstone Pancreatitis (GSP). *Surgical laparoscopy, endoscopy & percutaneous techniques* 25: 185-203, 2015. PMID: 25799261.
6. **Committee ASoP, Anderson MA, Fisher L, Jain R, Evans JA, Appalaneni V, et al.** Complications of ERCP. *Gastrointest Endosc* 75: 467-473, 2012. PMID: 22341094.
7. **Dholakia K, Pitchumoni CS, and Agarwal N.** How often are liver function tests normal in acute biliary pancreatitis? *J Clinical Gastroenterol* 38: 81-83, 2004. PMID: 22341094.
8. **Fagenholz PJ, Castillo CF, Harris NS, Pelletier AJ, and Camargo CA, Jr.** Increasing United States hospital admissions for acute pancreatitis, 1988-2003. *Annals of Epidemiology* 17: 491-497, 2007. PMID: 17448682.
9. **Frey CF, Zhou H, Harvey DJ, and White RH.** The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994-2001. *Pancreas* 33: 336-344, 2006. PMID: 17079936.
10. **Giljaca V, Gurusamy KS, Takwoingi Y, Higgie D, Poropat G, Stimac D, and Davidson BR.** Endoscopic ultrasound versus magnetic resonance cholangiopancreatography for common bile duct stones. *Cochrane Database Syst Rev* 2: CD011549, 2015. PMID: 25719224.
11. **Goodman AJ, Neoptolemos JP, Carr-Locke DL, Finlay DB, and Fossard DP.** Detection of gall stones after acute pancreatitis. *Gut* 26: 125-132, 1985. PMID: 2578422.
12. **Gullo L, Migliori M, Olah A, Farkas G, Levy P, Arvanitakis C, et al.** Acute pancreatitis in five European countries: etiology and mortality. *Pancreas* 24: 223-227, 2002. PMID: 11893928.
13. **Kondo S, Isayama H, Akahane M, Toda N, Sasahira N, Nakai Y, et al.** Detection of common bile duct stones: comparison between endoscopic ultrasonography, magnetic resonance cholangiography, and helical-computed-tomographic cholangiography. *Eur J Radiol* 54: 271-275, 2005. PMID: 15837409.
14. **Kotwal V, Talukdar R, Levy M, and Vege SS.** Role of endoscopic ultrasound during hospitalization for acute pancreatitis. *World J Gastroenterol* 16: 4888-4891, 2010. PMID: 20954274.
15. **Liu CL, Fan ST, Lo CM, Tso WK, Wong Y, Poon RT, et al.** Clinico-biochemical prediction of biliary cause of acute pancreatitis in the era of endoscopic ultrasonography. *Alimentary Pharmacol Therapeut* 22: 423-431, 2005. PMID: 16128680.
16. **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* 3: 1238-1244, 2005. PMID: 16361050.
17. **Moolla Z, Anderson F, and Thomson SR.** Use of amylase and alanine transaminase to predict acute gallstone pancreatitis in a population with high HIV prevalence. *World J Surg* 37: 156-161, 2013. PMID: 23015223.
18. **Mounzer R, Langmead CJ, Wu BU, Evans AC, Bishehsari F, Muddana V,et al.** Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. *Gastroenterology* 142: 1476-1482, 2012. PMID: 22425589.
19. **Neoptolemos JP, Hall AW, Finlay DF, Berry JM, Carr-Locke DL, and Fossard DP.** The urgent diagnosis of gallstones in acute pancreatitis: a prospective study of three methods. *Br J Surg* 71: 230-233, 1984. PMID: 6141833.
20. **Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al.** Burden of Gastrointestinal Disease in the United States: 2012 Update. *Gastroenterology*, 2012. PMID: 22885331.
21. **Polistina FA, Frego M, Bisello M, Manzi E, Vardanega A, and Perin B.** Accuracy of magnetic resonance cholangiography compared to operative endoscopy in detecting biliary stones, a single center experience and review of literature. *World J Radiol* 7: 70-78, 2015. PMID: 25918584.
22. **Runzi M, Saluja A, Lerch MM, Dawra R, Nishino H, and Steer ML.** Early ductal decompression prevents the progression of biliary pancreatitis: an experimental study in the opossum. *Gastroenterology* 105: 157-164, 1993. PMID: 8514033.
23. **Spanier B, Bruno MJ, and Dijkgraaf MG.** Incidence and mortality of acute and chronic pancreatitis in the Netherlands: A nationwide record-linked cohort study for the years 1995-2005. *World J Gastroenterol* 19: 3018-3026, 2013. PMID: 23716981.
24. **Tenner S, Baillie J, DeWitt J, Vege SS, and American College of G.** American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 108: 1400-1415; 1416, 2013. PMID: 23896955.
25. **Tenner S, Dubner H, and Steinberg W.** Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. *Am J Gastroenterol* 89: 1863-1866, 1994. PMID: 7942684.

26. **Toh SK, Phillips S, and Johnson CD.** A prospective audit against national standards of the presentation and management of acute pancreatitis in the South of England. *Gut* 46: 239-243, 2000. PMID: 10644319.
27. **Torgerson JS, Lindroos AK, Naslund I, and Peltonen M.** Gallstones, gallbladder disease, and pancreatitis: cross-sectional and 2-year data from the Swedish Obese Subjects (SOS) and SOS reference studies. *Am J Gastroenterol* 98: 1032-1041, 2003. PMID: 12809825.
28. **Tranter SE and Thompson MH.** Spontaneous passage of bile duct stones: frequency of occurrence and relation to clinical presentation. *Ann R Coll Surg Engl* 85: 174-177, 2003. PMID: 12831489.
29. **Tse F and Yuan Y.** Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst Rev* 5: CD009779, 2012. PMID: 22592743.
30. **Uy MC, Daez ML, Sy PP, Banez VP, Espinosa WZ, and Talingdan-Te MC.** Early ERCP in acute gallstone pancreatitis without cholangitis: a meta-analysis. *JOP : Journal of the pancreas* 10: 299-305, 2009. PMID: 19454823.
31. **van Santvoort HC, Bakker OJ, Besselink MG, Bollen TL, Fischer K, Nieuwenhuijs VB, et al.** Prediction of common bile duct stones in the earliest stages of acute biliary pancreatitis. *Endoscopy* 43: 8-13, 2011. PMID: 20972954.
32. **van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, et al.** A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* 141: 1254-1263, 2011. PMID: 21741922.
33. **Venneman NG, Buskens E, Besselink MG, Stads S, Go PM, Bosscha K, et al.** Small gallstones are associated with increased risk of acute pancreatitis: potential benefits of prophylactic cholecystectomy? *Am J Gastroenterol* 100: 2540-2550, 2005. PMID: 16279912. PMID: 16279912.
34. **Verma D, Kapadia A, Eisen GM, and Adler DG.** EUS vs MRCP for detection of choledocholithiasis. *Gastrointest Endosc* 64: 248-254, 2006. PMID: 16860077.
35. **Working Group IAPAPAAPG.** IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 13: e1-e15, 2013. PMID: 24054878.
36. **Yadav D and Lowenfels AB.** The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 144: 1252-1261, 2013. PMID: 23622135.
37. **Yadav D and Lowenfels AB.** Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 33: 323-330, 2006. PMID: 17079934.