

Biliary pancreatitis

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Gallstone-induced acute pancreatitis is a prevalent condition that is associated with an unacceptably high mortality rate. Early endoscopic intervention, including endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy within 24 to 72 h of hospital admission, can be used to remove stones in the common bile duct (CBD) and establish biliary drainage. Anecdotal evidence of its effectiveness led to formal testing in randomized clinical trials. Although the design and results of the four published studies have varied, the overall conclusion is that early endoscopic therapy reduces morbidity and mortality in patients with acute biliary pancreatitis. Benefits are especially apparent in patients who satisfy generally accepted criteria for severe pancreatitis. The author's practice is to undertake endoscopic retrograde cholangiopancreatography in patients with severe or worsening pancreatitis, or in patients with jaundice, cholangitis or dilation of the CBD. Endoscopic sphincterotomy is performed in patients with CBD stones or in patients with biliary pancreatitis and cholelithiasis who are not candidates for cholecystectomy. The roles of newer diagnostic modalities, including magnetic resonance cholangiopancreatography and endoscopic ultrasonography, are not yet clear.

Key Words: *Biliary pancreatitis; Endoscopic sphincterotomy; ERCP; Gallstone pancreatitis*

Gallstones are the leading cause of acute pancreatitis (AP) in many Western and Asian countries (1-3), accounting for 34% to 54% of the 4.8 to 24.2 cases per 100,000 each year of the disease (4-6). Despite advances in intensive care management, the case fatality rate of severe AP is still approximately 10%.

Early endoscopic intervention has been increasingly used in the management of acute biliary pancreatitis (ABP). It allows the removal of the offending stone(s) and the establishment of biliary drainage. Observational data (7,8) and, more importantly, four randomized controlled trials (RCTs) involving more than 800 patients have supported the use of endoscopic sphincterotomy (ES) (4,5,9,10). In specialized centres, success rates exceed 90%. This article summarizes the results of these studies and describes the optimal approach to the management of ABP.

La pancréatite biliaire

La pancréatite aiguë causée par un calcul biliaire est une pathologie prévalente associée à un taux de mortalité inacceptable. Une intervention endoscopique précoce, y compris une cholangiopancréatographie rétrograde endoscopique et une sphinctérectomie endoscopique dans les 24 heures à 72 heures suivant l'hospitalisation, peuvent permettre d'éliminer les calculs du canal cholédoque (CC) et d'établir un drainage biliaire. Des observations isolées de son efficacité ont donné lieu à des études officielles dans le cadre d'essais cliniques aléatoires. Bien que la conception et les résultats des quatre études publiées aient été variés, d'après la conclusion globale, un traitement endoscopique précoce réduit la morbidité et la mortalité chez les patients atteints d'une pancréatite biliaire aiguë. Les bénéfices sont particulièrement apparents chez les patients qui présentent les critères généralement acceptés de pancréatite grave. La pratique des auteurs consiste à entreprendre une cholangiopancréatographie rétrograde endoscopique chez les patients atteints d'une pancréatite grave ou à l'évolution défavorable ou chez ceux présentant une jaunisse, une cholangite ou une dilatation du CC. Une sphinctérectomie est effectuée chez les patients ayant un calcul CC ou chez ceux qui souffrent d'une pancréatite biliaire et d'une lithiase biliaire impossibles à traiter par cholécystectomie. Le rôle des récentes modalités diagnostiques, y compris la cholangiopancréatographie par résonance magnétique et l'écho-endoscopie, n'est pas encore clair.

PROGNOSTIC FACTORS

The majority of patients with ABP experience relatively minor episodes, from which they recover within a week with conservative therapy. On the other hand, a significant proportion of patients with severe pancreatitis die during their initial hospitalization (6). Early and accurate identification of patients with severe AP is crucial, because they require and are likely to benefit from intensive medical management and early endoscopic therapy.

Assessment of the severity of AP has been accomplished by:

- the presence of organ failure (11);
- early prognostic indices (12,13); and
- the presence of necrosis, abscesses and fluid collections, as visualized by dynamic contrast-enhanced computerized tomography (CT) (14).

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The development of organ failure is a reliable sign of severe pancreatitis. While criteria vary, it appears that the presence of respiratory failure (partial pressure of arterial oxygen less than 60 mmHg), renal failure (creatinine greater than 2 mg/dL [177 µmol/L]), shock and gastrointestinal bleeding are the most important determinants of severe pancreatitis. The mortality rate is virtually zero if there is no organ failure, but increases to nearly 20% if at least one of the above criteria is met (15). Patients with organ failure are more likely to have necrotizing than interstitial pancreatitis. However, waiting for such complications to occur may negate the benefits of early therapy.

Early prognostic indices have been employed during the patient's initial evaluation (12,13). These include the biliary version of Ranson's criteria (12) that are frequently used in the United States, the modified Imrie's criteria (13) that are used mainly in Europe, and APACHE-II scores (16) that are widely used in intensive care units. They reflect the effects of pancreatic injury and, if present, of concurrent biliary obstruction with or without cholangitis, on fluid and metabolic status and extra-pancreatic organs. Their sensitivities and specificities in predicting mortality are 90% and 80%, respectively.

CT with dynamic contrast enhancement has provided additional useful prognostic information (17). The use of intravenous contrast material permits the delineation of nonperfused tissue in and around the pancreas. Ischemia is a consequence of damage to the microcirculation. A grading system has been developed that reflects the amount of retroperitoneal (including pancreatic) necrosis: higher CT grades are associated with worse prognosis (17).

In addition to aiding clinical management, the use of prognostic indices facilitates the comparison of therapeutic studies undertaken in different institutions.

ENDOSCOPIC TREATMENT OF ABP

The first RCT of endoscopic retrograde cholangiopancreatography (ERCP) and ES was conducted by the Leicester group (4) from 1983 to 1987, after sporadic reports of rapid improvement of clinical and laboratory parameters with these techniques. The benefits of early endoscopic therapy were substantiated, and concerns about exacerbation of pancreatitis, cholangitis, hemorrhage and perforation were not realized. Since then, three more RCTs of this therapy have been conducted (5,9,10).

United Kingdom

The Leicester group (4) randomly assigned 121 patients with suspected ABP to receive either conservative therapy or ERCP within 72 h of admission. Patients who were found to have choledocholithiasis then underwent ES and stone extraction. The severity of pancreatitis was graded according to a modification of the Glasgow criteria (18). Of the 121 patients, 59 (25 of whom had severe pancreatitis) underwent ERCP and 62 (including 28 with severe pancreatitis) received conventional treatment. ERCP was technically successful in 94% of patients with mild and 80% of those with severe pancreatitis, and common bile duct (CBD) stones were found in 25% and 63% of cases, respectively. All CBD stones were removed endoscopically without complication. This study yielded several important findings.

- ERCP could be safely performed in patients with ABP in a specialized centre.

- Compared with conventional therapy, ERCP reduced the morbidity (24% versus 61%) and mortality (4% versus 18%) of patients with severe pancreatitis.
- ERCP was associated with reduced hospital stays for patients with severe pancreatitis.

Hong Kong

A second RCT was undertaken at the University of Hong Kong (5), where the incidence of choledocholithiasis as a cause of AP is quite high. Because of this fact, the results may not be applicable to other parts of the world. The investigators randomly assigned 195 patients with AP to early ERCP (within 24 h of admission) or conventional treatment. A severe attack was defined as one in which the serum urea concentration exceeded 45 mg/dL (16.2 mmol/L) and the plasma glucose concentration was greater than 198 mg/dL (11.0 mmol/L) on admission.

Biliary stones were present in the majority of the patients (127 of 195, or 65%). Of the 97 patients who underwent ERCP, 64 were found to have gallstones, and 37 patients with CBD stones underwent ES. Of the 63 patients with gallstones who were allocated to receive conventional therapy, 22 subsequently deteriorated and underwent ERCP. Ten of these patients proved to have choledocholithiasis. Endoscopic management reduced the morbidity (from 54% to 13%) and the mortality (from 18% to 3%) in patients with severe pancreatitis.

Both of these studies demonstrated the benefits of ERCP and ES in patients with severe AP, but neither found that the outcomes were improved in patients with mild disease (4,5). It is possible that the majority of practitioners may not be able to achieve the results described in these single-centre studies. Other studies with similar designs have not been undertaken, perhaps because of formidable logistical and perhaps even ethical barriers. Although some authorities have questioned the validity of the criteria for severe pancreatitis used in these studies, they are practical, have adequate sensitivity and specificity, and have been widely adopted in clinical practice.

Germany

A prospective multicentre German trial enrolled 238 patients with ABP who had no evidence of obstructive jaundice, and assigned them to either ERCP within 72 h of admission or conventional therapy (9). Of the 126 patients in the interventional group, 121 (96%) successfully underwent ERCP, and 58 proved to have choledocholithiasis. Twenty of the 112 patients in the control group subsequently required ERCP, and 13 of these underwent removal of CBD stones. There were no significant differences in the morbidity or mortality rates between the two groups, but patients who received early ERCP experienced a higher incidence of respiratory failure and more severe complications. Moreover, there was a trend toward increased mortality in the ERCP group, which was contrary to the findings of the other RCTs (4,5). Stratification of the patients according to the severity of disease did not affect the findings.

This study involved only patients with ABP who did not have obstructive jaundice, and, thus, it may be surmised that this subgroup of patients do not require ERCP. Many concerns about the design and results of this trial have been raised (19), however, and confirmatory studies are needed.

The first concern is about the small number of patients enrolled by each of the 22 centres that participated in the

German trial. On average, only 10.8 patients (range six to 29) were enrolled at each centre during a period of 54 months, or 2.4 patients per centre each year. Three sites enrolled 20 or more patients, and so the remaining 19 centres studied fewer than two patients per year. In contrast, the single-centre United Kingdom and Hong Kong trials enrolled 121 and 195 patients, respectively. It is known that ERCP and ES are technically demanding procedures, and that proficiency requires ongoing experience (19). Therefore, the lack of benefit from early endoscopic therapy may reflect the lack of available patients or inadequate expertise.

The second concern addresses the finding that early ERCP was associated with a five-fold increase in the incidence of respiratory failure, as defined by an inability to maintain a partial pressure of arterial oxygen above 60 mmHg with an oxygen mask, and a trend towards increased mortality rates. While hypoxemia is a frequent complication of severe pancreatitis, this complication was not associated with ERCP in either the United Kingdom or Hong Kong trial. The P value for the respiratory failure finding was 0.03. It has been argued that the significance level should have been corrected for the use of multiple comparisons (Bonferroni correction), instead of using the standard 0.05 threshold value.

Poland

The fourth study, recently completed in Poland, has been published in abstract form only (10). A total of 280 patients with suspected ABP underwent duodenoscopy within 24 h of admission. The 75 patients who were found to have stones impacted at the papilla underwent immediate ES. The remaining patients were randomly assigned to either immediate ERCP or conventional therapy. ERCP and ES were associated with a significant decrease in complications (17% versus 36%) and mortality (2% versus 13%). Moreover, earlier timing of ERCP correlated with decreased morbidity and mortality, and the benefits of early endoscopic therapy applied also to patients with mild pancreatitis. A detailed analysis of this study, however, will require publication as a full-length article.

The designs of these four RCTs differ from each other. Differences in the ethnic characteristics of the patients, the environment and even technical expertise might also have been important. Therefore, it is difficult to come to a single set of recommendations based on these data. The studies from the United Kingdom and Hong Kong support the use of early endoscopic intervention in patients with severe disease, while the Polish study suggests that patients with milder disease may also benefit. The German study appears to provide contradictory results, but it might actually have been complementary because it included patients who probably would not have been enrolled in the studies from the United Kingdom and Hong Kong. The results of a recent meta-analysis also support the use of early intervention (20).

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MICROLITHIASIS

In up to 30% of cases of AP, history, physical examination and routine studies do not reveal a clear etiology. Some of these patients have gallstones that are too small to be visualized with conventional imaging techniques. The association of microlithiasis and pancreatitis was reported as long as 50 years ago (21). Lee et al (22) found evidence of microlithiasis in 74% of 31 patients with an initial diagnosis of idiopathic pancreatitis. The patients who underwent either sphincterotomy or cholecystectomy experienced fewer recurrences of AP during follow-up compared with untreated patients (10% versus 73%). Ros et al (23) reported similar findings.

PREFERRED MANAGEMENT OF ABP

The results of randomized clinical trials provide some guidance for the management of patients with ABP. In accordance with these findings, the author performs urgent ERCP in patients with suspected or proven biliary origin when the following conditions are met:

- evidence of severe pancreatitis;
- coexisting cholangitis;
- jaundice;
- dilation of the CBD; and
- clinical deterioration in patients with initially favourable prognostic signs.

The author uses APACHE II criteria, organ failure and CT findings, if available, to identify patients with severe pancreatitis.

ES almost certainly protects against the recurrence of gallstone-induced pancreatitis. Therefore, the author considers performing this procedure in patients with severe gallstone pancreatitis, a dilated CBD, or gallbladder stones if cholecystectomy is not an option. In the author's experience, patients with microlithiasis have recurrent episodes of relatively mild AP. When other causes of AP are not apparent, the author routinely collects bile during ERCP and perform a microscopic analysis for crystals. In some cases, the author also undertakes sphincter of Oddi manometry.

FUTURE DIRECTIONS

Diagnostic ERCP is associated with significant morbidity and mortality rates. The use of other techniques to detect CBD stones, such as magnetic resonance cholangiopancreatography and endoscopic ultrasonography, may more precisely identify patients who require ERCP (24-26). In theory, this would reduce the overall risk of complications, but many technical and logistical barriers need to be overcome before these less invasive modalities could be applied in practice.

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