Conservative management of cholestasis with and without fever in acute biliary pancreatitis

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Abstract
The presence of cholestasis in both mild and severe forms of acute biliary pancreatitis (ABP) does not justify, of itself, early endoscopic retrograde cholangiography (ERC) or endoscopic sphincterotomy (ES). Clinical support treatment of acute pancreatitis for one to two weeks is usually accompanied by regression of pancreatic edema, of cholestasis and by stone migration to the duodenum in 60%-88% of cases. On the other hand, in cases with both cholestasis and fever, a condition usually characterized as ABP associated with cholangitis, early ES is normally indicated. However, in daily clinical practice, it is practically impossible to guarantee the coexistence of cholangitis and mild or severe acute pancreatitis. Pain, fever and cholestasis, as well as mental confusion and hypotension, may be attributed to inflammatory and necrotic events related to ABP. Under these circumstances, evaluation of the bile duct by endo-ultrasonography (EUS) or magnetic resonance cholangiography (MRC) before performing ERC and ES seems reasonable. Thus, it is necessary to assess the effects of the association between early and opportune access to the treatment of local and systemic inflammatory/infectious effects of ABP with cholestasis and fever, and to characterize the possible scenarios and the subsequent approaches to the common bile duct, directed by less invasive examinations such as MRC or EUS.

Key words: Biliary pancreatitis; Cholestasis; Endoscopic sphincterotomy; Cholangitis; Mortality; Magnetic resonance cholangiopancreatography; Endoscopic retrograde cholangiography; Endoscopic ultrasonography; Intensive care; Health system regulation

INTRODUCTION
The association between acute pancreatitis (AP) and the migration of gallbladder stones and sludge to the common bile duct and the intestinal lumen, the possibility that impaction of these stones in the ampulla of Vater will worsen the pancreatic injuries[1-4] and the detection of an impacted stone at autopsy in about half the cases of acute biliary pancreatitis (ABP)[5] have contributed to the adoption of early endoscopic retrograde cholangiography (ERC) and endoscopic sphincterotomy (ES) in ABP. The incorporation of diagnostic and therapeutic endoscopy into clinical practice, technology diffusion due to market forces and the influence of studies published in the last decades of the 20th century[6-8] have also been determinant factors in the adhesion to early ERC and ES in ABP.
However, on the basis of the results of recent studies and meta-analysis[9-18], as well as critical analyses[13,15], it has been concluded that the systematic adoption of early ERC followed by ES for ABP has exposed many patients to invasive diagnosis and unnecessary surgery. The most recent meta-analysis based on three prospective and randomized studies did not demonstrate any influence of ERC (with or without ES) on the morbidity or mortality rates of patients with mild or severe ABP, without cholangitis[13]. The conceptual difficulties for the characterization of ABP associated with cholangitis were reported in these studies, but aspects related to the diagnostic and therapeutic approaches to this condition are treated in a consensual manner.

The similar incidence of the severe form of AP in the different etiologies established in the literature[16,17] supports the thesis that the magnitude of the pancreatic insult can be pre-established at the start of the clinical manifestations, and the course of the initiated AP episode may not be influenced by ERC or ES[12-18]. Thus, the theory that the migration of small gallstones can trigger the onset of ABP and that their repeated passage, the impaction of the ampulla of Vater with larger stones[13,15] or the persistence of bilipancreatic obstruction may induce progression to the severe form of ABP[11] is still a matter of speculation.

Based on primary and secondary evidence[15], circumstances that delay access to reference services and clinical practice seem to contribute to the adoption of a more conservative approach to the management of the common bile duct in AP, as demonstrated by a study performed in the United Kingdom, in which the application of the protocol of the British Society of Gastroenterology was found not to be homogeneous. Only 45 of 93 (48%) patients with severe AP, particularly those with signs of biliary obstruction and cholangitis, were subjected to ERC and ES, and no increase in complications or mortality was detected[18].

The impaction of a gallstone in the common bile duct was recorded in 26% to 72% of ABP patients when surgery was performed in the early phase and was recorded in less than 10% of patients operated upon in an elective manner[20,21]. Spontaneous disobstruction of the bile duct was demonstrated in 71% to 88% of cases within 48 hours of the onset of ABP, with no changes in the course of the disease[2,3]. The spontaneous relief of cholestasis and of bilipancreatic obstruction assessed by endo-ultrasonography (EUS) followed by ERC in patients referred to a reference service with ABP plus cholestasis and/or cholangitis, ranged from 56% to 75%[2,3]. Reduction of pain and of hyperbilirubinemia was observed in 62% of the patients within 48 hours of the onset of ABP symptoms[20,21], and 60% of the patients subjected to conservative treatment did not present choledocholithiasis during elective surgery [cholecystectomy and intraoperative cholangiography (IC)] performed during the same hospitalization[2,22].

Thus, conservative treatment, in addition to produc-
ond week after the onset of symptoms. Thus, the excessive pressure on emergency and intensive care physicians to perform the CER and EE (habitually within 48 to 72 hours) or to employ surgical, percutaneous or endoscopic procedures for material collections and pancreatic necrosis during the early phase is incompatible with the currently available evidence.

The rate of complications after diagnostic ERC is significant (5% to 10%), and the mortality rate is not negligible (0.07% to 0.1%). When ES is added to ERC, the rate of complications ranges from 7% to 10% and the mortality rate from 0.2% to 2.2%[25,29]. In addition, clinical and scientific evidence does not support the argument that stone impaction in the biliopancreatic confluence aggravates pancreatitis[1-3] or that the migration of small stones from the gallbladder to the choledochus and their passage into the duodenum would cause mild acute pancreatitis and prepare the path for the migration of larger gallstones that might impact the biliopancreatic confluence and cause severe pancreatitis[4].

The controversy about the effect of early ERC and ES performed in patients with APB and choledocholithiasis has decreased. A study of ES performed within 48 h of admission in patients with a bile duct measuring ≥ 8 mm in diameter and with total bilirubin ≥ 1.20 mg/dL revealed choledocholithiasis in 72% of cases[32]. A second group of patients in the same study, with similar clinical and demographic conditions and treated conservatively, presented choledocholithiasis in 40% of cases, as identified by IC performed in elective biliary surgery during the same hospitalization. However, despite the elevated persistence of choledocholithiasis in the conservatively treated group, these patients did not show either progression of the pancreatic or peripancreatic injuries or worsening of the pancreatitis severity score. In addition, morbidity and mortality rates were similar for the two groups[13].

The incidence of choledocholithiasis detected by EUS in patients with APB with and without choledocholithiasis during a period of 3 days after the onset of symptoms was 33%, significantly higher than the 18% rate detected in examinations performed after 3 days. Although the patients with severe pancreatitis were submitted to early EUS more frequently than patients with the mild form of the disease, no relationship was observed between disease severity and the presence of gallstones. The presence of gallstones was significantly higher in patients with jaundice and cholangitis (44%) than among patients without jaundice (19.5%)[39]. A study of the common bile duct of 110 patients with APB without separating the group with choledocholithiasis, conducted within 24 h of admission and after a maximum of 60 hours from the onset of symptoms, detected a 40% rate of choledocholithiasis[10].

Thus, in APB with choledocholithiasis, it is possible to observe the evolution of the clinical manifestations and of choledocholithiasis. If possible, it is advisable to wait for the regression of pancreatic inflammation and stone migration, and to then select the most appropriate imaging modality to confirm disobstruction of the common bile duct.

A careful meta-analysis including three prospective and randomized studies (which were not, however, homogeneous regarding the characterization of the time for ERC and ES, the definition of cholangitis and complications, and laboratory and imaging stratification of cholangitis) did not demonstrate a beneficial effect of ERC with or without early ES on mild or severe APB without choledocholithiasis. Of the 450 patients studied, 230 were allocated to early ERC and 220 to conservative treatment, but only half of those subjected to early evaluation presented choledocholithiasis in the common bile duct[25]. Among the group subjected to early investigation and treatment, ERC was performed in 214 patients (93%), ES was performed in 114 patients (53%), and lithiasis was removed in 111 patients (52%). The rate of ERC complications was 2%. In the group undergoing conservative treatment (220 patients), ERC was performed in 33 patients (15%), and ES with stone removal was performed in 14 cases (43%). In this group, there were no complications after ERC. Overall evaluation showed that the incidence of choledocholithiasis was 48% following early endoscopic treatment and 6% following conservative treatment. These findings underscore the need to characterize patient groups for selective diagnosis and treatment.

Therapeutic choices for patients with APB vary according to the severity of pancreatitis and the presence of choledocholithiasis. In the ACP task force consensus conference, the following therapeutic options were identified: conservative treatment, ERC, ES, ERCP, and surgical treatment. The results obtained with conservative treatment of APB permit us to conclude that choledocholithiasis can regress or persist with or without fever and pain, within a short period of time.

The levels of bilirubin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase (ALP) are within normal limits in 14.5%, 12.3%, 11.2% and 26.4% of APB cases, respectively. Overall evaluation shows that about 15% to 20% of patients with APB have markers of choledocholithiasis within normal limits[23]. On the other hand, 92% of the patients with APB who presented 4 or 5 changes in a defined set of variables evaluated upon admission (diameter of the choledochus ≥ 9 mm, ALP ≥ 250 U/L, gamma-glutamyltransferase ≥ 350 U/L, total bilirubin ≥ 3 mg/dL and direct bilirubin ≥ 2 mg/dL) presented choledocholithiasis in the common bile duct[25]. Thus, patients with APB may be admitted without choledocholithiasis, with residual choledocholithiasis due to the passage of the stone and to pancreatic edema, with choledocholithiasis due to the persistence of the stone in the bile duct, or with cholangitis.

The relative sensitivity of MRC, ERC and EUS for the detection of choledocholithiasis in the common bile duct, taking as reference the extraction of gallstones by ES, is 80%, 90% and 95%, respectively[14]. MRC has high sensitivity (94%-100%) and specificity (91%-98%) in the detection of gallstones in APB when IC and ERC are taken as reference[25,36], although sensitivity is greatly reduced in the presence of gallstones smaller than 6 mm[10]. It should also be emphasized that the value of MRC and EUS in
the detection of choledocholithiasis and of bilipancreatic obstruction has been unequivocally demonstrated in two meta-analyses, with these methods appearing to be determinant factors for the indication of ES in ABP.

On the basis of the clinical and laboratory characterization of cholestasis and of the anesthetic surgical risk to patients, it is possible to define scenarios based on the use of more sensitive and less invasive imaging exams for the detection of gallstones, microstones and bile sludge. The selection of endoscopic treatment based on echoendoscopy may eventually impact the treatment of ABP and provide greater safety for the patients, as well as a more rational use of health care system resources.

DIFFERENT PRESENTATIONS OF ACUTE BILIARY PANCREATITIS AND ALTERNATIVES FOR MANAGEMENT

Patients with ABP who progress with regression of abdominal pain and cholestasis and who present a low anesthetic surgical risk can be subjected to cholecystectomy and IC alone, usually during the same hospitalization, about one week after the onset of symptoms. Videolaparoscopic choledocholithotomy is indicated when lithiasis identified by IC persists in the common bile duct. Patients with choledocholithiasis identified by IC that is not treated during cholecystectomy or patients with a high anesthetic surgical risk can be treated by ES (Figure 1).

When cholestasis and pain persist, evaluation of the common bile duct by MRC or EUS appears to be reasonable and, in the presence of choledocholithiasis, ES followed by cholecystectomy is a good option, performed preferably during the same hospitalization for patients with low anesthetic surgical risk. In patients who develop pancreatic injury (necrosis, peripancreatic fluid collection), it is preferable to postpone cholecystectomy until the evolution of these lesions can be defined, as they frequently regress or are converted to infected necrosis, abscesses or pseudocysts that can be treated endoscopically (Figure 1).

Finally, studies have unanimously recommended early ERC and EUS in cholangitis. However, it is practically impossible in clinical practice to ensure the coexistence of cholangitis and mild or severe acute pancreatitis with cholestasis and fever, in order to instigate ERC with early ES. Fever and cholestasis can be attributed only to the inflammatory and necrotic events of ABP and, under these circumstances, evaluation of the bile duct by MRC or EUS before performing ERC and ES also seems reasonable.

The reported incidence of cholangitis in association with ABP ranges from 2.5% to 20% and although it does not have a unique definition. Thus, the definition of the two conditions is borrowed and Charcot’s triad may simply represent either the manifestation of mild acute biliary pancreatitis with cholestasis and fever or a true association of these symptoms with cholangitis. Additionally, the presence of Reynold’s pentad (Charcot’s triad plus mental confusion and hypotension) may not be the manifestation of acute biliary pancreatitis with cholangitis, but may also represent an association with severe cholangitis. Thus, the time and mode of assessment of the biliary pathway, as well as the treatment of lithiasis, should be based on the possible association of the recommendations for ABP and cholangitis. On this basis, the systematic indication of ERC plus ES, especially in the case of mild presentation of the association of ABP with cholangitis, is not justified.

Patients with acute cholangitis associated with ABP can, when both conditions are in the mild form, be treated by admission to hospital and treatment with hydration and antibiotics (first- or second-generation cephalosporin or penicillin plus a β-lactamase inhibitor) for two or three days. Patients with moderate or severe cholangitis associated with ABP should be treated with fluid replacement, vasoactive amines, respiratory support and antibiotics for 5 to 7 d (penicillin plus a β-lactamase inhibitor and third- or fourth-generation cephalosporins possibly combined with metronidazole). A second line of antibiotics consisting of quinolone with or without metronidazole or carbapenemic agents can also be used. Selection of the antibiotic could be adjusted depending on other variables present upon admission of patients with AP, such as hepatic and renal functional status.

The time for biliary disobstruction in cholangitis is related to the severity of the presentation of the condition. In the mild and moderate forms with good response to clinical treatment, disobstruction may be elective. In moderate cholangitis with an unfavorable course over a period of 24 to 48 h or in severe cholangitis, the need for biliary disobstruction is urgent. The use of a guidewire and a minimal use of contrast in the biliopancreatic pathway are highly recommended, in order to prevent the worsening of cholangitis and pancreatitis. The installation of a nasobiliary catheter or prosthesis is preferable to the use of ES, especially in patients with clotting disorders. However, a response to clinical treatment occurs in 80% of cases and the need for urgent biliary disobstruction is rare. These observations coupled with the characteristics of public health systems and possible access to a reference hospital and its services have definitely influenced the management of ABP cases associated with and without cholangitis.

CONCLUSION

Over recent decades, the surgical treatment of biliary lithiasis and of its pancreatic complications has shifted from the early to the late phase, preferentially with the use of minimally invasive techniques, and with a need for specialized services and the participation of the various clinical specialists, concentrated in tertiary health services.

Within the context of the dynamic and diverse course of ABP patients with different care needs and of the management of patient flow, the definition of priorities and the appropriate access to services, resources and specialists are a challenge and may impair the application
of the clinical decisions recommended in protocols and consensuses\cite{19,42-45}.

Conservative treatment of ABP with cholangitis, similar to what occurs in cases without cholangitis, shows rates of spontaneous clearance of the common bile duct within two weeks of approximately 70%. Spontaneous clearance of the common bile duct prevents unnecessary invasive procedures that pose the risk of aggravating cholangitis and pancreatic inflammation.

In mild ABP associated with cholestasis and fever, despite the limitations in cholangitis characterization, the systematic application of early ERC and ES or of EUS and MRC is not justified. Under these circumstances, in addition to the limitations for the differentiation between inflammatory pancreatic disease and cholangitis, the recommendations for the treatment of mild and moderate cholangitis and ABP are conservative and therefore convergent. On the other hand, in the presence of severe ABP with cholangitis, EUS or MRC could guide the indication of bile duct decompression.

Thus, despite the limitations involved in controlled clinical studies of patients with ABP, the arguments presented, together with the recent critical literature reviews regarding ABP and cholangitis\cite{13,17,19,20}, support the hypothesis of conservative treatment of ABP when the condition is accompanied by fever and hyperbilirubinemia.

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