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EDITORIAL

Early Use of ERCP in Acute Biliary Pancreatitis with(out) Jaundice: An Unjaundiced View

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Blind belief in authority is the greatest enemy of truth
Albert Einstein

Acute pancreatitis is a disease with a wide spectrum of etiologies, including casuistic toxins and viruses, congenital malformations and different vascular pathologies. However, with the exception of areas with a high prevalence of alcohol abuse, "biliary" is the most common form of acute pancreatitis in the majority of countries [1, 2, 3]. It is traditionally thought that "biliary" acute pancreatitis form accounts for 40-60% of this disease, and such a frequency may, in fact, be even higher as microlithiasis can be responsible for many cases of so-called "idiopathic" acute pancreatitis [4, 5]. Unfortunately, since its inception as a clinical entity in 1889 and despite more than a century of research, the treatment of acute pancreatitis, regardless of its cause, remains mainly supportive [6]. A ray of hope rose in the 1980s with the introduction of endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy in routine clinical practice as it had the potential of being a pathogenetic treatment in patients with the gallstone etiology of acute pancreatitis. Nevertheless, despite two decades of clinical studies, the early use of this endoscopic intervention in patients with acute biliary pancreatitis is still a notoriously controversial issue.

Conventional reasons for such a controversy (differences in study populations, peculiarities of study designs, methodological issues of the studies conducted, etc.) are abundantly discussed by the rival authors of primary evidence (clinical trials) and complemented by the secondary evidence (systematic reviews) of their supporters [7, 8, 9, 10, 11, 12, 13].

Key words Algorithms; Cholangiopancreatography, Endoscopic Retrograde; Cholangiopancreatography, Magnetic Resonance; Endosonography; Pancreatitis, Acute Necrotizing

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However, it can be bewildering for an ordinary practitioner to decide who has the better argument. In case of such doubtfulness, the majority of physicians naturally tend to adhere to the position of a more authoritative evidence provider. In this case, a probability of biased interpretation of the data in a clinical study or inaccurate data calculations in a meta-analysis is neglected by default. However, a question remains unanswered: is this probability indeed negligible? Therefore, the present editorial purports to impartially investigate the wealth of evidence-based literature with particular emphasis on primary and secondary evidence which guide the current practice of early management of patients with acute biliary pancreatitis.

Primary Evidence

A pioneer randomized controlled trial aimed at comparing early ERCP with(out) endoscopic biliary decompression and conservative management in patients with acute pancreatitis dated back to 1988, when a study from Leicester (UK) showed the benefits of early endoscopic intervention [14]. It was followed by a randomized controlled trial from Hong Kong (China) [15]. Both of these trials found a reduction of complications (but not mortality) with the early use of ERCP. However, this effect was statistically significant solely in patients with predicted severe acute pancreatitis. To explain the findings of these trials, a "theory of persistent bile duct stones" was proposed, according to which small migrating main bile duct stones cause a mild attack of acute pancreatitis and rapidly pass into the duodenum, whereas subsequent big persistent stones intermittently obstruct the main bile duct and cause a severe attack of acute pancreatitis [16]. Therefore, ERCP might be allegedly justified in patients with severe but not mild acute pancreatitis. It should be borne in mind, however, that this theory was based on a retrospective study of 100 patients with gallstones, treated in the Leicester Royal Infirmary over a 10-year period.

The core finding of that study was that main bile duct stones (detected by means of ERCP) were more likely

to “persist” in patients with predicted severe acute pancreatitis, when compared with predicted mild acute pancreatitis, as there was a significant difference in the incidence of main bile duct stones between the subgroups of patients with predicted severe and predicted mild acute pancreatitis. However, this finding should be interpreted with great caution. First, the positive predicted value of the criteria used for the prediction of severity was only 50% (19 patients had an actual severe outcome out of 38 patients with predicted severe attack). It seems that to be valid, ideally, a theory should be based on an actual matter (in our case, actual severity) only; anyway, a theory which introduces a 50% misclassification error hardly reflects a true pathogenesis. Moreover, if the data were presented with respect to the actual (not predicted) course of acute pancreatitis, the statistical difference would vanish. Second, selection and information biases cannot be excluded as the study was retrospective, the patients were non-consecutive and the presence of choledocholithiasis was verified only by means of ERCP. Third, if the pathogenesis of severe acute biliary pancreatitis indeed included such an infrequent chain of events (small stones migrate from the gallbladder and cause mild acute pancreatitis, then pass into the duodenum, then big stones pass from the gallbladder, persistently obstruct the main bile duct and cause severe acute pancreatitis), the incidence of the severe form would markedly differ between patients with a biliary and those with a non-biliary etiology of acute pancreatitis. Most studies, however, did not show a difference in the incidence of severe acute pancreatitis between the etiologies [17, 18]. Fourth, a “theory of persistent bile duct stones” implies that there should be a causal relationship between the presence of main bile duct stones and the severity of acute pancreatitis. However, one should be aware that causality between any two variables cannot be assumed simply on the basis of their association as there may be other investigated or uninvestigated factors affecting the cause-effect relationship [19, 20].

One of such factors might be the duration of biliopancreatic obstruction. A number of experimental and clinical studies demonstrated that the severity of acute pancreatitis depends on the duration of the main bile duct obstruction [21, 22, 23]. In particular, a retrospective study of 97 patients with acute gallstone pancreatitis from Santa Fe (Argentina) revealed the following association between the duration of the obstruction and the severity of acute pancreatitis: 3 out of 37 (8.1%) had a severe lesion (pancreatic and/or peripancreatic necrosis and/or pancreatic abscess and/or pseudocyst) when the obstruction of the main bile duct lasted less than 24 h; 5 out of 47 (10.6%) when it lasted between 25 and 48 h; and 11 out of 13 (84.1%) when it lasted more than 48 h [22]. Notably, the diagnosis and complications of all 97 patients were verified either during surgery or autopsy; thus, the study dealt with the actual course of acute pancreatitis and not the predicted one. Strikingly, the incidence of severe acute pancreatitis in the subgroup of patients obstructed for more than 48 h differed significantly from those who disobstructed within 48 h ($P<0.001$). Recently, a prospective trial from Los Angeles (U.S.A.) yielded similar findings: 4 ot of 52 (7.7%) patients with acute biliary pancreatitis had a complication when the obstruction of the main bile duct lasted less than 48 h as compared with 7 out of 9 (77.8%) patients when it lasted more than 48 h ($P<0.001$) [23]. In addition, the group with a less than 48 h obstruction showed a significantly shorter time until elective cholecystectomy ($P<0.02$) and a shorter length of hospital stay than those having an obstruction of more than 48 h ($P<0.01$). Therefore, based on the facts mentioned above, it seems that duration of obstruction, but not predicted severity, is a critical determinant of ERCP usefulness.

Given that biliopancreatic obstruction might influence the effect of ERCP in patients with acute biliary pancreatitis, a German multicenter randomized controlled trial was designed to include only patients without clinical and radiological signs of biliopancreatic obstruction and found no benefits of early ERCP over conservative treatment [24]. Furthermore, the most recent randomized controlled trial from Buenos Aires (Argentina) [25], aimed at assessing the usefulness of early ERCP in the subgroup of patients with acute biliary pancreatitis who exhibited laboratory and radiological signs of biliopancreatic obstruction (but without signs of acute cholangitis), also revealed no benefits of early ERCP. The certain merits and demerits of each randomized controlled trial mentioned above were explicitly pointed out and discussed in a number of other publications [7, 11, 26, 27, 28]. Perhaps one of the most important drawbacks is that each individual trial was underpowered to draw a valid conclusion regarding the usefulness of early endoscopic intervention, thus, justifying a need for statistical aggregation of the data.

Secondary Evidence

The first systematic review on early ERCP *versus* conservative treatment in acute pancreatitis appeared in 1999 [29]. A meta-analysis found no association between the effect of ERCP and the predicted severity of acute pancreatitis. At the same time, it showed a significant reduction in the risk of complications and mortality in all patients with acute pancreatitis. However, the observed difference might be due to the erroneous inclusion of a randomized controlled trial from Katowice (Poland) as all the patients in the control group of that study received ERCP and not conservative treatment [30].

The second systematic review was conducted under the auspices of Cochrane collaboration [31]. A meta-analysis revealed no benefits of early ERCP over conservative treatment in terms of mortality. At the same time, the early use of endoscopic intervention resulted in a significant reduction in the odds of complications in patients with predicted severe but not

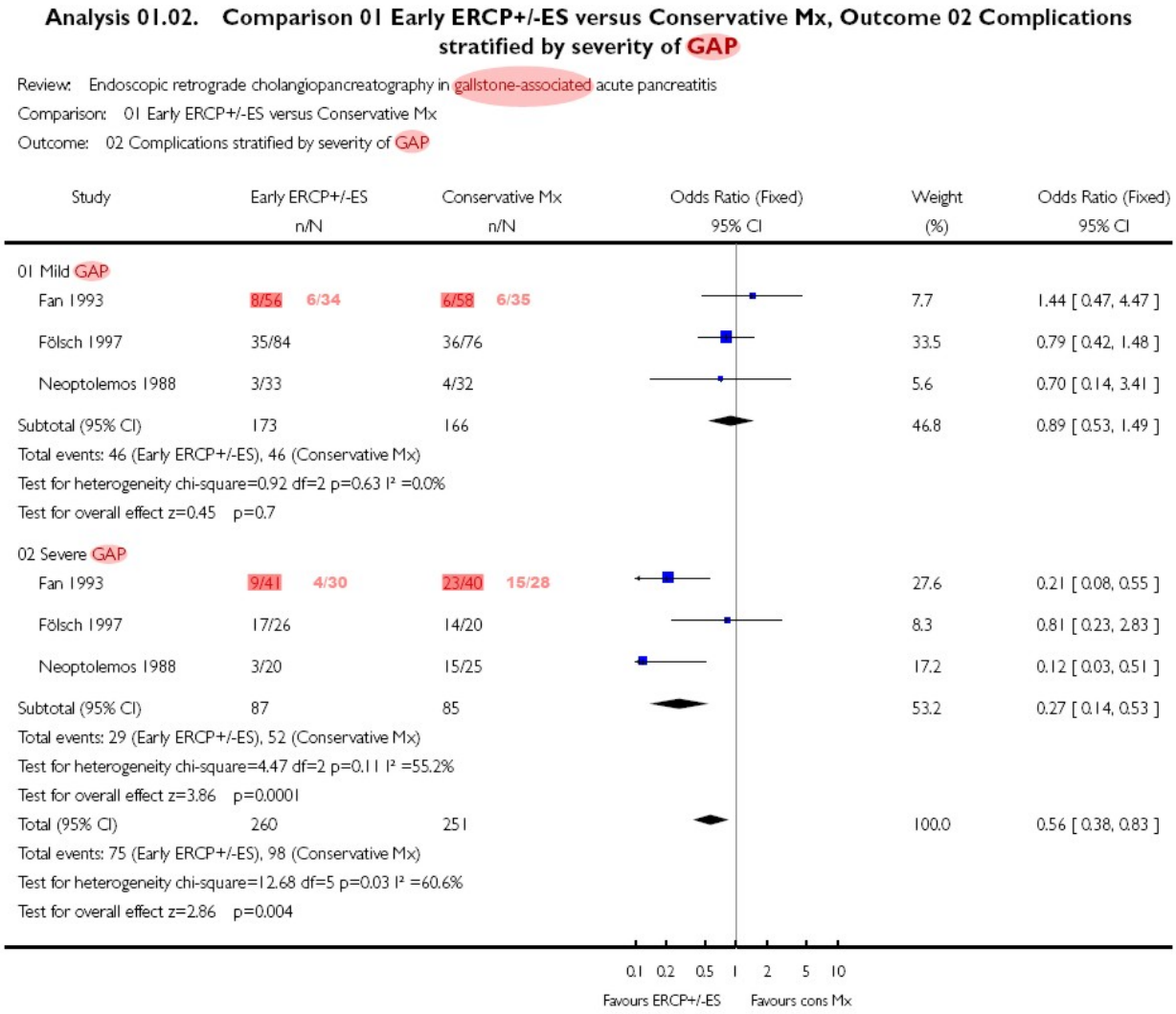

Figure 1. Inaccuracies in the Cochrane meta-analysis (modified from Ayub K *et al.* [31]). Red ovals show that the aim of the meta-analysis was to aggregate the data on patients with gallstone acute pancreatitis (GAP in the figure) only. Red rectangles show inaccurate figures. Correct figures from the original article by Fan *et al.* [15] are shown aside in red.

predicted mild acute pancreatitis. However, despite the fact that this meta-analysis was widely referred to as a source of state-of-the-art knowledge, its findings might be misleading for the following reasons. First, the outcome of the study was 'overall complications' which included a diversified range of systemic, local pancreatic and extrapancreatic complications. Second, though the aim of the authors was to "control for a possible modifying effect of acute cholangitis", they did not specify how this was done (if it was done at all). Third, although the Cochrane meta-analysis included a randomized controlled trial [15] in which 68 out of 195 (34.9%) had a non-biliary etiology of acute pancreatitis (awkwardly, the data on patients with only biliary etiology were readily available in the primary publication), a conclusion about the usefulness of ERCP in patients with biliary etiology was drawn (Figure 1). Curiously, none of the three authors of the Cochrane systematic review published a paper pertinent to acute pancreatitis or ERCP in a peer-reviewed journal since the referred systematic review appeared in 2004.

A subsequent meta-analysis, published in Italy [32], repeated the mistakes of the Cochrane meta-analysis and added its own: it included a study from China [33], which was highly unlikely to be randomized, and used a spurious summary estimate to assess the treatment effect [34]. Not surprisingly, the results of the Italian meta-analysis mirrored those of Cochrane collaboration.

In early 2008, two meta-analyses [35, 36] were published which purported to address the shortcomings of the preceding meta-analyses. One of them sought to compare the effect of early ERCP and conservative treatment on a uniformed outcome such as the incidence of local pancreatic complications (comprised of infected pancreatic necrosis, pancreatic abscess, and pancreatic pseudocyst, according to the current classification of acute pancreatitis) [35]. The study revealed no benefits of early ERCP in terms of local pancreatic complications and mortality both in patients with predicted mild and predicted severe acute pancreatitis. Another meta-analysis sought to avoid the confounding effect of acute cholangitis and therefore

included only those trials in which the data on patients without acute cholangitis were available [36]. This meta-analysis also demonstrated no benefits of early ERCP over conservative treatment in terms of complications and mortality. Again, neither patients with predicted mild nor those with predicted severe acute pancreatitis benefited from the early use of ERCP. Later, the idea of such an approach to statistical aggregation of the data was apparently borrowed and a replicated meta-analysis from the Philippines was presented in abstract form in late 2008 [37]. Not unexpectedly, it also showed no difference between ERCP and conservative treatment both in patients with mild acute pancreatitis and in those with a severe course of the disease. Summarizing the findings mentioned above, it seems that current recommendations and algorithms for early management of acute biliary pancreatitis should be revisited.

Time for Change

No doubt, if ERCP was a completely (or at least reasonably) harmless procedure, there would be no room for this editorial as well as dozens of clinical trials on the prevention of post-ERCP complications. However, ERCP is one of the most challenging endoscopic procedures with a reported rate of procedure-related complications of approximately 5-10% [38, 39]. Moreover, in some cases it may even lead to mortality. It is generally agreed that the main aim of ERCP in patients with acute biliary pancreatitis is to detect main bile duct stones; however, in fact, ERCP is capable of doing this in only 39-46% of cases [35]. This means that at least one in two patients undergoes a futile endoscopic intervention. Furthermore, given that recent randomized and non-randomized studies demonstrated a 71-88% rate of spontaneous disobstruction within 48 h after the onset of acute biliary pancreatitis (and subsequent uneventful course of acute pancreatitis) [22, 40], only a small subgroup of patients might, in fact, have a theoretical justification for undergoing ERCP. In addition, evolutionary pressure from competing technologies (endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP)) has greatly challenged the need for diagnostic ERCP [41]. This is evidenced by the results of a recent study from the U.S.A. which investigated trends in the utilization of ERCP since 1988 [42]. In a cohort of more than 400,000 patients, a steep rise was found in the usage of ERCP until 1996 whereas its utilization steadily fell afterwards (coincidentally or not, the first randomized controlled trial which underscored the lack of clinical benefits from ERCP was published at the same time - in January 1997 [43]).

Indeed, the use of both EUS and MRCP in routine clinical practice has become more and more widespread over the last decade. Scientific evidence for this trend is sound. The results of more than 70 observational studies (involving over 6,500 patients) on diagnostic performance of either EUS or MRCP were aggregated in two meta-analyses: each of them demonstrated excellent performance for both modalities in diagnosing choledocholithiasis [44, 45]. A summary of the findings from those meta-analyses is presented in Table 1. Furthermore, three recent randomized controlled trials of patients with suspected choledocholithiasis assessed the efficacy of two management strategies: EUS in the selection of patients for therapeutic ERCP in the case of detection of a main bile duct stone *versus* diagnostic ERCP with endoscopic sphincterotomy in the case of choledocholithiasis [46, 47, 48]. A meta-analysis of these trials showed that the use of EUS for the selection of patients who will need therapeutic ERCP has a significantly lower risk of complications (13 out of 153 patients (8.5%) *versus* 34 out of 150 patients (22.7%); relative risk 0.37; 95% confidence interval 0.21 to 0.68; P=0.001) in comparison with the use of ERCP for both the diagnosis and treatment of choledocholithiasis (Petrov MS, unpublished data).

Overall, EUS and MRCP have a similarly high performance in diagnosing main bile duct stones. However, the use of EUS seems to be a bit more favorable in the setting of acute pancreatitis as it allows the detection of microlithiasis and it is likely a more cost-effective option as ERCP can be performed during the same session. On the other hand, it is worth mentioning that all three randomized controlled trials mentioned above employed EUS solely to detect choledocholithiasis whereas two meta-analyses [44, 45] convincingly demonstrated a high performance of either EUS or MRCP not only in detecting choledocholithiasis but also in diagnosing of biliopancreatic obstruction (Table 1). Given that the presence of main bile duct obstruction rather than

Table 1. Summary of the meta-analyses on the performance of EUS [44] and MRCP [45] in diagnosing of choledocholithiasis and biliopancreatic obstruction.

	Choledocholithiasis		Biliopancreatic obstruction	
	EUS	**MRCP**	**EUS**	**MRCP**
No. of studies included	31	46	36	30
No. of patients included	3,075	3,592	3,532	1,954
Pooled sensitivity [a]	89% (87-91%)	92% (80-97%)	88% (85-91%)	97% (91-99%)
Pooled specificity [a]	94% (91-96%)	97% (90-99%)	90% (85-91%)	98% (91-99%)
Pooled positive likelihood ratio [a]	32 (20-46)	29 (23-49)	31 (17-52)	49 (25-62)
Pooled negative likelihood ratio [a]	0.11 (0.09-0.14)	Not reported	0.13 (0.10-0.17)	Not reported

[a] Values are pooled estimates (95% confidence intervals)

EUS: endoscopic ultrasonography; MRCP: magnetic resonance cholangiopancreatography

choledocholithiasis *per se* is associated with worse clinical outcomes in patients with acute biliary pancreatitis and provided that these patients undergo definitive treatment during index admission (as it is recommended by the current guidelines), the early use of ERCP should be limited to patients with persistent (lasting for at least 48 h) main bile duct obstruction (Figure 2). As such an obstruction is a relatively rare event, the cost-effectiveness of both EUS and MRCP in selecting patients with persistent biliopancreatic obstruction (who will most likely benefit from ERCP with sphincterectomy) might be similar. Anyway, at least at this time point, employing either EUS or MRCP in a given hospital, in fact, depends on its availability, local experience, logistical factors, etc. Further full-scale economic evaluations are required to determine the optimal minimally-invasive diagnostic modality in patients with acute biliary pancreatitis.

Another fertile ground for further research is the identification of a proper early indicator of biliopancreatic obstruction. Until now, acute cholangitis is considered to be the only unequivocal sign of obstruction. Consequently, there is a consensus in the literature about the usefulness of ERCP in this setting, although, for a long time, there has been no agreement on the diagnostic criteria of acute cholangitis [49, 50, 51]. Fortunately, such an agreement was reached recently and formulated in the form of the Tokyo guidelines [52]. However, acute cholangitis is a relatively late indicator of bilio-pancreatic obstruction; thus, a question remains as to how to detect a critical obstruction earlier. One of the possible alternatives is the so-called Acosta criteria (severe unremitting pain, bile-free gastric aspirate and persistent or increasing serum bilirubin level). It has been demonstrated that these criteria have a high sensitivity and specificity in a dedicated hospital [53], but it would be good to test their external validity in different settings before widespread implementation. Another surrogate marker of biliopancreatic obstruction is cholestasis (the conventional definition of which is unfortunately still lacking). In particular, Soetikno and Carr-Locke claimed that a serum bilirubin concentration greater than 5.0 mg/dL (85.5 µmol/L) and/or dilated main bile duct should be the indications for ERCP [54]. Later, a study from the Netherlands found that early endoscopic intervention is only beneficial in patients with a bilirubin level greater than 40 µmol/L and/or main bile duct diameter greater than 8 mm [55]. Although these finding might be valuable, the authors did not report on the duration of obstruction and the results were not adjusted for this important variable. In addition, the study was limited only to patients with predicted severe acute pancreatitis whereas recent studies have convincingly demonstrated that predicted severity does not influence the effect of

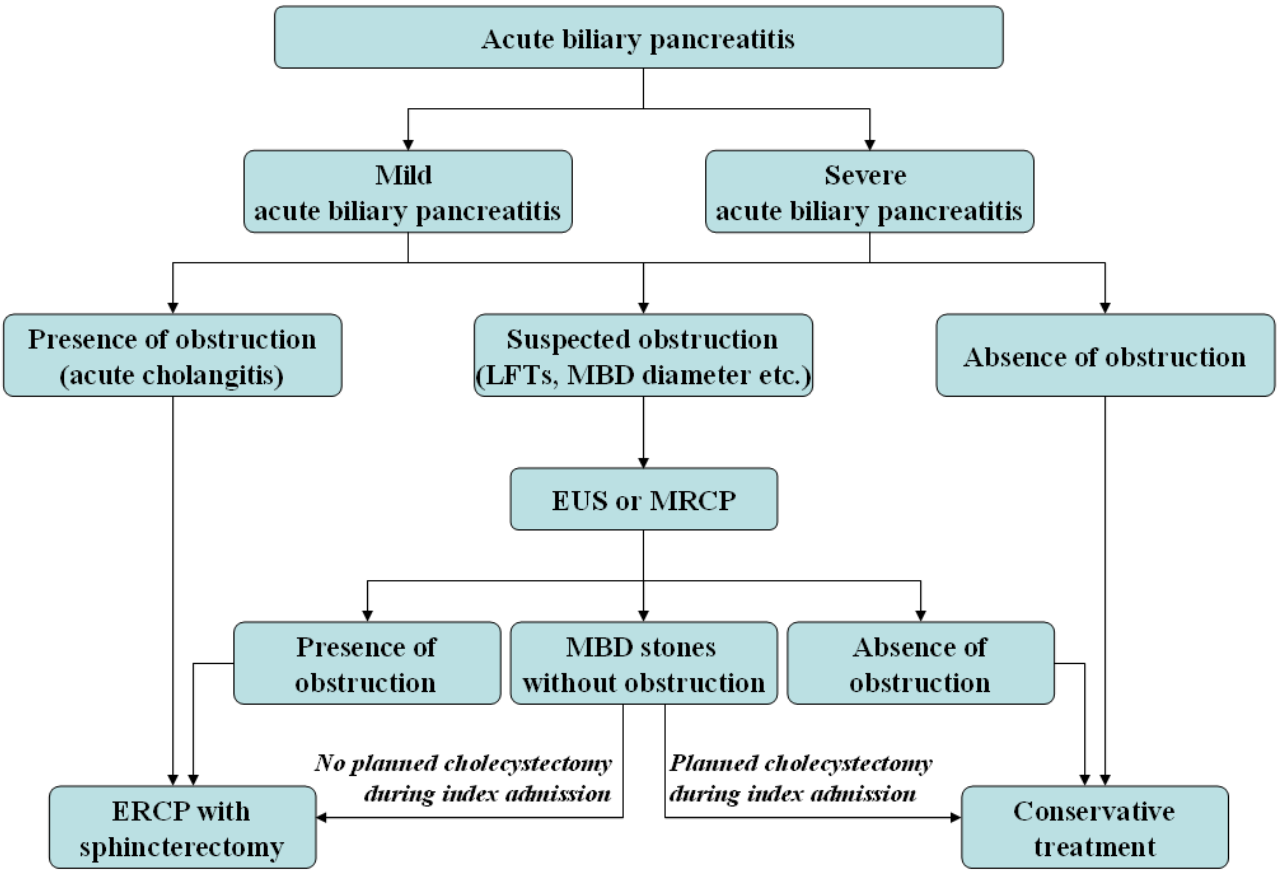

Figure 2. Algorithm for the early management of acute biliary pancreatitis.

ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasonography; LFTs: liver function tests; MBD: main bile duct; MRCP: magnetic resonance cholangiopancreatography

ERCP in patients with acute biliary pancreatitis [34, 35, 56] and, consequently, all patients with acute pancreatitis, regardless of the predicted severity, should be studied to assess the true effect of ERCP. Until future studies are able to address these issues, it seems prudent to use bilirubin (and other liver function tests) along with transabdominal ultrasonography only in order to pre-select patients and leave the definitive selection of patients for ERCP with sphincterectomy to EUS or MRCP (Figure 2).

Conclusions

1. Indications for early ERCP should not be based on predicted severity, but rather on the duration of the biliopancreatic obstruction.

2. Given that the absence of transient biliopancreatic obstruction is associated with an uneventful course of acute biliary pancreatitis and taking into account that, in the majority of patients, main bile duct stones pass spontaneously into the duodenum, early biliary imaging is not required either in patients without biliopancreatic obstruction or those with transient obstruction.

3. In patients with a suspicion of persistent obstruction, EUS or MRCP is indicated. Persistent obstruction can be arbitrarily defined as one lasting for at least 48 h. Further studies should define whether this period can be safely extended beyond this time point.

4. Early ERCP with biliary decompression is warranted only in patients with acute cholangitis and those with persistent obstruction.

Conflict of interest The author has no potential conflicts of interest

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