Lack of Consensus on the Role of Endoscopic Retrograde Cholangiography in Acute Biliary Pancreatitis in Published Meta-Analyses and Guidelines

A Systematic Review

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Objectives: Several randomized controlled trials studied the role of endoscopic retrograde cholangiopancreaticography (ERCP) and endoscopic sphincterotomy (ES) in acute biliary pancreatitis (ABP). No study assessed whether these trials resulted in international consensus in published meta-analyses and treatment guidelines.

Methods: A systematic review, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, of meta-analyses and guidelines on ERCP in ABP was performed in PubMed until August 2011.

The methodological quality of the meta-analysis and guidelines was assessed by a validated quality assessment tool.

Results: Eight meta-analyses and 12 guidelines fulfilled the inclusion criteria. There is consensus that ERCP is indicated in case of ABP with coexistent cholangitis and/or persistent cholestasis. By exception of the first meta-analysis, all included studies disapproved early ERCP in predicted mild ABP. Consensus is lacking regarding the role of early ERCP in predicted severe ABP, as 3 meta-analyses and 1 guideline do not advice this strategy. Routine early ERCP in predicted severe ABP is recommended in 7 of the 11 guidelines.

Conclusions: There is consensus in guidelines and meta-analyses that ERCP/ES is indicated in patients with ABP and coexisting cholangitis and/or persistent cholestasis. Consensus is lacking on the role of routine early ERCP/ES in patients with predicted severe ABP.

Key Words: acute biliary pancreatitis, ERCP, systematic review, guidelines, meta-analyses

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Acute pancreatitis is a common disease with an estimated incidence of 30/100.000 per year.[1–3] The leading cause is gallstones/sludge, which accounts for 35% to 60% of acute pancreatitis cases in the United States and Western Europe.[1–3] Biliary pancreatitis is mostly mild and self- limited.[1–3] Some 15% to 20% of patients will develop severe acute biliary pancreatitis (ABP) including necrotizing pancreatitis and/or multiple organ failure.[1–3]

In the Western world, the incidence of ABP has increased during the past decade by 35%.[4–6] Although mortality decreased by 35%, it still ranges from 2% to 14%, depending on the age of patients and the decade of presentation.[4,5,7,8] Expedited triage of moderate to severe cases for more aggressive fluid resuscitation on admission and aggressive management in intensive care units are possible explanations for the declining mortality rates.[6,9] Keeping in mind that mortality does not differ between the various causes of acute pancreatitis,[6,10–12] the outcome of treatment of ABP has probably truly improved over the past decades.

A treatment, which might have contributed to better outcomes of ABP, is emergency endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES), inspired by a landmark study of Neoptolemos et al[13] in 1988. The rationale for performing this study was based on several prevailing theories hypothesizing the merits of biliary decompression to ameliorate the severity of the pancreatitis, which include treatment and prevention of (ongoing) increased pressure in the pancreatic duct (infected), bile reflux into the pancreatic duct, and stimulation of pancreatic enzyme production/activation by duodenal bile exclusion.[14–19]

Based on the ampullary obstruction and reflux theory of Opie and Bernard, 2 surgical trials preceded the study of Neoptolemos.[20,21] In the years that followed, 6 randomized trials studied the effect of (early) biliary decompression versus conservative management on the course and outcome of patients with ABP.[13,22–28] These studies formed the basis for several meta-analyses and national guidelines. In light of the somewhat confusing and partly conflicting outcomes of the various randomized trials, we performed a systematic review to determine whether there is consensus in published meta-analyses

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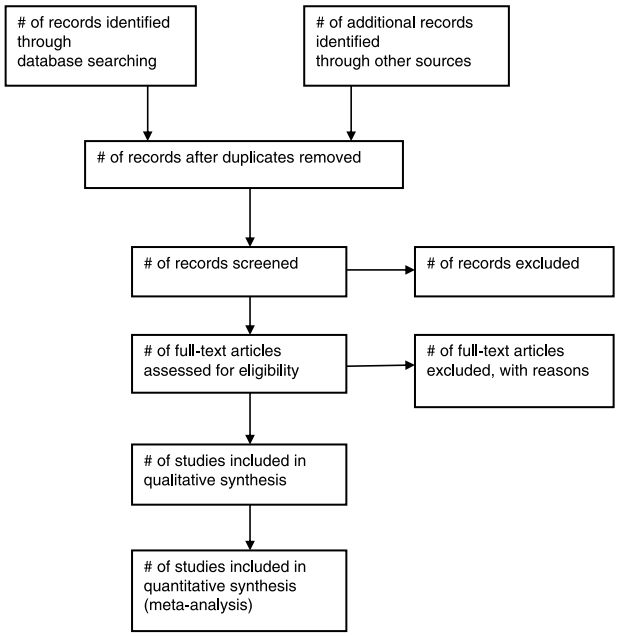

FIGURE 1. PRISMA flow diagram.

and guidelines on the role of an (emergency) ERCP and ES in the early management of biliary pancreatitis

MATERIALS AND METHODS

We conducted a systematic review of published English, German, and French literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29,30] The PRISMA Statement consists of a 27-item checklist and a 4-phase flow diagram. The checklist includes items deemed essential for transparent reporting of a systematic review. The PRISMA flow diagram is shown in Figure 1. Two PubMed searches were performed: (1) meta-analysis: emergency ERCP in ABP; and (2) guidelines: emergency ERCP in ABP. One author (E.J.M.v.G.) performed the selection and reviewed all full text papers. The included and excluded studies were discussed with 2 other authors (H.C.v.S and M.J.B). Cross references were carefully reviewed.

Search for Meta-Analyses

For meta-analysis, the subsequent search terms were used: "Pancreatitis AND (biliary OR gallstone OR gallstones OR cholelithiasis OR cholecystolithiasis)". The results were limited to articles published in the English language, and meta-analyses.

Search and Quality Assessment for/of Guidelines

Because the first meta-analysis[31] was published in 1999, the electronic searches of PubMed were limited from the January 1, 2000 to the August 15, 2011. The following search terms were used: "pancreatitis AND (guideline OR guidelines OR practice guideline OR practice guidelines OR consensus)". The results were limited to articles published in the English, German, and French languages. Furthermore, only guidelines endorsed by a professional body and their latest updates were included. The Dutch guideline was added to the results, although it is not indexed in PubMed.[32]

The quality of the guidelines was assessed with the Grilli score (Fig. 2)[33] and Appraisal of Guidelines for Research and Evaluation (AGREE) Collaboration (http://www.agreetrust.org). The Grilli score is an easy applicable quality assessment tool addressing 3 topics: description of the involved professionals, description of the sources of information, and explicit grading of evidence. The AGREE instrument provides a framework to assess the quality of guidelines by using 6 domains, with a total of 23 items. Every item can be scored with a 1–7 point range. The domains of AGREE are the following: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence.

Statistical Analysis

The 2010 journal impact factors were noted, and quality assessment of the guidelines calculated by the Grilli score (box 1). The relation between the Grilli score and impact factor was calculated with SPSS Pearson 2-tailed test (SPSS version 17).

RESULTS

Meta-Analyses: ERCP Versus Conservative Management of ABP

The initial PubMed search identified 24 articles for further review. Eight meta-analyses met the inclusion criteria and are presented in Table 1. Sixteen articles were excluded because they addressed other topics or were reviews. Impact factors

Description of the type of professionals involved in developing the guideline:		
Yes	If there was a description of the type of professionals and other stakeholders involved in the development process	2 points
Partially	If only a list of names with institutional affiliation was provided	1 point
No	If only names were reported, without further information	0 points
Description of the sources of information used to retrieve the relevant evidence:		
Yes	If it was explicitly stated that searches were undertaken, at least through MEDLINE	1 point
No	If no information was reported.	0 points
Explicit grading of the evidence in support of the main recommendations:		
Yes	If any form of explicit grading of the quality of the supporting evidence was reported	1 point
No	If otherwise	0 points

FIGURE 2. Checklist for quality assessment of guidelines endorsed by specialty societies.

TABLE 1. Meta-Analyses on the Use of Routine Emergency ERCP in Acute Biliary Pancreatitis

	Impact Factor Journal	Studies Included	Excluded Studies	Reason Exclusion	Morbidity (ERCP Versus Conservative)	Mortality	ERCP in Mild ABP	ERCP in Severe ABP	ERCP in Coexistent Cholangitis	Suspected Obstruction
Meta-analysis 1 (Sharma et al, 1999)[31]	6.12	Neoptolemos[13]	None	-	Overall: 25.0% vs 38.2% ($P < 0.001$)	Overall: 5.2% vs 9.1% ($P < 0.05$)	Yes	Yes	Yes	Yes
		Fan,[24] Nowak[25] Folsch[23]								
Meta-analysis 2 (Steinberg et al, 2001)[34]	2.61	Neoptolemos[13]	Nowak,[25] Fölsch[23]	Abstract/ timing ERCP	Mild: 16% vs 16% (ns)	Mild: 0% vs 0% (ns)	No	Yes	Yes	NS
		Fan,[24]		Excluding the nonbiliary pancreatitis cases from the Hong Kong study[24]	Severe: 54% vs 15% ($P < 0.01$)	Severe: 15% vs 2% ($P < 0.05$)				
Meta-analysis 3 (Ayub et al, 2004)[35]	5.65	Neoptolemos[13]	Nowak[25]	No conservative group	Mild ABP: OR = 0.89 (ns)	Overall, mild and severe ABP (ns)	No	Yes	Yes	NS
		Fan,[24] Fölsch[23]		Severe ABP: OR = 0.27 (95% CI, 0.14–0.53)						
Meta-analysis 4 (Heinrich et al, 2006)[36]	7.9	Neoptolemos[13]	Nowak[25]	Abstract	Overall: 31.3% vs 41.8% ($P = 0.03$)	Mild ABP (ns)	No	Yes	Yes	NS
		Fan,[24] Fölsch[23]		Mild ABP (ns) Severe ABP: 18.2% vs 57.1% ($P < 0.0001$)	Severe ABP: 3.6% vs 17.9% ($P = 0.03$)					
Meta-analysis 5 (Petrov et al, 2008)[37]	7.9	Neoptolemos[13]	Fan,[24]	ERCP in all acute pancreatitis	Overall: ns	Overall, mild and severe ABP (ns)	No	No	Excluded	NS
		Fölsch[23]	Nowak[25]	No conservative group	Mild and severe ABP (ns)					
		Oria[26]	Acosta[22]	Treatment group: only 47% ERCP						
Meta-analysis 6 (Moretti et al, 2008)[38]	2.97	Neoptolemos[13]	Nowak[25]	Abstract, different control group	Overall: 27% vs 36% ($P = 0.01$)	Overall, mild and severe ABP (ns)	No	Yes	NS	NS
		Fan,[24] Fölsch[23]	Acosta[22]	Different treatment group	Mild ABP (ns)					
		Zhou,[27] Oria[26]		Severe: rate difference 38.5% ($P = <0.0001$)						
Meta-analysis 7 (Petrov et al, 2008)[39]	3.31	Neoptolemos[13]	Nowak[25]	Abstract	Limited to local complications:	Overall, mild and severe ABP (ns)	No	No	NS	NS
		Fan,[24] Folsch[23] Oria,[26] Acosta[22]		Overall, mild and severe ABP (ns)						
Meta-analysis 8 (Uy et al, 2009)[40]	0.89 (estimated 2007)[41]	Fölsch[23]	Fan,[24]	All AP, cholangitis not excluded	Overall: ns	Overall, mild and severe ABP (ns)	No	No	Excluded	NS
		Oria[26]	Nowak[25]	No information on cholangitis	Mild and severe ABP (ns)					
			Zhou[27]	Did not exclude cholangitis.						
			Acosta[22]	Excluded only severe cholangitis.						
			Neoptolemos[13]	Did not exclude cholangitis.						

ns, not significant; NS, not specified.

ranged from 0.9 to 6.1. The number of included randomized trials varied from 2 to 5. Only 2 of 8 meta-analyses included the same studies.

Only the first meta-analysis concluded that an emergency ERCP/ES was beneficial in all patients with ABP (regardless of cholestasis/cholangitis), resulting in a significant reduction of morbidity and mortality ($P < 0.001$ and $P < 0.05$), particularly in predicted severe cases (Table 1).[31] The remaining 7 meta-analyses reported no beneficial effect of an emergency ERCP in patients with predicted mild ABP and did not specify the indication of an ES in predicted severe cases.

In case of predicted severe ABP, the meta-analysis of Steinberg and Heinrich[36] concluded that an emergency ERCP with or without ES resulted in a significant reduction of complications and mortality, but only in predicted severe cases of ABP (Table 1).[34] The meta-analyses of Ayub[35] and Moretti[38] reported a significant reduction in morbidity but not mortality, in the emergency ERCP group with predicted severe ABP, regardless of cholestasis/cholangitis (Table 1); whereas the meta-analyses of Petrov,[37] Uy,[40] and Petrov[39] concluded that an early ERCP in ABP was not associated with a significant reduction in morbidity and mortality in predicted severe cases (Table 1).

Guidelines: ERCP Versus Conservative Management of ABP

The initial database search regarding "guidelines" identified 299 articles for further review. After reading the abstracts, 22 potential guidelines were retrieved. Six papers were excluded because they lacked an official endorsement. Two older Japanese guidelines (2002 and 2006)[42–45] and one older Italian guideline[46] were excluded and were represented by the latest 2010 guidelines. The Dutch guideline was added to the search.[47] Two guidelines were excluded because they did not mention a policy regarding the endoscopic treatment of ABP.[48,49] This resulted in 12 guidelines, which are reported in Table 2. The reported impact factor of the guidelines varied between not specified to 12.9. Regarding the quality of the guidelines, there was no significant correlation between the Grilli factor (0–3, low; and 4, high quality) and AGREE score versus the journal impact factor ($P = 0.996$ and $P = 0.573$). The Grilli factor was significantly correlated to the AGREE score ($R = 0.762$; $P = 0.004$).

Clinical trials and meta-analyses formed the basis of most guidelines (Table 2). However, guidelines of the Societé Nationale Française de Gastroenterologie[50] and the American Gastroenterological Association[23] did not report the references. All guidelines recommend an emergency ERCP in patients with ABP with coexisting cholangitis and/or biliary obstruction (Table 2). According to the included guidelines, there is no indication for an emergency ERCP in patients with predicted mild ABP without cholangitis and/or biliary obstruction. In case of a predicted severe ABP, the guidelines are controversial.

The Japanese 2010 Guidelines[59–62] (Table 2) included the most clinical trials and meta-analyses and had a maximum Grilli score of 4. This is the only guideline that does not recommend an emergency ERCP in severe ABP. Four guidelines question the usefulness of an emergency ERCP in patients with predicted severe ABP: the French,[50] International Association of Pancreatology,[51] American Gastroenterological Association, and Italian-guidelines[58] (Table 2). The Grilli score of these guidelines varies between 2 and 4, and the number of studies (ie, clinical trials or meta-analyses) that were included is low. Six guidelines recommend an emergency ERCP in patients with predicted severe ABP: Dutch,[47] Chinese,[53] German,[57] World Congress of Gastroenterology,[52] American Thoracic Society,[54] British,[55] and American College of Gastroenterology guidelines.[56] The optimal time period for ERCP differed among the guidelines: within 72 hours after onset of symptoms (World Congress of Gastroenterology, American Thoracic Society, British, Dutch) or within 24 hours after hospital admission (German and American College of Gastroenterology).

The guidelines have several recommendations concerning the use of an early ES, whenever an early ERCP is performed. Six guidelines advise an ES whenever emergency ERCP is performed (Table 2). In 2 guidelines, an ES is advocated in case of biliary obstruction and/or cholangitis (Table 2). However, the indication of an early ES is not specified in 4 guidelines.

DISCUSSION

At present, according to published meta-analyses and national guidelines, 2 statements about early ERCP/ES in ABP seem undebated: (1) ERCP/ES does not have a clear advantage in patients with predicted mild ABP and (2) coexisting cholangitis is an indication for emergency ERCP/ES (within 24 hours of admission). However, consensus is lacking on the role of routine early ERCP/ES in all patients with predicted severe ABP, regardless of cholestasis.

How is it possible that meta-analyses on the same subject reach such different conclusions? There are 2 likely explanations for this to happen. The first possible explanation is time of publication. More recent meta-analyses or guidelines might reach different conclusions as new data have come available over time. However, this argument is contradicted by the observation that the latest meta-analyses (2006-2009; Table 1) are not concurrent in which of the most recent (randomized) clinical trials were included in their analysis: Acosta[22] (2006), Oria[26] (2007), and van Santvoort[47] (2009), which result in conflicting outcomes (like the older meta-analyses). The second likely explanation is what has just been alluded to that is selection of which studies to include in the meta-analysis. For example, in contrast to all other meta-analyses, only Sharma et al[31] included the study of Nowak et al[25] although only published in abstract. This already provides ample explanation why only this meta-analysis recommends early ERCP in predicted mild ABP. For the use of ERCP in predicted severe cases of ABP, the outcome of the 8 meta-analyses depend on the inclusion[27,35,36,,63] or exclusion[37,40] of the study of Neoptolemos[13] and/or Fan et al.[24]

In the light of contradictory recommendations of clinical trials, meta-analyses, and guidelines, we recently surveyed the daily clinical practice among Dutch gastroenterologists.[64] Of the 97% responders who would consider performing an early (<72 hours) ERCP in ABP, 14% stated that they always perform ERCP regardless of the presence of any condition or symptom. The remainder of the respondents considers ERCP only if a concomitant condition is present such as a dilated common bile duct (95%), coexistent cholangitis (87%), common bile duct stones (72%), jaundice (59%), ampullary stone (68%), or (predicted) severe-ABP (35%). Accordingly, the study of Van Santvoort et al demonstrated that in daily clinical practice in the Netherlands, the use of ERCP in predicted severe ABP varied from 0 to 100% in 15 of the largest Dutch hospitals.[47] Similar defiance of the national guidelines were reported in Italian and British surveys.[65–67] In a British survey among surgeons (n = 583), 35% advocated early ERCP/ES in patients with predicted severe biliary pancreatitis, and a further 14% advocated ERCP/ES for all patients with biliary pancreatitis regardless of the predicted severity.[68]

Interestingly, apart from the first meta-analysis, none specified the indication for early ES in patients with ABP. Furthermore, the indication for ES is also not specified in the American and Japanese guidelines. Literature concerning this

TABLE 2. Guidelines Addressing the Use of Routine Emergency ERCP/ES in Acute Biliary Pancreatitis

Guidelines	Year	Impact Factor Journal	Grilli Score	AGREE	Studies/ Meta-Analysis	Mild Biliary Pancreatitis	Severe Biliary Pancreatitis	Cholangitis	ERCP Advised in Suspected Obstruction	Endoscopic Sphincterotomy
Societé Nationale Française de Gastroenterologie[50] (French)	2001	1.7	2	51	NS	No	Debate	Yes	Yes	When ERCP is indicated
International Association of Pancreatology[51] (IAP)	2002	1.4	3	76	Neoptolemos, Fan, Folsch	No	Debate	Yes	Yes	When ERCP is indicated
World Congress of Gastroenterology[52] (WCG)	2002	2.3	3	65	Neoptolemos, Fan, Nowak, Folsch	No	Yes	Yes	Yes	When ERCP is indicated
Chinese society of Gastroenterology[53]	2004	1.6	0	23	NS	No	Yes	Yes	Yes	When ERCP is indicated
American Thoracic Society[54] (ATS)	2004	6.4	4	69	Neoptolemos, Fan, Nowak, Folsch, Sharma	No	<72h onset symptoms	Yes	Yes	N.S
British Society of Gastroenterology[55] (British)	2005	9.4	3	84	Neoptolemos, Fan, Folsch, Nowak	No	<72h onset symptoms	Yes	Yes	When ERCP is indicated
Dutch Society of Internal Medicine[32] (Dutch)	2005	NS	4	80	Neoptolemos, Fan, Nowak, Folsch	-	< 72h (NS)	Yes (<24h)	Yes (<24h)	Obstruction Cholangitis, CBDS
American College of Gastroenterology[56] (ACG)	2006	6.1	4	73	Neoptolemos, Fan, Nowak, Folsch, Sharma, Ayub		<24h admission	Yes	Elective ERCP in persistent obstruction	NS
American Gastroenterological Association[23] (AGA)	2007	12.9	2	70	NS	No	controversial	Yes (<24h)	Yes (<72h)	NS
German Society for Digestive Diseases and Metabolic Diseases[57] (German)	2007	1.2	4	85	Neoptolemos, Fan, Folsch, Oria, Ayub	No	Yes (<24h Admission)	Yes (<24h)	Yes (<24h)	Cholangitis, Jaundice, Cholestasis
Italian Association for the Study of the Pancreas[58] (Italian)	2010	3.0	4	54	Petrov, Moretti	No	controversial	Yes	Yes	When ERCP is indicated
Japanese Guidelines[59–62]	2010	1.9	4	82	Neoptolemos, Fan, Nowak, Folsch, Zhou, Acosta, Oria, Sharma, Ayub, Heinrich	No	No	Yes	Yes	NS

topic is remarkably scarce. Only one randomized clinical trial addressed this issue and reported a significantly decreased morbidity and mortality in patients with an early ERCP with ES compared with ERCP alone.[25] These results were partly confirmed by a univariate analysis in a prospective clinical trial of Van Santvoort et al.[47] In this study, ES was associated with a significant reduction in overall complication rate (adjusted odds ratio, 0.24; 95% confidence interval, 0.06–0.93; $P = 0.04$) albeit without a significant effect on mortality (adjusted odds ratio, 1.38; 95% confidence interval, 0.13–14.44; $P = 0.79$).

The present systematic review clearly demonstrates that despite numerous randomized trials, there is an obvious lack of consensus on the indications, the timing, and the procedural techniques (ES or not) in meta-analyses and nationwide guidelines. Three strategies might possibly improve consensus.

First, uniform criteria for inclusion of studies in meta-analyses and guidelines would increase the likelihood of reaching consensus. Future versions of the PRISMA guidelines for systematic reviews and meta-analyses could provide such criteria.

Second, rather than performing meta-analyses of literature reports, future meta-analyses should aim to aggregate and analyze individual patient data. It has been shown that individual patient data meta-analyses (IPDMA) provide more reliable outcomes than regular meta-analyses.[69]

Third, an obvious strategy would be to perform new high-quality randomized trials on relevant questions reflecting patient management in daily clinical practice, for example, about the role of (early) ERCP in patients with predicted severe ABP. Such a study should be adequately powered, using practical inclusion criteria, clear crossing-over criteria, a cannulation failure scenario, and end points that are clinical relevant with regard to patient outcome. Endoscopic sphincterotomy should be an integral part of ERCP treatment.[70] The preparation of such a trial has started and will be carried out by the Dutch Pancreatitis Study Group. In this Acute Biliary Pancreatitis: early ERC plus ES versus conservative treatment trial, a randomized, superiority, assessor-blinded multicenter trial, patients with ABP are randomized within 24 hours of admission between a conservative group and an ERC/ES group.

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