How to prevent post-ERCP pancreatitis ?

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Abstract

The incidence of post-ERCP pancreatitis (PEP) has remained constant since 30 years. During the last 10 years, large progresses have been made in the knowledge of (i) factors that predispose to PEP and (ii) measures that are effective to prevent PEP. Many of these measures have not yet been widely implemented. Complete recommendations for PEP prophylaxis are summarized in the review. For high-risk ERCPs, including ampullectomy, pancreatic sphincterotomy, precut biliary sphincterotomy, known or suspected sphincter of Oddi dysfunction, pancreatic guidewire-assisted biliary cannulation and endoscopic balloon sphincteroplasty, prophylactic pancreatic stent placement should be considered. For low-risk ERCPs, periprocedure rectal administration of NSAID is recommended. Prophylactic pancreatic stenting should be investigated in terms of education of endoscopists for insertion techniques, ease of stent insertion, reliability of spontaneous stent elimination and safety (demonstration of the absence of induced pancreatic changes). (Acta gastroenterol. belg., **2011**, 74, **543-547**).

Key words : Endoscopic retrograde cholangio-pancreatography, post-ERCP pancreatitis, review, NSAID, stent

Introduction

Post-ERCP pancreatitis (PEP) is the most frequent complication following ERCP. Despite advances in most fields of endoscopy since 30 years, a review of prospective studies published between 1977 and 2006 has found that the incidence of PEP has not decreased over this period (incidence in the 1977-1995 and 1996-2005 periods, 3.1% and 3.8%, respectively) (1). During the last 10 years, large progresses have been made in the knowledge of (i) factors that predispose to PEP and (ii) measures that are effective to prevent PEP. To facilitate implementation of these advances, they have been critically analysed in a Guideline issued by the European Society of Gastrointestinal Endoscopy (ESGE) (2). The most important statements are commented below ; many of the recommendations made have not yet been widely implemented in clinical practice. Therefore, the potential for improvement is large. All evidence statements plus recommendations issued by the ESGE are reproduced at the end of the article.

Comment about selected statements for PEP prophylaxis

The following five statements were selected for comments because they were thought to have the highest potential impact on the final outcome, i.e. PEP incidence : (i) most of them are based on the highest levels of evidence (1+ or 1++, corresponding to well-conducted meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a low risk of bias), (ii) they may have a direct impact on clinical practice and (iii) they can relatively easily be implemented.

The evidence level is explained for each statement ; according to the guideline methodology, the grade of recommendation only relates to the strength of the evidence on which the recommendation is based.

Independent patient-related and procedure-related risk factors for PEP are listed in Table 1. Risk factors synergistically increase the risk of PEP (Evidence level 1+).

Comment :

- Diagnostic ERCP should be avoided but it still accounts for a significant minority of ERCP (14% in a large and recent audit) (3). The threshold for performing ERCP in cases with unclear indications for a therapeutic intervention should sharply increase as the number of risk factors for PEP increases. For patients at very high risk of PEP (e.g., suspected sphincter of Oddi dysfunction in a young woman with normal bilirubin), referral to a high-volume centre should be considered.
- Patient's information about procedure risks should be different for patients with no/few vs. those with multiple risk factors for PEP.
- If risk factors for PEP are identified during ERCP, particular measures for PEP prophylaxis should be taken (e.g., administration of a non-steroidal anti-inflammatory drug [NSAID], prophylactic pancreatic stenting).

Note about the evidence level and recommendation grade : Evidence level was 1+ because definite risk factors were identified in a meta-analysis of large, prospective, studies (4). As only five potential risk factors for PEP were analyzed in that meta-analysis, we also reviewed five large, prospective, multicenter studies that analyzed potential risk factors for PEP using multivariate analysis (13,745 patients). Patient-related and procedure-related characteristics independently associated with PEP in at least one of these studies were reported as likely risk factors in Table 1.

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Table 1. — **Independent risk factors for PEP***

	Adjusted odds ratios (95% CI in brackets except where indicated otherwise)	**Pooled incidence of PEP in patients with vs. those without risk factor**
Patient-related risk factors		
- Definite risk factors		
• Suspected SOD	4.09 (3.37-4.96)	10.3% vs. 3.9%
• Female gender	2.23 (1.75-2.84)	4.0% vs. 2.1%
• Previous pancreatitis	2.46 (1.93-3.12)	6.7% vs. 3.8%
- Likely risk factors		
• Younger age	1.09-2.87 (range, 1.09-6.68)	6.1% vs. 2.4%
• Non-dilated extrahepatic bile ducts	NR	6.5% vs. 6.7%
• Absence of chronic pancreatitis	1.87 (1.00-3.48)	4.0% vs. 3.1%
• Normal serum bilirubin	1.89 (1.22-2.93)	10.0% vs. 4.2%
Procedure-related risk factors		
- Definite risk factors		
• Precut sphincterotomy	2.71 (2.02-3.63)	5.3% vs. 3.1%
• Pancreatic injection	2.2 (1.60-3.01)	3.3% vs. 1.7%
- Likely risk factors		
• High n° of cannulation attempts†	2.40-3.41 (range, 1.07-5.67)	3.7% vs. 2.3%
• Pancreatic sphincterotomy	3.07 (1.64-5.75)	2.6% vs. 2.3%
• Biliary balloon sphincter dilation	4.51 (1.51-13.46)	9.3% vs. 1.9%
• Failure to clear bile duct stones	3.35 (1.33-9.10)	1.7% vs. 1.6%

* Reproduced from ESGE Guideline to which the reader is referred for details (2).
PEP, post-ERCP pancreatitis ; CI, confidence interval ; NR, not reported.
Definite risk factors were those identified by a large meta-analysis (4) ; likely risk factors were identified in at least one prospective multicenter study.
†High (vs. low) n° of cannulation attempts was defined as a number of attempts before final cannulation of the desired duct > 5 or > 1, depending on the studies.

Routine rectal administration of 100 mg of diclofenac or indomethacin immediately before or after ERCP is recommended (Evidence level 1++, Recommendation grade A).

Comment :

- NSAID are used only by a minority -approximately 15%- of endoscopists to prevent PEP although they are cheap, safe and easy to administer (5). In a recent survey, the low use of NSAID was mainly ascribed to a lack of scientific evidence of its benefits. However, three different meta-analyses of randomized, placebo-controlled, studies showed that diclofenac or indomethacin (single dose, intrarectal) was effective to prevent PEP in patients at high as well as average risk (6-8). These drugs present the advantage of being effective even if they are administered immediately after ERCP. The oral route is ineffective (maybe because of defective drug absorption, for example due to decreased peristaltism induced by agents used during ERCP) while the intramuscular route might be effective (9,10). For facility, I personally use the intravenous route at the beginning of ERCP.
- Reluctant endoscopists should revise why they do not use NSAID at the light of scientific evidence and at least consider administering NSAID if an ERCP with sphincterotomy proves to be difficult (i.e., procedure-related risk factors such as high number of cannulation attempts, multiple pancreatic injections, precut sphincterotomy).

Note about the evidence level and recommendation grade : Evidence level was 1++ because the three different meta-analyses cited above have consistently shown beneficial effect of prophylactic rectal NSAIDs in preventing PEP. These meta-analyses included prospective, randomized, placebo-controlled studies that compared rectally administered diclofenac or indomethacin at a dose of 100 mg vs. placebo. It is interesting to note that studies that tested drugs for PEP prophylaxis were much more rigorous in their design than studies that tested endoscopic procedures (e.g., in pharmacological studies, the main outcome, PEP occurrence, is generally diagnosed by an evaluator blinded to the intervention performed – administration of drug or of placebo – which is not the case in most studies of endoscopic interventions such as those that tested prophylactic pancreatic stenting).

CO_2 is recommended for insufflations during ERCP (Evidence level 1+, Recommendation grade B), and might be particularly useful for outpatient ERCPs to reduce pain and to avoid confusion with PEP.

Comment :

- Replacement of air by CO_2 for gut distension has been demonstrated to decrease pain following ERCP in several randomized controlled trials (RCT) (11-13). These results confirmed data reported for other long-lasting endoscopic procedures. The lower incidence and severity of post-procedural pain is a clear benefit for the patient ; in addition it may help avoiding misinterpretation of post-procedural abdominal pain as being PEP.
- CO_2 is used by a minority -approximately 5%- of endoscopists, mostly for colonoscopy (14). In clinical practice, it may be more beneficial to the patient for ERCP than for colonoscopy. Apart from

their cost, systems delivering CO_2 are relatively easy to implement because they have long been used for laparoscopy in all hospitals (the infrastructure for having CO_2 cylinders available has been implemented by our surgeon colleagues). A system that delivers CO_2 at a variable flow may be preferred to decrease CO_2 consumption and the hassle of replacing CO_2 cylinders.

Note about the evidence level and recommendation grade : Evidence level was 1+ because two of three randomized controlled studies found a significant decrease in pain after ERCP with CO_2 compared to air.

The number of cannulation attempts should be minimized. The number of injections and volume of contrast medium injected into the pancreatic duct should be kept as low as possible (Evidence level 1+, Recommendation grade B). For deep biliary cannulation, the wire guided technique reduces the risk of PEP and increases the success rate of primary cannulation when compared with the standard contrast-assisted method. The wire guided technique is recommended for deep biliary cannulation (Evidence level 1++, Recommendation grade A).

Comment :

- Minimizing the number of cannulation attempts is part of the art of ERCP. Besides experience, it relies on careful exam preparation : the papilla should be touched with a catheter only once the set-up is complete, i.e. aim of the exam explained to the staff, patient deeply sedated or under general anaesthesia, relaxed duodenum, X-ray beam focused on the papilla, endoscopy assistant concentrated with ancillary devices ready.
- The efficacy of the wire guided technique for PEP prophylaxis has been demonstrated in a meta-analysis of three RCTs (15). However, it should be stressed that these three RCTs were less stringent than those that evaluated NSAID in at least one aspect : the assessor who diagnosed the development of PEP was not blinded to the allocation group (wire guided vs standard, contrast-assisted, cannulation). In contrast, pharmacological studies, including those with NSAID, used a placebo and hence had blind evaluation of the PEP endpoint.
- The wire guided technique has seen increasing popularity. A hydrophilic guidewire is recommended and, in case of initial failure, most experts inject a small amount of contrast medium to depict the anatomy of the lower part of the bile duct. Care should be taken at this time to avoid submucosal injection of contrast medium.

Note about the evidence levels and recommendation grades : the recommendation about the number of cannulation attempts was 2 ++ based on high quality cohort studies, including one by Freeman et al that included >2,000 patients (16) ; that about the number of injections and volume of contrast medium injected into the pancreatic duct was 1+ because a large meta-analysis found that pancreatic duct injection was an independent predictor of PEP (4) ; that about the wire guided cannulation technique was 1++ because two meta-analyses of randomized controlled trials found a lower PEP incidence with the wire guided compared to the standard cannulation technique (15,17).

Prophylactic pancreatic stent placement is recommended to prevent PEP in patients who are at high risk for development of PEP. Short, 5-French in diameter, plastic pancreatic stents with no internal flanges are currently recommended. Passage of the stent from the pancreatic duct should be evaluated within 5 to 10 days of placement and retained stents should be promptly removed endoscopically (Evidence level 1+, Recommendation grade A).

Comment :

- The efficacy of prophylactic pancreatic stent insertion to prevent PEP has been demonstrated in two meta-analyses of six studies (including 4 RCT) (18,19). Again, the assessor who diagnosed the development of PEP was not blinded to the allocation group (stent or not), in contrast with pharmacological studies.
- Prophylactic pancreatic stenting is not widely used : in a recent survey, for a series of conditions including needle-knife precut, previous PEP, suspected sphincter of Oddi dysfunction and ampullectomy, less than half of the endoscopists reported attempting prophylactic pancreatic stenting in ≥ 75% of cases (5). This is mostly due to a lack of experience with this technique. We must improve continuous medical education in this field because endoscopists with a low success of pancreatic stent placement should not attempt to place such a stent (the risk of PEP is high after a failed attempt at stent placement) (20). Although there is no consensus about the technique, interesting readings are available.
- A stent without an internal (pancreatic) flap is recommended (e.g., GPSOS model available from Cook Endoscopy [Winston-Salem, North Carolina, U.S.A.] although not listed in their current catalogue ; the GPSOS-SF model from the same manufacturer is very soft and may be difficult to insert alongside a biliary stent). Stents of a similar diameter with an internal flap tend to eliminate spontaneously much less frequently.
- Patients should be informed to have an abdominal plain film after prophylactic pancreatic stenting because, in the rare cases with no spontaneous stent elimination, pancreatitis is extremely frequent when the stent occludes.

Note about the evidence level and recommendation grade : Evidence level was 1+ because two independent meta-analyses of controlled studies have demonstrated

that stent placement significantly reduced the incidence of PEP in patients at high risk for PEP (18,19).

Other evidence statements and recommendations made by the ESGE

Evidence levels and grades of recommendation were those recommended by the Scottish Intercollegiate Guidelines Network, with Evidence levels 1 and Recommendation grade A being the strongest ones (21). Most important statements and recommendations are in bold.

Pancreatitis is the most frequent complication after ERCP with an incidence of 3.5% in unselected patients ; it is of mild or moderate severity in approximately 90% of cases (Evidence level 1+).

There is no evidence that hospital volume has an influence on the incidence of PEP ; data about a potential relationship between PEP incidence and the endoscopist volume are conflicting. Failed ERCP is more frequently seen when performed by endoscopists and in centers that perform a low annual number of procedures (Evidence level 2+).

Serum amylase values < 1.5 times the ULN obtained at 2-4 hours post-ERCP virtually exclude PEP ; values > 3 or 5 times the ULN at 4-6 hours post-ERCP have a positive predictive value for PEP (Evidence level 2+). It is recommended to measure serum amylase value in patients to be discharged on the day of ERCP ; patients with amylase values < 1.5 times ULN can be discharged without concern about risk of PEP. (Recommendation grade B).

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the incidence of PEP ; effective PEP prophylaxis has only been demonstrated using 100 mg of diclofenac or indomethacin administered rectally (Evidence grade 1++).

Nitroglycerin reduces the incidence of PEP ; however, when administered transdermally, it is ineffective (Evidence grade 1++). Side effects such as transient hypotension and headache may occur. We do not recommend the routine use of nitroglycerin for prophylaxis of PEP (Recommendation grade A).

Based on an ad-hoc meta-analysis of results from 10 high quality RCTs, somatostatin proved to be ineffective in preventing PEP (Evidence 1++). We do not recommend universal administration of prophylactic somatostatin in average risk patients undergoing ERCP (Recommendation grade A).

Octreotide administration did not affect the overall incidence of PEP when data from 8 high quality trials were pooled (Evidence 1++). Prophylaxis with octreotide is not recommended (Recommendation grade A).

Prophylaxis with gabexate or ulinastatin does not reduce the incidence of PEP (Evidence 1++). Neither drug is recommended for prophylaxis of PEP (Recommendation grade A).

There is no evidence that glucocorticoids, drugs reducing sphincter of Oddi pressure (other than nitroglycerin), antioxidants, heparin, interleukin-10, or some anti-inflammatory drugs (other than diclofenac and indomethacin), such as pentoxifylline, semapimod and the recombinant platelet activating factor acetylhydrolase reduce the incidence of PEP (Evidence grades from 1-to 1++). None of these drugs is recommended for PEP prophylaxis (Recommendation grade A).

Trauma resulting from repeated attempts at biliary cannulation has been proven to be a risk factor for the development of PEP (Evidence level 2++).

Injection of contrast medium into the pancreatic duct is an independent predictor of PEP (Evidence level 1+).

Compared to traditional, high-osmolality contrast agents, low-osmolality contrast agents are costlier but without reduction in the rates of PEP (Evidence level 1-). The routine use of these agents for ERCP is not recommended (Recommendation grade B).

Use of CO_2 as a replacement of air for luminal insufflation during ERCP does not influence the incidence of PEP but decreases the incidence and severity of post-procedure abdominal pain (Evidence level 1+).

The incidence of post-sphincterotomy pancreatitis is not influenced by the type of electrosurgical current used (whether pure-cut or blended) (Evidence level 1+). Blended current is recommended for biliary sphincterotomy, particularly in patients at high risk of bleeding (Recommendation grade A).

Data about the usefulness and safety of pancreatic guidewire placement to facilitate biliary cannulation in difficult cases are conflicting. Prophylactic pancreatic stent placement decreases the incidence of PEP with this technique (Evidence level 2+). Pancreatic guidewire-assisted biliary cannulation may facilitate biliary cannulation mostly in case of inadvertent but repeated cannulation of the pancreatic duct (22) ; if this method is used, prophylactic pancreatic stent placement should be performed (Recommendation grade B).

Various techniques of precut biliary sphincterotomy have been described ; the fistulotomy technique may present a lower incidence of PEP than standard needle knife sphincterotomy but further RCTs are required to determine which technique is safer and more effective, based upon the papillary anatomy. There is no evidence that the success and complication rates of biliary precut are affected with the level of endoscopist experience in this technique but published data only report on the experience of one endoscopist (Evidence level 2-). Prolonged cannulation attempts using standard techniques may impart a risk for PEP greater than the precut sphincterotomy itself (Evidence level 2+). Precut sphincterotomy should be performed by endoscopists with expertise in standard cannulation techniques (Recommendation grade D). The decision to perform precut biliary sphincterotomy, the timing, and the technique are based on anatomic findings, endoscopist preference and procedural indication (Recommendation Grade C).

Compared to endoscopic sphincterotomy, endoscopic papillary balloon dilation (EPBD) using small calibre balloons (≤ 10 mm) is associated with a significantly higher incidence of PEP and significantly less bleeding (Evidence level 1++). EPBD is not recommended as an alternative to sphincterotomy in routine ERCP but may be useful in patients with coagulopathy and altered anatomy (e.g., Billroth II) (Recommendation grade A). If balloon dilation is performed in young patients the placement of a prophylactic pancreatic stent should be strongly considered (Evidence level 4, Recommendation grade D).

Potential advantages of performing large balloon dilation in addition to endoscopic sphincterotomy for extraction of difficult biliary stones remain unclear (Evidence level 3). Endoscopic sphincterotomy plus large balloon dilation does not seem to increase the risk of PEP and can avoid the need for mechanical lithotripsy in selected patients but not enough data are available to recommend routine use over biliary sphincterotomy alone in conjunction to lithotripsy techniques (Recommendation grade D).

Pancreatic sphincter of Oddi manometry should be performed with a modified triple lumen perfusion catheter with simultaneous aspiration or a microtransducer catheter (non-water perfused) (Recommendation grade B).

Prophylactic pancreatic stent placement is recommended to prevent PEP in patients who are at high-risk for development of PEP. Short, 5-French diameter, plastic pancreatic stents with no internal flanges are currently recommended. Passage of the stent from the pancreatic duct should be evaluated within 5 to 10 days of placement and retained stents should be promptly removed endoscopically (Evidence level 1+ ; Recommendation grade A).

Conclusion

For high-risk ERCPs, including ampullectomy, pancreatic sphincterotomy, precut biliary sphincterotomy, known or suspected sphincter of Oddi dysfunction, pancreatic guidewire-assisted biliary cannulation and endoscopic balloon sphincteroplasty, prophylactic pancreatic stent placement should be considered. For low-risk ERCPs, periprocedure rectal administration of NSAID is recommended.

Prospects for future research

Prophylactic pancreatic stenting should be investigated in terms of education of endoscopists for insertion techniques, ease of stent insertion, reliability of spontaneous stent elimination and safety (demonstration of the absence of induced pancreatic changes).

Disclosure of conflicting interests

The author declares no conflict of interest.

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