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REVIEW

Endoscopic retrograde cholangiopancreatography associated pancreatitis: A 15-year review

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Abstract

The aim of this article is to review the literature regarding post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. We searched for and evaluated all articles describing the diagnosis, epidemiology, pathophysiology, morbidity, mortality and prevention of post-ERCP pancreatitis (PEP) in adult patients using the PubMed database. Search terms included endoscopic retrograde cholangiopancreatography, pancreatitis, ampulla of vater, endoscopic sphincterotomy, balloon dilatation, cholangiography, adverse events, standards and utilization. We limited our review of articles to those published between January 1, 1994 and August 15, 2009 regarding human adults and written in the English language. Publications from the reference sections were reviewed and included if they were salient and fell into the time period of interest. Between the dates queried, seventeen large (> 500 patients) prospective and four large retrospective trials were conducted. PEP occurred in 1%-15% in the prospective trials and in 1%-4% in the retrospective trials. PEP was also reduced with pancreatic duct stent placement and outcomes were improved with endoscopic sphincterotomy compared to balloon sphincter dilation in the setting of choledocholithiasis. Approximately 34 pharmacologic agents have been evaluated for the prevention of PEP over the last fifteen years in 63 trials. Although 22 of 63 trials published during our period of review suggested a reduction in PEP, no pharmacologic therapy has been widely accepted in clinical use in decreasing the development of PEP. In conclusion, PEP is a well-recognized complication of ERCP. Medical treatment for prevention has been disappointing. Proper patient selection and pancreatic duct stenting have been shown to reduce the complication rate in randomized clinical trials.

Key words: Cholangiopancreatography endoscopic retrograde; Adverse effects; Pancreatitis; Prevention and control/therapy; Risk assessment; Risk factors; Ampulla of vater; Sphincter of oddi; Humans

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INTRODUCTION

The first endoscopic pancreatogram was obtained in 1968, and in 1974, biliary sphincterotomy was first described[1-2]. This was followed by the first report of

Table 1 Clinical trials evaluating the incidence of overall complications and post-ERCP pancreatitis

Author	Country	Year published	*n*	No. ERCP	Overall complications (%)	Post-ERCP pancreatitis (%)
Large prospective trials						
Wang[20]	China	2009	2691	3178	7.92	4.31
Kapral[62]	Austrian	2008	NR[a]	3132	12.60	5.10
Dundee[23]	Australia	2007	563	700	5.71	3.71
Williams[24]	United Kingdom	2007	4561	5234	5.00	1.60
Bhatia[25]	India	2006	1497	1497	NR[a]	3.80
Cheng 2006 and Sherman 2003[b][111,154]	United States	2006	1115	NR[a]	NR[a]	15.10
Andriulli[59]	Italy	2004	1127	1050	NR[a]	4.80
Christensen[13]	Denmark	2004	NR[a]	1177	15.90	3.80
Barthet	France	2002	658	1159	NR[a]	3.50
Vandervoort[10]	United States	2002	1223	1223	11.20	7.20
Freeman[58]	United States	2001	NR[a]	1963	NR[a]	6.70
Masci[35]	Italy	2001	2103	2044	4.95	1.80
DePalma[27]	Italy	1999	535	NR[a]	NR[a]	5.30
Deans[11]	United Kingdom	1997	958	1000	2.40	1.00
Johnson[28]	United States	1997	1979	NR[a]	NR[a]	10.40
Freeman[29]	United States and Canada	1996	2347	NR[a]	9.80	5.40
Loperfido[12]	Italy	1995	2769	NR[a]	4.00	1.30
Large retrospective trials						
Cotton[29]	United States	2009	11497	NR[a]	4.00	2.60
Lukens[30]	United States	2009	2606	3924	3.12	0.97
Andriulli[31]	Italy	2007	16855	NR[a]	6.85	3.47
Cheon[60]	United States	2007	9872	14331	NR[a]	4.00

[a]Not reported; [b]Same patient cohort; ERCP: Endoscopic retrograde cholangiopancreatography.

papillotomy for the management of choledocholithiasis[3] and in subsequent years, numerous endoscopic techniques evolved to address pancreaticobiliary disease. As computerized axial tomography and magnetic resonance imaging have improved, endoscopic retrograde cholangiopancreatography (ERCP) has evolved from primarily a diagnostic procedure into primarily a therapeutic procedure.

As the indications for ERCP have increased, a greater focus on recognizing and preventing complications has emerged. Asymptomatic hyperamylasemia, cardiopulmonary depression, hypoxia, aspiration, intestinal perforation, bleeding, cholangitis, adverse medication reactions, sepsis, acute pancreatitis and death all are recognized complications of ERCP. Post-ERCP pancreatitis (PEP) remains the leading cause of morbidity and mortality post procedure and has been at the center of studies designed to improve procedural outcomes[4-9].

Over the last 15 years, in large prospective trials the overall and pancreatitis complication rates following ERCP have ranged from 2.4% to 15.9%[10-13] and 1.0% to 15.1%[14-16] respectively. Some studies have suggested that lower rates of PEP can be achieved; however the incidence of pancreatitis remains high particularly in at-risk patient populations. Pancreatitis continues to be the major cause of post-procedure morbidity and mortality[17-22] (Table 1).

DIAGNOSIS OF PEP

PEP has been defined as the presence of new pancreatic-type abdominal pain associated with at least a threefold increase in serum amylase concentration occurring 24 h after an ERCP, with pain severe enough to require admission to the hospital or to extend an admitted patient's length of stay. This definition was developed in 1991 based upon approximately 15 000 procedures evaluated during a consensus workshop. The severity of PEP was defined according to length of stay (mild pancreatitis 2-3 d, moderate pancreatitis 4-10 d and severe pancreatitis more than 10 d or intensive care admission or local complications secondary to pancreatitis)[23]. This consensus definition has not been uniformly adopted and many studies published after 1991 have used different criteria to define PEP and classify severity.

Several studies have challenged the serum amylase threshold of three times the upper limit of normal, arguing that this definition is not always consistent with the clinical and morphological features of pancreatitis[24-30]. Variations in the published studies regarding the criteria for serum amylase elevationhave included twice[28-31], four times[10,32-33] and five times[25-26,33-35] the upper limit of the normal.

In regard to the severity of PEP, there is also heterogeneity in criteria used in published studies. Some authors have used the Atlanta criteria published in 1993 to define severity[36-38]. The Atlanta criteria incorporate systemic complications of PEP by integrating the Acute Physiologic and Chronic Health Evaluation (APACHE) Ⅱ classification and the Ranson's criteria to define the severity[38-40]. An APACHE Ⅱ score greater than 8 or a Ranson's score with 3 or more of 11 criteria would be defined as severe PEP. Some studies have used the APACHE Ⅱ classification alone to grade the severity of PEP[41]. Other studies have used combinations of criteria to define the presence and severity of PEP or have

Table 2 Patient and procedural risk factors associated with post-ERCP pancreatitis

Patient related factors
Female sex
Young age
History of or suspected sphincter of oddi dysfunction
History of pancreatitis, recurrent pancreatitis or post-ERCP pancreatitis
Procedure related factors
Difficult or multiple cannulation attempts
Multiple pancreatic contrast injections
Pancreatic acinarization
Precut sphincterotomy
Endoscopic papillary balloon dilation
Sphincter of oddi manometry
Distal common bile duct diameter ≤ 1 cm
Presence of a pancreatic stricture
Procedures not involving stone removal

established unique definitions[31,36,42-45]. The heterogeneity of criteria in the literature on PEP hinders direct comparison of the published clinical trials.

PATHOPHYSIOLOGY OF PEP

The pathophysiology of PEP is not well understood. Mechanical, hydrostatic, chemical, enzymatic, allergic, thermal, cytokine and microbiological factors have all been proposed as causes[37,46-49]. Many studies suggest that PEP results from mechanical trauma with injury of the papilla or pancreatic sphincter causing swelling of the pancreatic duct and obstruction to the flow of pancreatic enzymes. This hypothesis remains controversial and no consensus related to the pathogenesis of PEP has been established.

The cascade of events leading to acute pancreatitis has been characterized in three phases. The first phase is characterized by premature activation of trypsin within the pancreatic acinar cells[50]. The second phase is characterized by intrapancreatic inflammation. The third phase is characterized by extrapancreatic inflammation[50]. Inflammation in the second and third phases has been described in a four step process with (1) activation of inflammatory cells; (2) chemoattraction of activated inflammatory cells; (3) activation of adhesion molecules resulting in binding of inflammatory cells to the endothelium; and (4) migration of activated inflammatory cells into areas of inflammation[50]. Recent studies have evaluated proinflammatory markers (TNF, IL-1, IL-6, IL-8, PAF and IL-10) in the setting of PEP[51-54]. While three randomized control trials suggested a protective effect using low and high dose (4 μg/kg and 20 μg/kg) interleukin 10 given intravenously 15-30 min prior to ERCP[14], subsequent studies using similar IL-10 protocols did not support these findings[55-56]. Though not demonstrated to date, modulation of proinflammatory pathways could represent an appealing goal for studies evaluating PEP and the systemic inflammatory response.

PROCEDURAL RELATED FACTORS ASSOCIATED WITH PEP

Although the triggers of the inflammatory cascade are not yet well understood, procedural and patient- related factors have been clearly associated with the incidence of PEP. ERCP is the most technically difficult endoscopic procedure performed in both inpatient and outpatient settings by trainees and experienced endoscopists. While trauma to the duodenum or papilla during endoscopy without cannulation rarely causes pancreatitis, cannulation of the papilla, especially in moderate to difficult cases, has been associated with high rates of PEP[7]. Procedures involving multiple (> 1-4) or failed attempts at cannulation, multiple pancreatic injections (≥ 2-5), pancreatic acinarization and prolonged cannulation time (> 10 min) have been associated with PEP. Operator experience, ampullary balloon dilation, pre-cut access sphincterotomy, endoscopic sphincterotomy (ES), sphincter of Oddi manometry, distal common bile duct diameters of ≤ 1 cm, presence of a pancreatic stricture, papillectomy and procedures not involving stone removal have also been associated with higher risks for developing PEP[10,12,20,29,35,46,57-60] (Table 2).

OPERATOR EXPERIENCE

While there is no established mandate for procedure volume for competence in ERCP, a prospective study published in 1996 to evaluate the number of supervised ERCPs a physician must perform to achieve procedural competence was reported to be at least 180 procedures[61]. In the United States, the American Society for Gastrointestinal Endoscopy and the American College of Gastroenterology have published quality indicators for ERCP. It is expected that competent endoscopists will be able to perform sphincterotomy, clear the common bile duct of stones, provide relief of biliary obstruction and successfully place stents for bile leaks in ≥ 85% of cases[62].

There have been few studies published in regard to operator experience in ERCP and this issue remains controversial. A recent study in Austria demonstrated a case volume exceeding 50 ERCPs per year had higher success and lower overall complication rates[63]. It is generally agreed that the case mix at high volume and academic referral centers may include a greater proportion of difficult and high-risk cases which may confound the relationship between experience and complication rates.

While operator experience is felt to be critical for high quality outcomes, many large prospective and retrospective trials have not shown consistent data correlating inexperience with PEP. Higher rates of bleeding have been reported after endoscopic sphincterotomy with a mean case volume of < 1 per wk[19] and trainee involvement was associated with severe or fatal complications in a recent retrospective analysis[64].

Table 3 Frequency of post-ERCP pancreatitis - conventional contrast based cannulation versus guide-wire cannulation in randomized trials

Author	Year published	Country	*n*	Rate of pancreatitis		*P* value
				CC (%)	GWC (%)	
Lee[72]	2009	Korea	300	11.30	2.00	0.001
Bailey[73]	2008	Australia	430	7.90	6.20	0.48
Artifon[70]	2007	Brazil and United States	300	16.60	8.60	0.037
Lella[69]	2004	Italy	392	4.10	0.00	< 0.01
Cortas[68]	1999	Canada	47	10.30	5.60	NR[a]

n: Patients included in final analysis; GWC: Guide-wire cannulation (papillotome with guide-wire assistance); CC: Conventional cannulation (papillotome with contrast injection); [a]Not reported.

A large prospective trial however, found that case volume had no effect on the incidence of PEP[29]. A prospective survey of ERCP in the United Kingdom in 2007 based on self reported surveys demonstrated that 15% of all credentialed endoscopists performed less than 50 ERCPs per year as compared to 61% of those in training with 11% of deaths with endoscopists performing less than 50 ERCPs per year. Although the rates of PEP were low at 1.5%, the success rates for bile duct stone extraction and biliary stent placement were 62% and 73% respectively. The authors summarized that in the UK there is a need for fewer operators and greater experience in those performing therapeutic endoscopy[65]. In the same year, a study in France showed no risk associated with operator inexperience[66].

CANNULATION TECHNIQUES

Cannulation techniques to access the pancreatic and biliary ducts include the use of sphincterotomes or straight or curved catheters with guide-wires or contrast injection. When an initial attempt at cannulation fails, access may be achieved after placement of a pancreatic guide-wire or stent to help guide the endoscopist towards the common bile duct and away from the pancreatic duct. Precut access papillotomy is frequently employed in referral centers when conventional approaches fail. Rare or experimental techniques such as the use of endoscopic scissors or endoscopic dissection with a cotton swab have been reported but are rarely employed in clinical practice[67].

Compared to standard catheters, the use of sphincterotomes may reduce failed attempts to obtain biliary access, decrease time required to cannulate the common bile duct and decrease the rate of PEP[68-69]. Selective sphincterotome cannulation with a guide wire may be associated with a reduced rate of PEP compared to cannulation with contrast injection[68-72] (Table 3). In 2008, a large prospective controlled trial randomized 430 patients into sphincterotome plus guide-wire versus conventional cannulation arms. The series demonstrated a significantly higher rate of cannulation with guide-wires but failed to show a significant difference in the rate of PEP between the two approaches[73]. The authors reported an 8.8%-14.9% increased risk of PEP after greater than 4 attempts at the papilla, highlighting the importance of cannulation with fewer attempts. These findings are consistent with previous studies[10,73].

PANCREATIC DUCT INJECTION

Multiple pancreatic duct injections (≥ 2-5)[10,20,29,59] and pancreatic acinarization[12,20,35] have been recognized as risk factors for PEP. Differences in the osmolality and ionicity of contrast media have been studied with varying results in terms of impact on PEP[30,33,60,74-76]. A recent meta-analysis of thirteen randomized controlled trials indicated there was no significant difference between high and low- osmolality contrast media[76]. Earlier studies suggested that there was a decreased risk of PEP with the use of non–ionic contrast agents[74], however this has not been consistently demonstrated[75]. One large retrospective analysis of 14 331 ERCPs suggested that less opacification of the pancreatic duct, head versus tail, resulted in significantly lower rates of PEP[60]. Although there is heterogeneity, clinical trial data suggest that hydrostatic pressure may play a role in the development of pancreatitis.

PANCREATIC DUCT STENTING

The theory that PEP is caused by pancreatic duct obstruction is supported by the majority of randomized controlled trials that demonstrate a decreased incidence of pancreatitis in high risk patients with the placement of a pancreatic duct stent[18,77-84]. In the three largest studies published to date evaluating the rate of pancreatitis with pancreatic duct stent placement, there were significant differences with decreased rates of PEP of 10.4%, 14.8% and 52.3%[17,78-79]. While pancreatic duct stenting has been shown to decrease the risk of PEP, it has not been able to prevent it. Despite stent placement, pancreatitis occurs in 2.0%-14% of cases[78-79,81,83-84] and some studies fail to demonstrate a statistically significant protective effect[60,83-84] (Table 4).

BILIARY STONE EXTRACTION

In the setting of choledocholithiasis, endoscopic papillary balloon dilatation (EPBD), ES and mechanical

Table 4 Randomized controlled trials evaluating the effect of pancreatic duct stenting on prevention of post-ERCP pancreatitis

Author	Country	Year published	*n*	Rate of post-ERCP pancreatitis		*P* value
				Without stent (%)	With stent (%)	
Tsuchiya[84]	Japan	2007	64	12.50	3.10	NR[a]
Sofuni[78]	Japan	2007	201	13.60	3.20	0.02
Harewood[77]	United States	2005	19	33.00	0.00	0.02
Fazel[85]	United States	2003	74	28.00	5.00	< 0.05
Tarnasky[18]	United States	1998	80	26.00	7.00	0.03
Smithline[87]	United States	1993	93	18.00	14.00	0.299

n: Patients included in final analysis; [a]Not reported.

Table 5 Frequency of post-ERCP pancreatitis - endoscopic sphincterotomy *vs* endoscopic papillary balloon dilation in randomized studies

Author	Year published	Country	*n*	Rate of pancreatitis		*P* value
				ES (%)	EPBD (%)	
DiSario[98][b]	2004	United States	237	0.83	15.38	< 0.05
Fujita[87]	2003	Japan	282	2.80	10.90	< 0.05
Vlavianos[92]	2003	United Kingdom	202	1.01	4.86	NR[a]
Arnold[89]	2001	Germany	60	10.00	20.00	NR[a]
Bergman[99]	1997	The Netherlands	202	6.93	6.93	NR[a]

n: Patients included in final analysis; ES : Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; [b]Multi-centered; [a]Not reported.

lithotripsy are the techniques used to extract obstructing stones. There have been multiple studies that have established the increased rate of PEP with EPBD ranging from 4.9%-20.0% versus 0.42%-10.0% with ES[85-88]. Prospective trials support this observation; however it is difficult to generalize the findings given the many factors that contribute to procedural complications[89-93] (Table 5). Balloon dilation may also be required in some clinical settings. If a patient has had a prior sphincterotomy and has limited remaining tissue for incision, balloon dilation may be necessary to enlarge the bile duct insertion and enable stone extraction.

PATIENT-RELATED RISK FACTORS ASSOCIATED WITH PEP

Given the high risk of PEP in certain populations, identifying a clear indication is critical in reducing the complication rate. It has been well recognized that ERCP is riskiest in patients who need it the least[21,94]. Large prospective trials have demonstrated that female gender, age less than 60-70 years, suspected SOD and recurrent or prior PEP were associated with a higher risk of PEP[10,12,20,29,35,57,95] (Table 2). Though widely accepted, there has been some heterogeneity across studies. For example, one smaller trial suggested an age of less than 50 as a significant risk factor[95]. A recent large retrospective study of 16 855 patients demonstrated the highest rates of PEP were associated with patients with SOD but there was no significant increase in younger patients or in women[64]. Alternatively, a meta-analysis evaluating five patient- related risk factors demonstrated a relative risk of SOD of 4.09 (95% CI 1.93 to 3.12; $P < 0.001$) and female gender of 2.23 (95% CI 1.75 to 2.84; $P < 0.001$)[96]. One study demonstrated a 10 fold increase in the development of PEP in patients with SOD[97].

Some factors may be protective as well. Studies have suggested that the absence of chronic pancreatitis[58], the presence of obesity[98], older age (> 80)[99] and a history of alcohol consumption or cigarette smoking may be associated with a decreased risk of PEP[100]. Proper patient selection and identification of patients at higher risk is the most effective means of reducing the incidence of PEP.

PHARMACOLOGIC AGENTS EVALUATED IN PREVENTION/REDUCITON OF PEP

There has been great interest in the affect of pharmacologic agents on PEP. Preventing cellular injury and pancreatic tissue auto-digestion may involve blocking the premature activation of proteolytic enzymes within the acinar cells[19,101-109]. Though conceptually straightforward, the goal of blocking this activation has been difficult to achieve. Multiple trials have been performed with a goal of reducing the incidence or severity of PEP. Approximately 34 (Table 6) pharmacologic agents and procedures (e.g. topical application of pharmacologic agents injected or sprayed on to the papilla) have been evaluated for potential prevention of PEP in controlled trials. Most clinical trials have been disappointing and a minority of studies has demonstrated benefit (Table 7)[14,15,31,34,42-45,55,56,59,96,110-161].

Allopurinol has been shown in two of five pro-

Table 6 Pharmacologic agents evaluated for potential reduction/prevention of post-ERCP pancreatitis

Pharmacologic agent	RCT showed benefit
Allopurinol	Yes
Cephtazidime	Yes
Diclofenac	Yes
Gabexate	Yes
Glyceryl trinitrate	Yes
Hydrocortisone	Yes
Indomethacin	Yes
Interleukin-10 (IL-10)	Yes
Nafamostat mesylate	Yes
Octreotide	Yes
Somatostatin	Yes
Ulinastatin	Yes
Anticholinergic drugs	No
Aprotinin	No
Botulinum toxin	No
Calcitonin	No
Epinephrine	No
Fresh frozen plazma	No
Glucagon	No
H-2 Blocker	No
Heparin	No
Lidocaine	No
Methylprednisolone	No
N-aceytyl cysteine (NAC)	No
Natural beta-carotene	No
Nifedipine	No
Nitroglycerin	No
Parenteral nutrition	No
Pentoxifylline	No
Prednisone	No
Recombinant PAF acetylhydrolase (rPAF-AH)	No
Selenium	No
Semapimod	No

spective trials to decrease the incidence of PEP[110,112]. In these trials showing benefits, allopurinol was given in 300 mg or 600 mg doses at 15 h and 3 h prior to ERCP. When reviewing other studies of allopurinol, these effects were not significant in patients dosed on a different 4 h and 1 h regimen and with varying dose concentrations of allopurinol[111,113,114]. This may suggest that not only the dose but timing of allopurinol administration is important in the reduction of PEP. Diclofenac, a non steroidal anti-inflammatory drug, was evaluated in three trials. With diclofenac 100 mg PR dosed immediately after ERCP, the incidence of PEP was decreased[44,131] but a trial evaluating diclofenac 50 mg PO at 30-90 min prior to ERCP and up to 4-6 h post ERCP showed no decrease in PEP[132]. In regard to glyceryl trinitrate[129], hydrocortisone[118] and interleukin-10[14], all agents were shown in one randomized control trial to show benefit. However in studies with larger numbers of patients[31,56,128] these findings were found to be statistically insignificant.

Gabexate[145,146,148], octreotide[135,136], somatostatin[156,159] and ulinastatin[152] have all been reported to show a reduction in PEP. However there have been studies evaluating each of these agents with similar designs that report no significant reduction in the incidence of PEP. These differences could be explained by the selection of patients, number of patients, clinical presentation and timing of administration or dosage of the agent under investigation.

While the use of allopurinol, cephtazidime, diclofenac, gabexate, glyceryl trinitrate, hydrocortisone, indomethacin, interleukin-10, nafamostat mesylate, octreotide, somatostatin and ulinastatin have shown promise in clinical trials, there is currently no accepted pharmacologic intervention to prevent pancreatitis and in some cases (gabexate, nafamostat and somatostatin) the pharmacologic agent is not approved for use in some countries. Nevertheless, pharmacologic prevention remains an active area of research.

MANAGEMENT OF PEP

Once mild or moderate PEP has occurred it usually quickly resolves with conservative therapy. Although there are no specific guidelines for the treatment of PEP, a recent study demonstrated that a protocol-based management strategy was associated with less severe pancreatitis, shorter lengths of hospital stay, need for fewer imaging studies and less use of antibiotics[102]. Practice guidelines for acute pancreatitis treatment are available and may be applicable to PEP as well[50].

In patients with persistent or severe PEP, two important markers of severity are multisystem organ failure and pancreatic necrosis, both of which require aggressive management[23]. Early identification of organ failure, pancreatic necrosis, perforation (especially in the setting of endoscopic sphincterotomy), biliary damage/leak and pancreatic fluid collections are important clinical branch points, potentially requiring more intensive intervention. Checking serum transaminases, amylase and lipase is not routinely recommended post-ERCP. If assessed, elevations are commonly observed post procedure. These elevations are likely secondary to intermittent biliary, pancreatic or papillary obstruction. 46% of patients in a recent study were reported to have elevated liver test elevations after ERCP and only 5.4% of them had PEP[103]. Asymptomatic elevations are not an indication for a change in management and repeat ERCP is performed only with a clear indication.

Although there is controversy related to enteral feeding during treatment of acute pancreatitis, patients who are unlikely to resume oral nutrition within five days require nutritional support which can be provided *via* TPN or enteral routes. There appears to be some advantages to enteral feeding and a recent study found that initiating oral nutrition after mild acute pancreatitis with a low fat soft diet appeared to be safe but did not result in a shorter length of hospitalization[104].

CONCLUSION

Acute pancreatitis is the most common complication after ERCP. The pathophysiology is not well understood

Table 7 Randomized controlled trails of pharmacologic agents evaluated for reduction or prevention of post-ERCP pancreatitis

Agent	Author	Factor studied	*n*	Rate of post-ERCP pancreatitis (%)			*P* value
				Overall	Control	Intervention	
Allopurinol							
	Martinez-Torres[110]	Allopurinol 300 mg PO at 15 h; 300 mg PO at 3 h before ERCP	170	NR[a]	9.40	2.30	0.049
	Romagnuolo[111]b	Allopurinol 300 mg PO at 1 h before ERCP	586	NR[a]	4.10	5.50	0.440
	Katsinelos[112]	Allopurinol 600 mg PO at 15 h; 600 mg PO at 3 h before ERCP	243	10.20	17.80	3.20	< 0.001
	Mosler[113]	Allopurinol 600 mg PO at 4 h; 300 mg PO at 1 h before ERCP	346	12.55	12.14	12.96	0.520
	Budzynska[114]	Allopurinol 200 mg PO at 15 h; 200 mg PO at 3 h before ERCP	300	10.70	7.90	12.10	0.320
Beta-carotene							
	Lavy[115]	Natural beta-carotene 2 g at 12 h before ERCP	321	9.60	9.60	10.00	NR[a]
Botulinum toxin							
	Gorelick[116]	Botulinum toxin injection after biliary sphincterotomy	26	NR[a]	43.00	25.00	0.340
Cephtazidime							
	Raty[117]	Cephtazidime 2g Ⅳ 30 min before ERCP	321	NR[a]	9.38	2.58	0.009
Hydrocortisone							
	Kwanngern[118]	Hydrocortisone 100 mg Ⅳ at 1 h before ERCP	120	6.67	11.86	1.64	0.031
	Manolakopoulos[119]b	Hydrocortisone 100 mg Ⅳ at 30 min before ERCP	340	10.00	13.00	7.10	0.380
	De Palma[31]	Hydrocortisone 100 mg Ⅳ immediately before ERCP	529	5.30	4.90	5.70	NS
Prednisone							
	Sherman[120]b	Prednisone 40 mg PO at 15 h and at 3 h before ERCP	1115	15.07	13.60	16.60	0.190
	Budzynska[114]	Prednisone 40 mg at 15 h; 40 mg at 3 h before ERCP		10.70	7.90	12.00	0.330
Methylprednisolone							
	Dumot[43]	Methylprednisolone 125 mg Ⅳ immediately before ERCP	286	NR[a]	8.70	12.40	0.340
Heparin							
	Barkay[42]	Unfractionated heparin 5000 IU SC 20-30 min before ERCP	106	NR[a]	7.40	7.80	NS
	Rabenstein[121]	Low molecular weight heparin Certoparin 3000 IU SC the day before ERCP	448	8.50	8.81	8.14	0.870
Interlukin-10							
	Sherman[56]b	IL-10 8 μg/kg Ⅳ 15-30 min before ERCP	305	17.38	14.30	15.40	0.830
		IL-10 20 μg/kg Ⅳ 15-30 min before ERCP				22.00	0.140
	Deviere[14]	IL-10 4 μg/kg Ⅳ 30 min before ERCP	144	29.90	24.40	10.41	0.046
		IL-10 20 μg/kg Ⅳ 30 min before ERCP				6.81	0.017
	Dumot[55]	IL-10 8 μg/kg Ⅳ 15 min before ERCP	200	10.00	9.10	10.90	0.650
N-acetyl cystine							
	Milewski[122]	NAC 600 mg Ⅳ BID × 2 d after ERCP	106	9.43	11.76	7.27	NS
	Katsinelos[123]	NAC 70 mg/kg 2 h before and 35 mg/kg 4 h intervals for 24 h after procedure	249	10.80	9.60	12.10	> 0.500
Nifedipine							
	Prat[124]	Nifedipine 20 mg PO 3-6 h before ERCP	155	15.50	17.70	13.20	NS
	Sand[125]	Nifedipine 20 mg PO q 8 h the day of ERCP	166	3.61	4.00	4.00	NR[a]
Nitroglycerin							
	Hao[126]	Glyceryl trinitrate 5 mg Ⅳ and 100 mg vitamin C 5 min before ERCP maneuvers	74	16.20	25.00	7.90	0.012
	Beauchant[127]b	Nitroglycerin bolus of 0.1 mg, then 35 g/kg/min Ⅳ for 6 h after ERCP	208	12.00	15.00	10.00	0.260
	Kaffes[128]	Transdermal glyceryl trinitrate patch (15 mg) precordial area 30-40 min before ERCP	318	NR[a]	7.40	7.70	NS
	Moreto[129]	Transdermal glyceryl trinitrate patch (15 mg) precordial area 30-40 min before ERCP	144	9.00	15.00	4.00	0.030
	Sudhindran[130]	Glyceryl trinitrate 2 mg SL 5 min before ERCP	186	13.00	18.00	8.00	< 0.050
Diclofenac							
	Khoshbaten[131]	Diclofenac 100 mg PR immediately after ERCP	100	15.00	26.00	4.00	< 0.010
	Cheon[132]	Diclofenac 50 mg at 30-90 min before and at 4-6 h after ERCP	207	16.40	16.70	16.20	NS
	Murray[44]	Diclofenac 100 mg PR immediately after ERCP	220	11.00	15.45	6.36	0.049
Indomethacin							
	Sotoudehmanesh[133]	Indomethacin 100 mg PR after ERCP	442	4.98	6.78	3.16	OR 0.4 (0.2 - 1.1)

Octreotide							
	Kisli[134]	Octreotide 0.1 mg gtt 60 min before ERCP and continued during and after ERCP	120	NR[a]	11.49	15.15	NS
	Li[135]b	Octreotide 0.3 mg gtt 1 h before -6 h after ERCP; then 0.1 mg SC; 12 h later 0.1 mg SC	832	3.85	5.26	2.42	0.046
	Thomopoulos[136]	Octreotide 500 μg TID starting 24 h before ERCP	201	10.89	8.90	2.00	0.03
	Testoni[137]b	Octreotide 200 μg TID × 24 h before ERCP	114	NR[a]	14.30	12.00	NS
	Hardt[138]	Octreotide 200 μg SC the night before ERCP	94	NR[a]	NR[a]	NR[a]	NS
	Duvnjak[139]	Octreotide 0.5 mg SC 60 min before ERCP	209	NR[a]	9.52	3.85	NS
	Arvanitidis[140]	Octreotide 0.1 mg SC 30 min before; 8 h and 16 h after ERCP	73	10.95	11.11	10.81	NS
	Tulassay[45]b	Octreotide 0.1 mg SC 45 min after ERCP	1199	7.84	6.00	5.90	NS
	Arcidiacono[141]	Octreotide 0.1 mg SC 120 and 30 min before; 4 h after ERCP	151	6.62	NR[a]	NR[a]	NS
	Baldazzi[142]	Octreotide 0.1 mg SC 45 min before; 6 h after ERCP	100	NR[a]	NR[a]	NR[a]	NR[a]
	Testoni[143]	Octreotide 0.2 mg SC before ERCP	60	NR[a]	NR[a]	NR[a]	NS
	Testoni[34]	Octreotide 200 μg TID × 3 d before ERCP	60	NR[a]	NR[a]	NR[a]	NS
Gabexate							
	Ueki[144]	Gabexate 600 mg Ⅳ 60-90 min before and 22 h after ERCP	68	2.90	NR[a]	2.90	NS
	Manes[145]b	Gabexate mesylate 500 mg within 1 h before ERCP	608	5.60	9.40	3.90	< 0.01
		Gabexate mesylate 500 mg within 1h after ERCP				3.40	< 0.01
	Xiong[146]	Gabexate 300 mg Ⅳ 30 min before gtt until 4 h after ERCP	200	6.70	10.50	3.10	0.04
	Fujishiro[151]b	Gabexate 900 mg/1500 mL gtt for 13 h beginning 1 h before ERCP	139	NR[a]	NR[a]	4.30	NS
	Andriulli[59]b	Gabexate 500 mg 30 min before gtt until 6 h after ERCP	1127	5.60	4.80	5.80	NS
	Masci[96]b	Gabexate 500 mg Ⅳ 30 min before gtt until 6.5 h after ERCP and 1 g Ⅳ for 13 h after ERCP	434	1.80	2.20	1.40	NS
	Andriulli[147]b	Gabexate 500 mg Ⅳ 30 min before and 2 h after ERCP	579	8.60	6.50	8.10	NS
	Cavallini[148]b	Gabexate 1 g Ⅳ 30-90 min before gtt until 12 h after ERCP	418	5.00	8.00	2.00	0.03
Nafamostat mesylate							
	Choi[149]	Nafamostat mesylate 20 mg gtt 1 h before and for 24 h after ERCP	704	5.40	7.40	3.30	0.018
Ulinastatin							
	Yoo[150]	Ulinastatin 100 000 U gtt after ERCP for 5.5 h	227	6.20	5.60	6.70	0.715
	Ueki[144]	Ulinastatin 150 000 units 60-90 min before & for 22 h after ERCP	68	2.90	2.90	2.90	NS
	Fujishiro[151]b	Ulinastatin 150 000 units 1 h before, during; 11 h after ERCP				6.50	NS
		Ulinastatin 50 000 units				8.50	NS
	Tsujino[152]b	Ulinastatin 150 000 U gtt 10 min before ERCP	406	5.17	7.40	2.90	0.041
Pentoxifylline							
	Kapetanos[153]	Pentoxifylline 400 mg PO TID before ERCP	320	4.38	3.00	5.60	0.28
Recombinant PAF acetylhydrolase							
	Sherman[154]b	Recombinant PAF acetylhydrolase (rPAF-AH) 1 mg/kg gtt < 1 h before ERCP	600	17.60	19.60	17.50	0.59
		Recombinant PAF acetylhydrolase (rPAF-AH) 5 mg/kg gtt < 1 h before ERCP				15.90	0.34
Semapimod							
	van Westerloo[155]	Semapimod Ⅳ 50 mg/100 mL glucose gtt 1 h before ERCP	242	11.98	14.88	9.09	0.117
Somatostatin							
	Lee[156]b	Somatostatin 3 mg in 500 mL NS gtt 12 h starting 30min before ERCP	391	6.65	9.60	3.60	0.02
	Andriulli[59]b	Somatostatin 750 μg Ⅳ 30 min before and continued for 6 h after ERCP				6.30	NS
	Arvanitidis[157]	Somatastatin 4 μg/kg gtt 12 h on identification of the papilla and before introduction of the catheter	372	NR[a]	9.80	1.70	< 0.05
		Somatostatin 3 mg gtt 12 h on identification of the papilla and before introduction of the catheter				1.70	< 0.05

	Poon[158]	Somatostatin 250 mg IV bolus immediately after ERCP	270	NR[a]	13.30	4.40	0.01
	Andriulli[147][b]	Somatastatin 750 μg IV 30 min before and 2 h after ERCP				11.50	NS
	Poon[159]	Somatostatin 3 mg in 500 mL NS gtt for 12 h starting 30 min before ERCP	220	5.91	10.00	3.00	0.03
	Bordas[160]	Natural somatostatin 4 mg/kg IV on identification of the papilla and before introduction of the catheter	160	NR[a]	10.00	2.50	< 0.05
Topical spray on papilla							
	Matsushita[15]	Epinephrine (10 mL of 0.02%) sprayed on papilla before cannulation	370	1.10	2.16	0.00	0.123
	Schwartz[161]	Lidocaine (10 mL of 1%) sprayed on the major papilla before cannulation	294	4.08	3.04	4.32	0.73

PEP: Post-ERCP pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; IL-10: Ingerlukin-10; NAC: N-acetyl cystine; NS: Not significant; [a]Not reported/unable to acquire primary data from publication; [b]Multi-centered.

but theories regarding mechanical, hydrostatic, chemical, enzymatic, allergic, thermal, cytokine and microbiological factors have been proposed. While trauma during endoscopy without cannulation rarely causes pancreatitis, procedural factors involving cannulation, access and pancreaticobiliary drainage have been associated with PEP. Although operator experience is important in high quality outcomes, many large prospective and retrospective trials have not shown consistent data associating inexperience with increased incidence, perhaps due to the importance of case-mix in outcome. Patient-related risk factors are well recognized with Sphincter of Oddi dysfunction and a history of PEP conferring additional risk in the post-procedure setting. However, obesity, older age, alcohol consumption and cigarette smoking may be protective. Approximately 34 pharmacologic agents have been evaluated and 63 clinical trials have been performed in an effort to identify an agent to prevent PEP. Over the last 15 years, no pharmacologic agent has been accepted in reducing PEP due to a lack of reproducibility, heterogeneity in outcomes and/or limitations in study design. Proper patient selection and identification of risk factors pre-procedure is the most effective means of reducing the incidence of PEP.

REFERENCES

1 **McCune WS**, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of vater: a preliminary report. *Ann Surg* 1968; **167**: 752-756
2 **Peel AL**, Hermon-Taylor J, Ritchie HD. Technique of transduodenal exploration of the common bile duct. Duodenoscopic appearances after biliary sphincterotomy. *Ann R Coll Surg Engl* 1974; **55**: 236-244
3 **Zimmon DS**, Falkenstein DB, Kessler RE. Endoscopic papillotomy for choledocholithiasis. *N Engl J Med* 1975; **293**: 1181-1182
4 **Zimmon DS**, Falkenstein DB, Riccobono C, Aaron B. Complications of endoscopic retrograde cholangiopancreatography. Analysis of 300 consecutive cases. *Gastroenterology* 1975; **69**: 303-309
5 **Bilbao MK**, Dotter CT, Lee TG, Katon RM. Complications of endoscopic retrograde cholangiopancreatography (ERCP). A study of 10,000 cases. *Gastroenterology* 1976; **70**: 314-320
6 **Skude G**, Wehlin L, Maruyama T, Ariyama J. Hyperamylasaemia after duodenoscopy and retrograde cholangiopancreatography. *Gut* 1976; **17**: 127-132
7 **Deschamps JP**, Allemand H, Janin Magnificat R, Camelot G, Gillet M, Carayon P. Acute pancreatitis following gastrointestinal endoscopy without ampullary cannulation. *Endoscopy* 1982; **14**: 105-106
8 **Odes HS**, Novis BN, Barbezat GO, Bank S. Effect of calcitonin on the serum amylase levels after endoscopic retrograde cholangiopancreatography. *Digestion* 1977; **16**: 180-184
9 **Börsch G**, Bergbauer M, Nebel W, Sabin G. [Effect of somatostatin on amylase level and pancreatitis rate following ERCP]. *Med Welt* 1984; **35**: 109-112
10 **Vandervoort J**, Soetikno RM, Tham TC, Wong RC, Ferrari AP Jr, Montes H, Roston AD, Slivka A, Lichtenstein DR, Ruymann FW, Van Dam J, Hughes M, Carr-Locke DL. Risk factors for complications after performance of ERCP. *Gastrointest Endosc* 2002; **56**: 652-656
11 **Deans GT**, Sedman P, Martin DF, Royston CM, Leow CK, Thomas WE, Brough WA. Are complications of endoscopic sphincterotomy age related? *Gut* 1997; **41**: 545-548
12 **Loperfido S**, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, De Bernardin M, Ederle A, Fina P, Fratton A. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest Endosc* 1998; **48**: 1-10
13 **Christensen M**, Matzen P, Schulze S, Rosenberg J. Complications of ERCP: a prospective study. *Gastrointest Endosc* 2004; **60**: 721-731
14 **Devière J**, Le Moine O, Van Laethem JL, Eisendrath P, Ghilain A, Severs N, Cohard M. Interleukin 10 reduces the incidence of pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2001; **120**: 498-505
15 **Matsushita M**, Takakuwa H, Shimeno N, Uchida K, Nishio A, Okazaki K. Epinephrine sprayed on the papilla for prevention of post-ERCP pancreatitis. *J Gastroenterol* 2009; **44**: 71-75
16 **Gottlieb K**, Sherman S. ERCP and biliary endoscopic sphincterotomy-induced pancreatitis. *Gastrointest Endosc Clin N Am* 1998; **8**: 87-114
17 **Fogel EL**, Eversman D, Jamidar P, Sherman S, Lehman GA. Sphincter of Oddi dysfunction: pancreaticobiliary sphincterotomy with pancreatic stent placement has a lower rate of pancreatitis than biliary sphincterotomy alone. *Endoscopy* 2002; **34**: 280-285
18 **Tarnasky PR**, Palesch YY, Cunningham JT, Mauldin PD, Cotton PB, Hawes RH. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. *Gastroenterology* 1998; **115**: 1518-1524

19 **Silviera ML**, Seamon MJ, Porshinsky B, Prosciak MP, Doraiswamy VA, Wang CF, Lorenzo M, Truitt M, Biboa J, Jarvis AM, Narula VK, Steinberg SM, Stawicki SP. Complications related to endoscopic retrograde cholangiopancreatography: a comprehensive clinical review. *J Gastrointestin Liver Dis* 2009; **18**: 73-82

20 **Wang P**, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, Huang Q, Zhang X, He LP, Sun WS, Zhao Q, Shi RH, Tian ZB, Li YQ, Li W, Zhi FC. Risk factors for ERCP-related complications: a prospective multicenter study. *Am J Gastroenterol* 2009; **104**: 31-40

21 **Cohen S**, Bacon BR, Berlin JA, Fleischer D, Hecht GA, Loehrer PJ Sr, McNair AE Jr, Mulholland M, Norton NJ, Rabeneck L, Ransohoff DF, Sonnenberg A, Vannier MW. National Institutes of Health State-of-the-Science Conference Statement: ERCP for diagnosis and therapy, January 14-16, 2002. *Gastrointest Endosc* 2002; **56**: 803-809

22 **Brugge WR**, Van Dam J. Pancreatic and biliary endoscopy. *N Engl J Med* 1999; **341**: 1808-1816

23 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393

24 **Testoni PA**, Bagnolo F, Caporuscio S, Lella F. Serum amylase measured four hours after endoscopic sphincterotomy is a reliable predictor of postprocedure pancreatitis. *Am J Gastroenterol* 1999; **94**: 1235-1241

25 **Testoni PA**, Cicardi M, Bergamaschini L, Guzzoni S, Cugno M, Buizza M, Bagnolo F, Agostoni A. Infusion of C1-inhibitor plasma concentrate prevents hyperamylasemia induced by endoscopic sphincterotomy. *Gastrointest Endosc* 1995; **42**: 301-305

26 **Testoni PA**, Bagnolo F. Pain at 24 hours associated with amylase levels greater than 5 times the upper normal limit as the most reliable indicator of post-ERCP pancreatitis. *Gastrointest Endosc* 2001; **53**: 33-39

27 **Testoni PA**, Bagnolo F, Natale C, Primignani M. Incidence of post-endoscopic retrograde-cholangiopancreatography/sphincterotomy pancreatitis depends upon definition criteria. *Dig Liver Dis* 2000; **32**: 412-418

28 **Weiner GR**, Geenen JE, Hogan WJ, Catalano MF. Use of corticosteroids in the prevention of post-ERCP pancreatitis. *Gastrointest Endosc* 1995; **42**: 579-583

29 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918

30 **Johnson GK**, Geenen JE, Johanson JF, Sherman S, Hogan WJ, Cass O. Evaluation of post-ERCP pancreatitis: potential causes noted during controlled study of differing contrast media. Midwest Pancreaticobiliary Study Group. *Gastrointest Endosc* 1997; **46**: 217-222

31 **De Palma GD**, Catanzano C. Use of corticosteriods in the prevention of post-ERCP pancreatitis: results of a controlled prospective study. *Am J Gastroenterol* 1999; **94**: 982-985

32 **Sherman S**, Ruffolo TA, Hawes RH, Lehman GA. Complications of endoscopic sphincterotomy. A prospective series with emphasis on the increased risk associated with sphincter of Oddi dysfunction and nondilated bile ducts. *Gastroenterology* 1991; **101**: 1068-1075

33 **Sherman S**, Hawes RH, Rathgaber SW, Uzer MF, Smith MT, Khusro QE, Silverman WB, Earle DT, Lehman GA. Post-ERCP pancreatitis: randomized, prospective study comparing a low- and high-osmolality contrast agent. *Gastrointest Endosc* 1994; **40**: 422-427

34 **Testoni PA**, Lella F, Bagnolo F, Caporuscio S, Cattani L, Colombo E, Buizza M. Long-term prophylactic administration of octreotide reduces the rise in serum amylase after endoscopic procedures on Vater's papilla. *Pancreas* 1996; **13**: 61-65

35 **Masci E**, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, Minoli G, Crosta C, Comin U, Fertitta A, Prada A, Passoni GR, Testoni PA. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol* 2001; **96**: 417-423

36 **Abid GH**, Siriwardana HP, Holt A, Ammori BJ. Mild ERCP-induced and non-ERCP-related acute pancreatitis: two distinct clinical entities? *J Gastroenterol* 2007; **42**: 146-151

37 **Chen CC**, Wang SS, Lu RH, Lu CC, Chang FY, Lee SD. Early changes of serum proinflammatory and anti-inflammatory cytokines after endoscopic retrograde cholangiopancreatography. *Pancreas* 2003; **26**: 375-380

38 **Bradley EL 3rd**. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg* 1993; **128**: 586-590

39 **Knaus WA**, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med* 1981; **9**: 591-597

40 **Ranson JH**, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet* 1974; **139**: 69-81

41 **Bhatia V**, Garg PK, Tandon RK, Madan K. Endoscopic retrograde cholangiopancreatography-induced acute pancreatitis often has a benign outcome. *J Clin Gastroenterol* 2006; **40**: 726-731

42 **Barkay O**, Niv E, Santo E, Bruck R, Hallak A, Konikoff FM. Low-dose heparin for the prevention of post-ERCP pancreatitis: a randomized placebo-controlled trial. *Surg Endosc* 2008; **22**: 1971-1976

43 **Dumot JA**, Conwell DL, O'Connor JB, Ferguson DR, Vargo JJ, Barnes DS, Shay SS, Sterling MJ, Horth KS, Issa K, Ponsky JL, Zuccaro G. Pretreatment with methylprednisolone to prevent ERCP-induced pancreatitis: a randomized, multicenter, placebo-controlled clinical trial. *Am J Gastroenterol* 1998; **93**: 61-65

44 **Murray B**, Carter R, Imrie C, Evans S, O'Suilleabhain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2003; **124**: 1786-1791

45 **Tulassay Z**, Döbrönte Z, Prónai L, Zágoni T, Juhász L. Octreotide in the prevention of pancreatic injury associated with endoscopic cholangiopancreatography. *Aliment Pharmacol Ther* 1998; **12**: 1109-1112

46 **Sherman S**, Lehman GA. ERCP- and endoscopic sphincterotomy-induced pancreatitis. *Pancreas* 1991; **6**: 350-367

47 **Pezzilli R**, Romboli E, Campana D, Corinaldesi R. Mechanisms involved in the onset of post-ERCP pancreatitis. *JOP* 2002; **3**: 162-168

48 **Messmann H**, Vogt W, Holstege A, Lock G, Heinisch A, von Fürstenberg A, Leser HG, Zirngibl H, Schölmerich J. Post-ERP pancreatitis as a model for cytokine induced acute phase response in acute pancreatitis. *Gut* 1997; **40**: 80-85

49 **Oezcueruemez-Porsch M**, Kunz D, Hardt PD, Fadgyas T, Kress O, Schulz HU, Schnell-Kretschmer H, Temme H, Westphal S, Luley C, Kloer HU. Diagnostic relevance of interleukin pattern, acute-phase proteins, and procalcitonin in early phase of post-ERCP pancreatitis. *Dig Dis Sci* 1998; **43**: 1763-1769

50 **Banks PA**, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006; **101**: 2379-2400

51 **Kilciler G**, Musabak U, Bagci S, Yesilova Z, Tuzun A, Uygun A, Gulsen M, Oren S, Oktenli C, Karaeren N. Do the changes in the serum levels of IL-2, IL-4, TNFalpha, and IL-6 reflect the inflammatory activity in the patients with post-ERCP pancreatitis? *Clin Dev Immunol* 2008; **2008**: 481560

52 **Sultan S**, Baillie J. What are the predictors of post-ERCP pancreatitis, and how useful are they? *JOP* 2002; **3**: 188-194

53 **Demols A**, Deviere J. New frontiers in the pharmacological

prevention of post-ERCP pancreatitis: the cytokines. *JOP* 2003; **4**: 49-57
54 **Pande H**, Thuluvath P. Pharmacological prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Drugs* 2003; **63**: 1799-1812
55 **Dumot JA**, Conwell DL, Zuccaro G Jr, Vargo JJ, Shay SS, Easley KA, Ponsky JL. A randomized, double blind study of interleukin 10 for the prevention of ERCP-induced pancreatitis. *Am J Gastroenterol* 2001; **96**: 2098-2102
56 **Sherman S**, Cheng CL, Costamagna G, Binmoeller KF, Puespoek A, Aithal GP, Kozarek RA, Chen YK, Van Steenbergen W, Tenner S, Freeman M, Monroe P, Geffner M, Deviere J. Efficacy of recombinant human interleukin-10 in prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis in subjects with increased risk. *Pancreas* 2009; **38**: 267-274
57 **Williams EJ**, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson ML, Williamson PR, Lombard M. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. *Endoscopy* 2007; **39**: 793-801
58 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434
59 **Andriulli A**, Solmi L, Loperfido S, Leo P, Festa V, Belmonte A, Spirito F, Silla M, Forte G, Terruzzi V, Marenco G, Ciliberto E, Sabatino A, Monica F, Magnolia MR, Perri F. Prophylaxis of ERCP-related pancreatitis: a randomized, controlled trial of somatostatin and gabexate mesylate. *Clin Gastroenterol Hepatol* 2004; **2**: 713-718
60 **Cheon YK**, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, Lehman GA. Frequency and severity of post-ERCP pancreatitis correlated with extent of pancreatic ductal opacification. *Gastrointest Endosc* 2007; **65**: 385-393
61 **Jowell PS**, Baillie J, Branch MS, Affronti J, Browning CL, Bute BP. Quantitative assessment of procedural competence. A prospective study of training in endoscopic retrograde cholangiopancreatography. *Ann Intern Med* 1996; **125**: 983-989
62 **Baron TH**, Petersen BT, Mergener K, Chak A, Cohen J, Deal SE, Hoffinan B, Jacobson BC, Petrini JL, Safdi MA, Faigel DO, Pike IM. Quality indicators for endoscopic retrograde cholan giopancreatography. *Am J Gastroenterol* 2006; **101**: 892-897
63 **Kapral C**, Duller C, Wewalka F, Kerstan E, Vogel W, Schreiber F. Case volume and outcome of endoscopic retrograde cholangiopancreatography: results of a nationwide Austrian benchmarking project. *Endoscopy* 2008; **40**: 625-630
64 **Cotton PB**, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009; **70**: 80-88
65 **Williams EJ**, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson M, Williamson PJ, Lombard M. Are we meeting the standards set for endoscopy? Results of a large-scale prospective survey of endoscopic retrograde cholangio-pancreatograph practice. *Gut* 2007; **56**: 821-829
66 **Vitte RL**, Morfoisse JJ. Evaluation of endoscopic retrograde cholangiopancreatography procedures performed in general hospitals in France. *Gastroenterol Clin Biol* 2007; **31**: 740-749
67 **Freeman ML**, Guda NM. ERCP cannulation: a review of reported techniques. *Gastrointest Endosc* 2005; **61**: 112-125
68 **Cortas GA**, Mehta SN, Abraham NS, Barkun AN. Selective cannulation of the common bile duct: a prospective randomized trial comparing standard catheters with sphincterotomes. *Gastrointest Endosc* 1999; **50**: 775-779
69 **Lella F**, Bagnolo F, Colombo E, Bonassi U. A simple way of avoiding post-ERCP pancreatitis. *Gastrointest Endosc* 2004; **59**: 830-834
70 **Artifon EL**, Sakai P, Cunha JE, Halwan B, Ishioka S, Kumar A. Guidewire cannulation reduces risk of post-ERCP pancreatitis and facilitates bile duct cannulation. *Am J Gastroenterol* 2007; **102**: 2147-2153
71 **Ito K**, Fujita N, Noda Y, Kobayashi G, Obana T, Horaguchi J, Takasawa O, Koshita S, Kanno Y. Pancreatic guidewire placement for achieving selective biliary cannulation during endoscopic retrograde cholangio-pancreatography. *World J Gastroenterol* 2008; **14**: 5595-5600; discussion 5599
72 **Lee TH**, Park do H, Park JY, Kim EO, Lee YS, Park JH, Lee SH, Chung IK, Kim HS, Park SH, Kim SJ. Can wire-guided cannulation prevent post-ERCP pancreatitis? A prospective randomized trial. *Gastrointest Endosc* 2009; **69**: 444-449
73 **Bailey AA**, Bourke MJ, Williams SJ, Walsh PR, Murray MA, Lee EY, Kwan V, Lynch PM. A prospective randomized trial of cannulation technique in ERCP: effects on technical success and post-ERCP pancreatitis. *Endoscopy* 2008; **40**: 296-301
74 **Barkin JS**, Casal GL, Reiner DK, Goldberg RI, Phillips RS, Kaplan S. A comparative study of contrast agents for endoscopic retrograde pancreatography. *Am J Gastroenterol* 1991; **86**: 1437-1441
75 **Johnson GK**, Geenen JE, Bedford RA, Johanson J, Cass O, Sherman S, Hogan WJ, Ryan M, Silverman W, Edmundowicz S. A comparison of nonionic versus ionic contrast media: results of a prospective, multicenter study. Midwest Pancreaticobiliary Study Group. *Gastrointest Endosc* 1995; **42**: 312-316
76 **George S**, Kulkarni AA, Stevens G, Forsmark CE, Draganov P. Role of osmolality of contrast media in the development of post-ERCP pancreatitis: a metanalysis. *Dig Dis Sci* 2004; **49**: 503-508
77 **Harewood GC**, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. *Gastrointest Endosc* 2005; **62**: 367-370
78 **Sofuni A**, Maguchi H, Itoi T, Katanuma A, Hisai H, Niido T, Toyota M, Fujii T, Harada Y, Takada T. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. *Clin Gastroenterol Hepatol* 2007; **5**: 1339-1346
79 **Freeman ML**. Pancreatic stents for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Clin Gastroenterol Hepatol* 2007; **5**: 1354-1365
80 **Tarnasky PR**. Mechanical prevention of post-ERCP pancreatitis by pancreatic stents: results, techniques, and indications. *JOP* 2003; **4**: 58-67
81 **Fazel A**, Quadri A, Catalano MF, Meyerson SM, Geenen JE. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. *Gastrointest Endosc* 2003; **57**: 291-294
82 **Simmons DT**, Petersen BT, Gostout CJ, Levy MJ, Topazian MD, Baron TH. Risk of pancreatitis following endoscopically placed large-bore plastic biliary stents with and without biliary sphincterotomy for management of postoperative bile leaks. *Surg Endosc* 2008; **22**: 1459-1463
83 **Smithline A**, Silverman W, Rogers D, Nisi R, Wiersema M, Jamidar P, Hawes R, Lehman G. Effect of prophylactic main pancreatic duct stenting on the incidence of biliary endoscopic sphincterotomy-induced pancreatitis in high-risk patients. *Gastrointest Endosc* 1993; **39**: 652-657
84 **Tsuchiya T**, Itoi T, Sofuni A, Itokawa F, Kurihara T, Ishii K, Tsuji S, Kawai T, Moriyasu F. Temporary pancreatic stent to prevent post endoscopic retrograde cholangiopancreatography pancreatitis: a preliminary, single-center, randomized controlled trial. *J Hepatobiliary Pancreat Surg* 2007; **14**: 302-307
85 **Arnold JC**, Benz C, Martin WR, Adamek HE, Riemann JF. Endoscopic papillary balloon dilation vs. sphincterotomy for removal of common bile duct stones: a prospective randomized pilot study. *Endoscopy* 2001; **33**: 563-567

86 **Disario JA**. Endoscopic balloon dilation for extraction of bile duct stones: the devil is in the details. *Gastrointest Endosc* 2003; **57**: 282-285

87 **Fujita N**, Maguchi H, Komatsu Y, Yasuda I, Hasebe O, Igarashi Y, Murakami A, Mukai H, Fujii T, Yamao K, Maeshiro K. Endoscopic sphincterotomy and endoscopic papillary balloon dilatation for bile duct stones: A prospective randomized controlled multicenter trial. *Gastrointest Endosc* 2003; **57**: 151-155

88 **Vlavianos P**, Chopra K, Mandalia S, Anderson M, Thompson J, Westaby D. Endoscopic balloon dilatation versus endoscopic sphincterotomy for the removal of bile duct stones: a prospective randomised trial. *Gut* 2003; **52**: 1165-1169

89 **Song SY**, Lee KS, Na KJ, Ahn BH. Tension pneumothorax after endoscopic retrograde pancreatocholangiogram. *J Korean Med Sci* 2009; **24**: 173-175

90 **García-Cano J**. Fatal pancreatitis after endoscopic balloon dilation for extraction of common bile duct stones in an 80-year-old woman. *Endoscopy* 2007; **39** Suppl 1: E132

91 **Mao Z**, Zhu Q, Wu W, Wang M, Li J, Lu A, Sun Y, Zheng M. Duodenal perforations after endoscopic retrograde cholangiopancreatography: experience and management. *J Laparoendosc Adv Surg Tech A* 2008; **18**: 691-695

92 **Margantinis G**, Sakorafas GH, Kostopoulos P, Kontou S, Tsiakos S, Arvanitidis D. Post-ERCP/endoscopic sphincterotomy duodenal perforation is not always a surgical emergency. *Dig Liver Dis* 2006; **38**: 434-436

93 **Park DH**, Kim MH, Lee SK, Lee SS, Choi JS, Song MH, Seo DW, Min YI. Endoscopic sphincterotomy vs. endoscopic papillary balloon dilation for choledocholithiasis in patients with liver cirrhosis and coagulopathy. *Gastrointest Endosc* 2004; **60**: 180-185

94 **Cotton PB**. ERCP is most dangerous for people who need it least. *Gastrointest Endosc* 2001; **54**: 535-536

95 **Christoforidis E**, Goulimaris I, Kanellos I, Tsalis K, Demetriades C, Betsis D. Post-ERCP pancreatitis and hyperamylasemia: patient-related and operative risk factors. *Endoscopy* 2002; **34**: 286-292

96 **Masci E**, Mariani A, Curioni S, Testoni PA. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. *Endoscopy* 2003; **35**: 830-834

97 **Tarnasky P**, Cunningham J, Cotton P, Hoffman B, Palesch Y, Freeman J, Curry N, Hawes R. Pancreatic sphincter hypertension increases the risk of post-ERCP pancreatitis. *Endoscopy* 1997; **29**: 252-257

98 **Deenadayalu VP**, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Temkit M, Lehman GA, Sherman S. Does obesity confer an increased risk and/or more severe course of post-ERCP pancreatitis?: a retrospective, multicenter study. *J Clin Gastroenterol* 2008; **42**: 1103-1109

99 **Lukens FJ**, Howell DA, Upender S, Sheth SG, Jafri SM. ERCP in the very elderly: outcomes among patients older than eighty. *Dig Dis Sci* 2010; **55**: 847-851

100 **Debenedet AT**, Raghunathan TE, Wing JJ, Wamsteker EJ, DiMagno MJ. Alcohol use and cigarette smoking as risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis. *Clin Gastroenterol Hepatol* 2009; **7**: 353-8e4

101 **Cooper ST**, Slivka A. Incidence, risk factors, and prevention of post-ERCP pancreatitis. *Gastroenterol Clin North Am* 2007; **36**: 259-276, vii-viii

102 **Reddy N**, Wilcox CM, Tamhane A, Eloubeidi MA, Varadarajulu S. Protocol-based medical management of post-ERCP pancreatitis. *J Gastroenterol Hepatol* 2008; **23**: 385-392

103 **Silverman WB**, Thompson RA. Management of asymptomatically/minimally symptomatic post-ERCP serum liver test elevations: first do no harm. *Dig Dis Sci* 2002; **47**: 1498-1501

104 **Jacobson BC**, Vander Vliet MB, Hughes MD, Maurer R, McManus K, Banks PA. A prospective, randomized trial of clear liquids versus low-fat solid diet as the initial meal in mild acute pancreatitis. *Clin Gastroenterol Hepatol* 2007; **5**: 946-951; quiz 886

105 **Dundee PE**, Chin-Lenn L, Syme DB, Thomas PR. Outcomes of ERCP: prospective series from a rural centre. *ANZ J Surg* 2007; **77**: 1013-1017

106 **Barthet M**, Lesavre N, Desjeux A, Gasmi M, Berthezene P, Berdah S, Viviand X, Grimaud JC. Complications of endoscopic sphincterotomy: results from a single tertiary referral center. *Endoscopy* 2002; **34**: 991-997

107 **Andriulli A**, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788

108 **Disario JA**, Freeman ML, Bjorkman DJ, Macmathuna P, Petersen BT, Jaffe PE, Morales TG, Hixson LJ, Sherman S, Lehman GA, Jamal MM, Al-Kawas FH, Khandelwal M, Moore JP, Derfus GA, Jamidar PA, Ramirez FC, Ryan ME, Woods KL, Carr-Locke DL, Alder SC. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. *Gastroenterology* 2004; **127**: 1291-1299

109 **Bergman JJ**, Rauws EA, Fockens P, van Berkel AM, Bossuyt PM, Tijssen JG, Tytgat GN, Huibregtse K. Randomised trial of endoscopic balloon dilation versus endoscopic sphincterotomy for removal of bileduct stones. *Lancet* 1997; **349**: 1124-1129

110 **Martinez-Torres H**, Rodriguez-Lomeli X, Davalos-Cobian C, Garcia-Correa J, Maldonado-Martinez JM, Medrano-Muñoz F, Fuentes-Orozco C, Gonzalez-Ojeda A. Oral allopurinol to prevent hyperamylasemia and acute pancreatitis after endoscopic retrograde cholangiopancreatography. *World J Gastroenterol* 2009; **15**: 1600-1606

111 **Romagnuolo J**, Hilsden R, Sandha GS, Cole M, Bass S, May G, Love J, Bain VG, McKaigney J, Fedorak RN. Allopurinol to prevent pancreatitis after endoscopic retrograde cholang iopancreatography: a randomized placebo-controlled trial. *Clin Gastroenterol Hepatol* 2008; **6**: 465-471; quiz 371

112 **Katsinelos P**, Kountouras J, Chatzis J, Christodoulou K, Paroutoglou G, Mimidis K, Beltsis A, Zavos C. High-dose allopurinol for prevention of post-ERCP pancreatitis: a prospective randomized double-blind controlled trial. *Gastrointest Endosc* 2005; **61**: 407-415

113 **Mosler P**, Sherman S, Marks J, Watkins JL, Geenen JE, Jamidar P, Fogel EL, Lazzell-Pannell L, Temkit M, Tarnasky P, Block KP, Frakes JT, Aziz AA, Malik P, Nickl N, Slivka A, Goff J, Lehman GA. Oral allopurinol does not prevent the frequency or the severity of post-ERCP pancreatitis. *Gastrointest Endosc* 2005; **62**: 245-250

114 **Budzyńska A**, Marek T, Nowak A, Kaczor R, Nowakowska-Dulawa E. A prospective, randomized, placebo-controlled trial of prednisone and allopurinol in the prevention of ERCP-induced pancreatitis. *Endoscopy* 2001; **33**: 766-772

115 **Lavy A**, Karban A, Suissa A, Yassin K, Hermesh I, Ben-Amotz A. Natural beta-carotene for the prevention of post-ERCP pancreatitis. *Pancreas* 2004; **29**: e45-e50

116 **Gorelick A**, Barnett J, Chey W, Anderson M, Elta G. Botulinum toxin injection after biliary sphincterotomy. *Endoscopy* 2004; **36**: 170-173

117 **Räty S**, Sand J, Pulkkinen M, Matikainen M, Nordback I. Post-ERCP pancreatitis: reduction by routine antibiotics. *J Gastrointest Surg* 2001; **5**: 339-345; discussion 345

118 **Kwanngern K**, Tiyapattanaputi P, Wanitpukdeedecha M, Navicharern P. Can a single dose corticosteroid reduce the incidence of post-ERCP pancreatitis? A randomized, prospective control study. *J Med Assoc Thai* 2005; **88** Suppl 4: S42-S45

119 **Manolakopoulos S**, Avgerinos A, Vlachogiannakos J, Armonis A, Viazis N, Papadimitriou N, Mathou N, Stefanidis G, Rekoumis G, Vienna E, Tzourmakliotis D, Raptis SA. Octreotide versus hydrocortisone versus placebo in the prevention of post-ERCP pancreatitis: a multicenter randomized controlled trial. *Gastrointest Endosc* 2002; **55**: 470-475

120 **Sherman S**, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Earle D, Temkit M, Lehman GA. Does prophylactic administration of corticosteroid reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study. *Gastrointest Endosc* 2003; **58**: 23-29

121 **Rabenstein T**, Fischer B, Wiessner V, Schmidt H, Radespiel-Tröger M, Hochberger J, Mühldorfer S, Nusko G, Messmann H, Schölmerich J, Schulz HJ, Schönekäs H, Hahn EG, Schneider HT. Low-molecular-weight heparin does not prevent acute post-ERCP pancreatitis. *Gastrointest Endosc* 2004; **59**: 606-613

122 **Milewski J**, Rydzewska G, Degowska M, Kierzkiewicz M, Rydzewski A. N-acetylcysteine does not prevent post-endoscopic retrograde cholangiopancreatography hyperamylasemia and acute pancreatitis. *World J Gastroenterol* 2006; **12**: 3751-3755

123 **Katsinelos P**, Kountouras J, Paroutoglou G, Beltsis A, Mimidis K, Zavos C. Intravenous N-acetylcysteine does not prevent post-ERCP pancreatitis. *Gastrointest Endosc* 2005; **62**: 105-111

124 **Prat F**, Amaris J, Ducot B, Bocquentin M, Fritsch J, Choury AD, Pelletier G, Buffet C. Nifedipine for prevention of post-ERCP pancreatitis: a prospective, double-blind randomized study. *Gastrointest Endosc* 2002; **56**: 202-208

125 **Sand J**, Nordback I. Prospective randomized trial of the effect of nifedipine on pancreatic irritation after endoscopic retrograde cholangiopancreatography. *Digestion* 1993; **54**: 105-111

126 **Hao JY**, Wu DF, Wang YZ, Gao YX, Lang HP, Zhou WZ. Prophylactic effect of glyceryl trinitrate on post-endoscopic retrograde cholangiopancreatography pancreatitis: a randomized placebo-controlled trial. *World J Gastroenterol* 2009; **15**: 366-368

127 **Beauchant M**, Ingrand P, Favriel JM, Dupuychaffray JP, Capony P, Moindrot H, Barthet M, Escourrou J, Plane C, Barrioz T, Lacoste L, Ingrand I. Intravenous nitroglycerin for prevention of pancreatitis after therapeutic endoscopic retrograde cholangiography: a randomized, double-blind, placebo-controlled multicenter trial. *Endoscopy* 2008; **40**: 631-636

128 **Kaffes AJ**, Bourke MJ, Ding S, Alrubaie A, Kwan V, Williams SJ. A prospective, randomized, placebo-controlled trial of transdermal glyceryl trinitrate in ERCP: effects on technical success and post-ERCP pancreatitis. *Gastrointest Endosc* 2006; **64**: 351-357

129 **Moretó M**, Zaballa M, Casado I, Merino O, Rueda M, Ramírez K, Urcelay R, Baranda A. Transdermal glyceryl trinitrate for prevention of post-ERCP pancreatitis: A randomized double-blind trial. *Gastrointest Endosc* 2003; **57**: 1-7

130 **Sudhindran S**, Bromwich E, Edwards PR. Prospective randomized double-blind placebo-controlled trial of glyceryl trinitrate in endoscopic retrograde cholangiopancreatography-induced pancreatitis. *Br J Surg* 2001; **88**: 1178-1182

131 **Khoshbaten M**, Khorram H, Madad L, Ehsani Ardakani MJ, Farzin H, Zali MR. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. *J Gastroenterol Hepatol* 2008; **23**: e11-e16

132 **Cheon YK**, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, Schmidt S, Lazzell-Pannell L, Lehman GA. Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. *Gastrointest Endosc* 2007; **66**: 1126-1132

133 **Sotoudehmanesh R**, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. *Am J Gastroenterol* 2007; **102**: 978-983

134 **Kisli E**, Baser M, Aydin M, Guler O. The role of octreotide versus placebo in the prevention of post-ERCP pancreatitis. *Hepatogastroenterology* 2007; **54**: 250-253

135 **Li ZS**, Pan X, Zhang WJ, Gong B, Zhi FC, Guo XG, Li PM, Fan ZN, Sun WS, Shen YZ, Ma SR, Xie WF, Chen MH, Li YQ. Effect of octreotide administration in the prophylaxis of post-ERCP pancreatitis and hyperamylasemia: A multicenter, placebo-controlled, randomized clinical trial. *Am J Gastroenterol* 2007; **102**: 46-51

136 **Thomopoulos KC**, Pagoni NA, Vagenas KA, Margaritis VG, Theocharis GI, Nikolopoulou VN. Twenty-four hour prophylaxis with increased dosage of octreotide reduces the incidence of post-ERCP pancreatitis. *Gastrointest Endosc* 2006; **64**: 726-731

137 **Testoni PA**, Bagnolo F, Andriulli A, Bernasconi G, Crotta S, Lella F, Lomazzi A, Minoli G, Natale C, Prada A, Toti GL, Zambelli A. Octreotide 24-h prophylaxis in patients at high risk for post-ERCP pancreatitis: results of a multicenter, randomized, controlled trial. *Aliment Pharmacol Ther* 2001; **15**: 965-972

138 **Hardt PD**, Kress O, Fadgyas T, Doppl W, Schnell-Kretschmer H, Wüsten O, Klör HU. Octreotide in the prevention of pancreatic damage induced by endoscopic sphincterotomy. *Eur J Med Res* 2000; **5**: 165-170

139 **Duvnjak M**, Supanc V, Simicevi VN, Hrabar D, Troskot B, Smirci-Duvnjak L, Bekavac-Beslin M. Use of octreotide-acetate in preventing pancreatitis-like changes following therapeutic endoscopic retrograde cholangiopancreatography. *Acta Med Croatica* 1999; **53**: 115-118

140 **Arvanitidis D**, Hatzipanayiotis J, Koutsounopoulos G, Frangou E. The effect of octreotide on the prevention of acute pancreatitis and hyperamylasemia after diagnostic and therapeutic ERCP. *Hepatogastroenterology* 1998; **45**: 248-252

141 **Arcidiacono R**, Gambitta P, Rossi A, Grosso C, Bini M, Zanasi G. The use of a long-acting somatostatin analogue (octreotide) for prophylaxis of acute pancreatitis after endoscopic sphincterotomy. *Endoscopy* 1994; **26**: 715-718

142 **Baldazzi G**, Conti C, Spotti EG, Arisi GP, Scevola M, Gobetti F, Agliardi CM, Galasso P, Bonomi E, Bianchi F. [Prevention of post-ERCP acute pancreatitis with octreotide]. *G Chir* 1994; **15**: 359-362

143 **Testoni PA**, Lella F, Bagnolo F, Buizza M, Colombo E. Controlled trial of different dosages of octreotide in the prevention of hyperamylasemia induced by endoscopic papillosphincterotomy. *Ital J Gastroenterol* 1994; **26**: 431-436

144 **Ueki T**, Otani K, Kawamoto K, Shimizu A, Fujimura N, Sakaguchi S, Matsui T. Comparison between ulinastatin and gabexate mesylate for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a prospective, randomized trial. *J Gastroenterol* 2007; **42**: 161-167

145 **Manes G**, Ardizzone S, Lombardi G, Uomo G, Pieramico O, Porro GB. Efficacy of postprocedure administration of gabexate mesylate in the prevention of post-ERCP pancreatitis: a randomized, controlled, multicenter study. *Gastrointest Endosc* 2007; **65**: 982-987

146 **Xiong GS**, Wu SM, Zhang XW, Ge ZZ. Clinical trial of gabexate in the prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Braz J Med Biol Res* 2006; **39**: 85-90

147 **Fujishiro H**, Adachi K, Imaoka T, Hashimoto T, Kohge N, Moriyama N, Suetsugu H, Kawashima K, Komazawa Y, Ishimura N, Ishihara S, Amano Y, Kinoshita Y. Ulinastatin

shows preventive effect on post-endoscopic retrograde cholangiopancreatography pancreatitis in a multicenter prospective randomized study. *J Gastroenterol Hepatol* 2006; **21**: 1065-1069

148 **Andriulli A**, Clemente R, Solmi L, Terruzzi V, Suriani R, Sigillito A, Leandro G, Leo P, De Maio G, Perri F. Gabexate or somatostatin administration before ERCP in patients at high risk for post-ERCP pancreatitis: a multicenter, placebo-controlled, randomized clinical trial. *Gastrointest Endosc* 2002; **56**: 488-495

149 **Cavallini G**, Tittobello A, Frulloni L, Masci E, Mariana A, Di Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancrea tography. Gabexate in digestive endoscopy--Italian Group. *N Engl J Med* 1996; **335**: 919-923

150 **Choi CW**, Kang DH, Kim GH, Eum JS, Lee SM, Song GA, Kim DU, Kim ID, Cho M. Nafamostat mesylate in the prevention of post-ERCP pancreatitis and risk factors for post-ERCP pancreatitis. *Gastrointest Endosc* 2009; **69**: e11-e18

151 **Yoo JW**, Ryu JK, Lee SH, Woo SM, Park JK, Yoon WJ, Lee JK, Lee KH, Hwang JH, Kim YT, Yoon YB. Preventive effects of ulinastatin on post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients: a prospective, randomized, placebo-controlled trial. *Pancreas* 2008; **37**: 366-370

152 **Tsujino T**, Komatsu Y, Isayama H, Hirano K, Sasahira N, Yamamoto N, Toda N, Ito Y, Nakai Y, Tada M, Matsumura M, Yoshida H, Kawabe T, Shiratori Y, Omata M. Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancre atography: a randomized, controlled trial. *Clin Gastroenterol Hepatol* 2005; **3**: 376-383

153 **Kapetanos D**, Kokozidis G, Christodoulou D, Mistakidis K, Sigounas D, Dimakopoulos K, Kitis G, Tsianos EV. A randomized controlled trial of pentoxifylline for the prevention of post-ERCP pancreatitis. *Gastrointest Endosc* 2007; **66**: 513-518

154 **Sherman S**, Alazmi WM, Lehman GA, Geenen JE, Chuttani R, Kozarek RA, Welch WD, Souza S, Pribble J. Evaluation of recombinant platelet-activating factor acetylhydrolase for reducing the incidence and severity of post-ERCP acute pancreatitis. *Gastrointest Endosc* 2009; **69**: 462-672

155 **van Westerloo DJ**, Rauws EA, Hommes D, de Vos AF, van der Poll T, Powers BL, Fockens P, Dijkgraaf MG, Bruno MJ. Pre-ERCP infusion of semapimod, a mitogen-activated protein kinases inhibitor, lowers post-ERCP hyperamylasemia but not pancreatitis incidence. *Gastrointest Endosc* 2008; **68**: 246-254

156 **Lee KT**, Lee DH, Yoo BM. The prophylactic effect of somatostatin on post-therapeutic endoscopic retrograde cholangiopancreatography pancreatitis: a randomized, multicenter controlled trial. *Pancreas* 2008; **37**: 445-448

157 **Arvanitidis D**, Anagnostopoulos GK, Giannopoulos D, Pantes A, Agaritsi R, Margantinis G, Tsiakos S, Sakorafas G, Kostopoulos P. Can somatostatin prevent post-ERCP pancreatitis? Results of a randomized controlled trial. *J Gastroenterol Hepatol* 2004; **19**: 278-282

158 **Poon RT**, Yeung C, Liu CL, Lam CM, Yuen WK, Lo CM, Tang A, Fan ST. Intravenous bolus somatostatin after diagnostic cholangiopancreatography reduces the incidence of pancreatitis associated with therapeutic endoscopic retrograde cholangiopancreatography procedures: a randomised controlled trial. *Gut* 2003; **52**: 1768-1773

159 **Poon RT**, Yeung C, Lo CM, Yuen WK, Liu CL, Fan ST. Prophylactic effect of somatostatin on post-ERCP pancreatitis: a randomized controlled trial. *Gastrointest Endosc* 1999; **49**: 593-598

160 **Bordas JM**, Toledo-Pimentel V, Llach J, Elena M, Mondelo F, Ginès A, Terés J. Effects of bolus somatostatin in preventing pancreatitis after endoscopic pancreatography: results of a randomized study. *Gastrointest Endosc* 1998; **47**: 230-234

161 **Schwartz JJ**, Lew RJ, Ahmad NA, Shah JN, Ginsberg GG, Kochman ML, Brensinger CM, Long WB. The effect of lidocaine sprayed on the major duodenal papilla on the frequency of post-ERCP pancreatitis. *Gastrointest Endosc* 2004; **59**: 179-184

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