

Advances in pancreatobiliary endoscopy

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Purpose of review

The role of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography (ERCP) continues to mature. We will review the progress of pancreatobiliary endoscopy in the evaluation and treatment of benign and malignant pancreatobiliary diseases.

Recent findings

First, minimizing contrast injection of the pancreas, wire-guided cannulation and prophylactic pancreatic stenting have been re-emphasized in recent studies as the most important endoscopic interventions that can lower the risk of post-ERCP pancreatitis. The role of preoperative ERCP in patients with jaundice secondary to pancreatic cancer was raised in a randomized trial; the widespread use of preoperative biliary drainage is now up for debate. The use of ERCP, intraoperative cholangiography, endoscopic ultrasound and magnetic resonance cholangiopancreatography in the evaluation of suspected common bile duct stones is discussed. We conclude by evaluating studies of fully covered, self-expandable metallic stents, with an emphasis on their potential use in benign biliary disease.

Summary

Given the risk of complications and development of alternative imaging modalities, diagnostic ERCP is rarely indicated. However, therapeutic ERCP has been bolstered by advances such as fully covered metallic stents and cholangioscopy.

Keywords

cannulation, endoscopic retrograde cholangiopancreatography, pancreatic cancer, pancreatic stent, self-expandable metallic stent

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Introduction

This review highlights recent advances in pancreatobiliary endoscopy from January 2009 through February 2010.

Post-endoscopic retrograde cholangiopancreatography pancreatitis

Several recent studies explore various techniques and clinical predictors of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP).

Wire-guided cannulation

Numerous studies [1–3] have associated pancreatic duct injection with an increased risk of PEP. However, the clinical implication of accessing the pancreatic duct using a guidewire without contrast injection during attempted bile duct cannulation is unclear [4,5]. Lee *et al.* [6**] in Korea attempted to clarify this issue by performing a randomized trial comparing wire-guided cannulation (WGC) with a conventional cannulation technique. In the WGC group, the endoscopist introduced the tip of a

papillotome 2–3 mm into the papillary orifice, then probed with a hydrophilic guidewire until bile duct cannulation was achieved. In the conventional group, the papillotome was introduced into the papillary orifice and contrast injected to delineate the anatomy. A needle knife fistulotomy was performed after 10 min of effort or following five injections or wire cannulations of the pancreatic duct in either group. All ERCPs were performed by a single endoscopist with more than 2500 cases experience and an annual volume of more than 350 procedures. Prophylactic pancreatic duct stenting was not used in this study.

Successful biliary cannulation was similar in the WGC (99%) and conventional (97%) groups. Although rates of unintentional pancreatic duct cannulation were comparable, the frequency of PEP was significantly lower in the WGC group (2 compared with 11.3%, $P=0.001$). Other procedure-related complications, including bleeding and perforation, were similar. After controlling for potential confounding variables in a multipredictor model, WGC corresponded with a significantly lower

odds of PEP [(odds ratio 0.1, 95% confidence interval (CI) 0.02–0.49].

This was a well designed study addressing a common concern (i.e., methods to reduce PEP) among pancreatobiliary endoscopists, and the results corroborated those of two recent meta-analyses [7^{••},8^{••}]. Cheung *et al.* [8^{••}] noted an even greater reduction in PEP rates among patients with guidewire cannulation of the pancreatic duct (1.1%) compared with contrast injection of the pancreatic duct [9.5%, relative risk (RR) 0.19]. WGC appears to be the preferred cannulation technique for the expert endoscopist. However, it is unclear whether these results can be extrapolated to the community-based practitioner who performs ERCP less frequently. Furthermore, the impact of prophylactic pancreatic duct stenting on these results, particularly among patients who met criteria for difficult cannulation (which represented 19% in the WGC group and 25% in the conventional group), is unknown. Nevertheless, WGC is the preferred approach for selective bile duct cannulation.

Difficult bile duct cannulation

When deep cannulation of the biliary tree is unsuccessful, many endoscopists perform a needle knife sphincterotomy (NKS) to gain access. It is well established that the risk of PEP increases with multiple cannulation attempts and injection of the pancreatic duct [1–3]. Bailey *et al.* [9[•]] hypothesized that the incremental procedure-related risks associated with NKS were related to these factors, and not the NKS itself. After combining data from two previously published clinical trials, 94 of 732 (12.8%) patients required NKS to gain biliary access. On multivariate regression analysis, independent predictors of PEP included female sex, suspected sphincter of Oddi dysfunction, partial pancreatic drainage, 10–14 and at least 15 attempts at papilla cannulation. NKS was not an independent predictor after controlling for these variables. No major bleeding or perforations were reported in the NKS group.

The early use of NKS to reduce the rate of PEP has been suggested in earlier studies, but the widespread safety of NKS by less-experienced endoscopists remains unclear [10]. When technically feasible, a pancreatic duct stent should be placed in all cases of NKS to minimize the risk of PEP [11,12]. In the hands of an experienced endoscopist, the frequency of PEP following NKS or pull-type pancreatic sphincterotomy is similar, as long as a prophylactic pancreatic duct stent is placed [13[•]]. It is unclear whether these data can be extrapolated to physicians who perform ERCP less frequently.

Alternatives to NKS include use of a pancreatic duct guidewire or stent to facilitate bile duct cannulation [14[•],15]. Herreros de Tejada *et al.* [14[•]] conducted a

randomized trial comparing the use of a pancreatic guidewire to facilitate bile duct cannulation (also known as double-guidewire technique) with persistence using standard techniques. The authors reported no significant difference in cannulation rates and a trend to higher rates of PEP with the use of a pancreatic guidewire. By necessitating a second guidewire, the double-guidewire technique may be more costly with marginal benefit. Further studies comparing these alternatives to NKS are warranted.

Risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis

Cotton *et al.* [16^{••}] adds to a body of literature evaluating risk factors for post-ERCP complications with the largest, single-center cohort to date. In a retrospective review of 11 497 ERCPs performed over a 12-year period, the overall complication rate was 4.0%, the majority arising from PEP (2.6%). A summary of predictors identified on multivariate regression analysis of any complication, PEP, bleeding, and severe or fatal complications are summarized in Table 1. There were too few cases of perforation [16^{••}] to conduct a regression analysis of this particular outcome. Common themes across these complications are the particularly high risk of pancreatography, manometry (i.e., performing ERCP to evaluate for suspected sphincter of Oddi dysfunction) and other complex indications according to the American Society for Gastrointestinal Endoscopy guidelines [17]. Although the size of this cohort is impressive, the retrospective analysis raises the issue of detection bias and limited evaluation of long-term (>1 week postprocedure) complications. In addition, specific techniques and recent developments in ERCP such as NKS, WGC and balloon dilation of the biliary orifice were not included in this analysis. Nevertheless, these results reiterate the old mantra, ‘Don’t mess with the pancreas’. Perhaps more appropriately, endoscopists who plan for or inadvertently cannulate the pancreatic duct, or those who perform ERCP in patients at high risk for PEP, should be comfortable with deploying a prophylactic pancreatic duct stent.

Prophylactic pancreatic duct stenting

Stenting of the pancreatic duct remains the only proven endoscopic intervention that lowers the incidence of PEP. However, there are limited data suggesting the optimal stent diameter and length. In addition to preventing PEP, ‘the ideal’ prophylactic pancreatic duct stent would spontaneously pass in every case. An earlier retrospective study demonstrated significantly higher rates of dislodgement using 3 Fr compared with 5 Fr stents, and a trend to lower rates of PEP [18]. Chahal *et al.* [19^{••}] conducted a prospective, randomized trial to address this issue. Patients considered high risk for developing post-ERCP pancreatitis were randomized

Table 1 Significant predictors of and protective factors for post-ERCP complications^a

Overall complications	Post-ERCP pancreatitis (any severity)	Bleeding	Severe or fatal complications
Predictors			
Indication: suspected SOD Biliary sphincterotomy	Indication: suspected SOD Major papilla pancreatogram Minor papilla pancreatogram	Biliary sphincterotomy	Poor health status (American Society of Anesthesiologists class III) Obesity Suspected or known bile duct stones Pancreatic manometry Complex (grade 3) procedures ^b
Protective factors			
Pancreatic duct stent placement Prior acute pancreatitis	Indication: biliary stent exchange Indication: suspected SOD with pancreatic duct stent placement ^c		

ERCP, endoscopic retrograde cholangiopancreatography; SOD, sphincter of Oddi dysfunction.

^a These factors were identified as significant predictors following multivariate regression analysis. Adapted from Cotton *et al.* [16^{••}].

^b On the basis of guidelines from the American Society for Gastrointestinal Endoscopy [17].

^c Compared with patients with an indication of SOD without pancreatic duct stent placement.

to a short (2 or 3 cm), 5 Fr stent or a longer (8 or 10 cm), 3 Fr stent. Importantly, 'successful' pancreatic duct stent placement required deployment of the longer 3 Fr stents beyond the genu. In patients in whom this was not technically feasible, the patient was crossed over to the 5 Fr group. The study was designed to compare spontaneous dislodgement rates but did not have an adequate sample size to compare the frequency of PEP between groups.

Among 249 patients enrolled, 133 were randomized to the 3 Fr group; of these, 11 patients were crossed over to the 5 Fr group due to tortuosity of the pancreatic duct precluding deeper wire access. Alternatively stated, the technical failure rate was 0% in the 5 Fr group and 9% in the 3 Fr group ($P=0.0003$). Spontaneous dislodgement rates were significantly higher in the 5 Fr group (97 versus 89% in the 3 Fr group by intention-to-treat analysis, $P=0.001$). Of note, 50% of 5 Fr stents had migrated within 24 h of placement. Nevertheless, the rates of PEP were not significantly different, with a trend to lower rates in the 5 Fr group (9% in the 5 Fr versus 14% in the 3 Fr group, $P=0.3$). Early stent migration (defined as <24 h postplacement) was not identified as a risk factor for PEP.

To date, this is the only prospective study comparing prophylactic pancreatic stent characteristics. However, as this study was not powered to compare rates of PEP, it is difficult to draw conclusions from the authors' secondary observations. The trend to higher rates of PEP in the 3 Fr group likely stems from the high failure rate and prolonged effort to successfully deploy the stent. In addition, the observation that early (within 24 h of placement) stent migration was not a predictor of PEP may be as a result of type II statistical error.

The 'ideal' pancreatic duct stent results in the lowest rate of PEP, while maintaining a high rate of spontaneous

migration. The Chahal study raises more questions. Future investigations on this topic will need to be designed to address the most important question: which stent results in the lowest rate of pancreatitis? Stent diameter and length are likely to be important, but other characteristics such as stents which are placed with minimal contrast injection, at the earliest stage in the ERCP and requiring the least amount of additional equipment (e.g., guidewires and pushing catheters) will undoubtedly be the most cost-effective. Finally, the clinical significance of stent-induced injury to the pancreatic duct is largely unknown. A recent case series of eight patients who developed severe complications as a result of stent-induced pancreatic duct strictures highlights the potential of pancreatic stenting doing 'more harm than good' [20].

Pharmacologic prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis

Meanwhile, the search for a pharmacologic agent to prevent PEP continues, with another negative study evaluating allopurinol published by Romagnuolo *et al.* [21^{*}]. In this randomized trial of 586 patients undergoing ERCP at two medical centers, only 66 (11%) were considered at high baseline risk for PEP. The frequency of PEP was similar between the allopurinol (5.5%) and placebo (4.1%) groups. Studies evaluating pharmacologic or other strategies to prevent PEP should focus on patients at high risk, in whom the incremental benefit is expected to be highest.

Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis

In patients with acute biliary pancreatitis, early (typically defined as <72 h of symptom onset or presentation) ERCP is clearly beneficial for cases of concurrent cholangitis. However, there is mixed data on the benefit of

early ERCP in patients with acute pancreatitis and concurrent cholestasis. Van Santvoort *et al.* [22**] performed a prospective, cohort study of patients with predicted severe acute pancreatitis (based on standard instruments including APACHE-II scores), who were being enrolled in a randomized clinical trial studying the role of probiotics. Patients were categorized as cholestatic and not cholestatic; those with suspected cholangitis were excluded. Early ERCP was performed at the discretion of the treating physician. Among patients with cholestasis ($n=78$), early ERCP was associated with significantly fewer overall complications (25 versus 54%, $P=0.02$), primarily due to lower rates of pancreatic necrosis, infected pancreatic necrosis, bacteremia, and pneumonia. There was no benefit of early ERCP among patients without cholestasis ($n=75$). Of note, common bile duct stones or sludge were highly prevalent in the cholestatic (89%) and noncholestatic (75%) groups.

Despite numerous scoring systems including APACHE-II, Ranson's criteria and others, it can often be difficult to predict which patients with acute pancreatitis will deteriorate during their hospital course. Furthermore, distinguishing cholangitis from severe acute pancreatitis with cholestasis is challenging. Although this is a well designed study, there is the potential for undetected confounding variables as early ERCP was determined by the treating physician. Future randomized clinical trials should further evaluate the benefit of early ERCP in acute biliary pancreatitis of variable severity with concurrent cholestasis in the absence of overt cholangitis.

Role of preoperative biliary drainage in patients with resectable pancreatic cancer

Among patients with obstructive jaundice, preoperative biliary drainage via ERCP has virtually become the standard for most patients despite conflicting evidence supporting its impact on postoperative outcomes [23,24]. A clinical trial from the Netherlands randomized patients with obstructive jaundice (limited to a bilirubin <14.6 mg/dl) and resectable pancreatic cancer to preoperative endoscopic drainage via stent placement or surgery alone within 1 week of presentation [25**]. Among patients who underwent preoperative drainage, surgery was delayed 4–6 weeks. The primary outcome was the frequency of serious complications within 120 days of randomization, including complications related to preoperative drainage or the surgical intervention.

Over a 5-year period, 202 patients were enrolled. Successful preoperative biliary drainage was only achieved in 75% of cases at the first attempt; this increased to 94% following second attempt ERCP or percutaneous drainage. Complications related to preoperative biliary drainage occurred in 46% of patients in the drainage group

compared with 2% in the surgery-alone group. Preoperative biliary drainage was performed in five of 94 patients assigned to the surgical group for logistical reasons (three patients), cholangitis (one), and severe hyperglycemia (one). Among patients in the surgery-alone group, the RR of developing a surgery-related complication was not significantly lower (RR 0.79, 95% CI 0.57–1.11). However, the rate of any serious complication (related to surgery and preoperative biliary drainage) was significantly fewer among surgery-alone patients (RR 0.54, 95% CI 0.41–0.71). This statistical difference is primarily explained by two factors: first, the frequency of ERCP-related complications in the preoperative drainage group was higher than expected, with 30% of patients requiring a stent exchange preoperatively. Second, 61 of 202 patients (30%) in the entire cohort only underwent a palliative bypass surgery despite being staged resectable at the time of enrollment; in the subgroup of patients who underwent palliative bypass, complication rates were significantly higher in the drainage arm (55%) compared with surgery alone (18%, $P=0.003$).

In this clinical trial, preoperative biliary drainage did not impact on the overall rate of postoperative complications as suggested by earlier studies [26–28]. In addition, the overall rate of palliative surgical bypass (30%) suggests inadequate preoperative staging. Preoperative drainage is more likely to benefit those patients who are deeply jaundiced (bilirubin >15 mg/dl) at the time of presentation – these patients were excluded from the van der Gaag study. Other factors including baseline nutritional status, ability to schedule and perform surgical resection within 1 week of diagnosis, and use of neoadjuvant chemotherapy are likely to impact on the need for preoperative drainage. The National Cancer Institute is encouraging further study of neoadjuvant chemotherapy based on limited data from academic centers [29]. Finally, the use of short, fully covered metallic bile duct stents may offer superior short-term drainage while reducing the need for repeat preoperative interventions and palliative biliary bypass.

Common bile duct stones

In general, endoscopic removal of common bile duct stones via ERCP with biliary sphincterotomy is preferred to surgical and percutaneous approaches due to high success rates and lower morbidity. In cases of large (>1.5 cm) common bile duct stones that were difficult to extract after sphincterotomy alone, Ersoz *et al.* [30] initially described the combination of large (10–20 mm) balloon dilation of the papillary orifice with complete biliary sphincterotomy. Although isolated balloon dilation of the biliary orifice with 8–10 mm balloons has a lower risk of hemorrhage and perforation compared with biliary sphincterotomy, the frequency and severity

of PEP are significantly greater [31,32]. With this in mind, Kim *et al.* [33^{*}] performed a randomized clinical trial comparing complete biliary sphincterotomy with limited sphincterotomy plus large balloon (15–18 mm) dilation for the extraction of large common bile duct stones. Among 55 patients who were enrolled, complete stone removal during the first session (85 versus 86%) and need for mechanical lithotripsy (33 versus 32%) were nearly identical between groups. Although no complications were reported in this study of limited sample size, the use of balloon dilation after partial sphincterotomy appears to be safer than balloon dilation alone. A much larger study would be needed to evaluate differences in procedure-related complications between these techniques; with relatively low rates of perforation and hemorrhage reported following complete biliary sphincterotomy, the advantage of this approach is questionable. Balloon dilation of the papillary orifice following partial or complete biliary sphincterotomy appears to be a safe and effective technique to facilitate extraction of large common bile duct stones. However, this technique is unlikely to become the standard approach for routine choledocholithiasis as a result of the additional cost of a balloon dilation catheter.

The role of endoscopic retrograde cholangiopancreatography for patients with an intermediate probability of common bile duct stones

A randomized clinical trial in the surgical literature compared preoperative ERCP with intraoperative common bile duct exploration for patients with symptomatic cholelithiasis and an intermediate suspicion for common bile duct stones [34^{*}]. The authors hypothesized that a single-stage intervention, combining laparoscopic cholecystectomy with common bile duct exploration, would reduce the length of hospitalization and overall costs by reducing the required number of procedures. Patients were randomized to preoperative ERCP versus laparoscopic common bile duct exploration; if stones were identified in the latter group, the surgeon performed a balloon dilation of the papillary orifice prior to flushing the stones into the duodenum. Among 112 patients enrolled, more common bile duct stones were identified by ERCP (56%) compared with laparoscopy (30%, $P = 0.007$); successful stone clearance was higher in the ERCP group (98 versus 88%, $P = 0.28$), although this did not reach statistical significance. Length of hospitalization was shorter in the laparoscopy group (5.3 versus 6.6 days), but total patient charges were similar (US\$ 24 399 versus US\$ 26 656). However, this may reflect the surgeon's inability to perform cholecystectomy on the same day as the ERCP due to a scheduling conflict. As no complications were reported, the authors concluded that common bile duct exploration at the time of laparoscopic cholecystectomy is feasible and may reduce the need for ERCP.

Among others, the risk of bile duct injury associated with laparoscopic exploration is likely operator dependent; furthermore, the complication rate of balloon dilation without a previous biliary sphincterotomy (at least partial) or a prophylactic pancreatic stent, is higher than biliary sphincterotomy alone [35]. For patients with low or intermediate suspicion for common bile duct stones, a less invasive modality such as magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) is preferred to either intraoperative cholangiography or ERCP for stone detection [36^{*},37]. EUS is likely comparable to ERCP for identifying common bile duct stones; in fact, findings from Karakan *et al.* [36^{*}] suggest EUS may be superior to ERCP in identifying small (<4 mm) stones.

Cholangioscopy

Direct visualization of the extrahepatic biliary tree (also known as cholangioscopy) continues to develop with the advent of a single operator, fiberoptic cholangioscope that fits through the working channel of a therapeutic duodenoscope [38,39]. An excellent review of cholangioscopy by Ross and Kozarek [40^{*}] summarizes the technique and indications for cholangioscopy, including indeterminate biliary strictures and refractory bile duct stones. Bhat and Kochman [41] described another potential use for cholangioscopy, using direct visualization to pass guidewires into the left and right hepatic systems across a difficult hilar stricture. Large, comparative trials evaluating fiberoptic cholangioscopy or direct peroral cholangioscopy with standard radiographic visualization using ERC are lacking. Kawakami *et al.* [42] reported the incremental yield of peroral cholangioscopy using an ultraslim, 3.1 mm endoscope (CHF-B260, Olympus) through the working channel of a therapeutic duodenoscope (TJF-240 or TJF-260V; Olympus Medical Systems, Tokyo, Japan) with ERC and fluoroscopically guided biopsies in the evaluation of intraepithelial tumor spread of localized bile duct tumors. Cholangioscopy improved the sensitivity from 80 to 100%, but was limited in some cases by the inability to traverse the stricture using the cholangioscope. The image quality using an ultraslim video endoscope appears to be superior to single operator, fiberoptic cholangioscopy (Spyglass, Boston Scientific, Natick, MA, USA). However, the diagnostic and therapeutic potential (e.g., site-directed biopsies and use of electrohydraulic or laser lithotripsy) of these devices should be compared.

Expanding use of self-expandable metallic stents

Because of their greater diameter compared with standard polyethylene stents, self-expandable metallic stents (SEMS) permit longer patency and are more

cost-effective for the treatment of unresectable malignant biliary obstruction among patients whose life expectancy is at least 3–6 months. Limited endoscopic removability and per-unit cost have precluded the use of SEMS for the treatment of benign biliary strictures with the exception of outlying cases. More recently, fully covered SEMS (fcSEMS) have been designed to prevent tumor ingrowth and epithelial hyperplasia. These devices offer superior patency compared with plastic stents and the potential for endoscopic removability.

In the largest case series using fcSEMS for benign biliary strictures secondary to a number of etiologies (e.g., chronic pancreatitis, postorthotopic liver transplant, postoperative, and gallstone-induced), 41 patients underwent successful placement and subsequent endoscopic removal of a fcSEMS (GORE Viabil, Conmed, Utica, NY, USA) [43**]. Of these, 83% (65% in cerebral palsy) demonstrated stricture resolution after a median follow-up of 3.8 months (range 1.2–7.7 months). As expected, all fcSEMS were successfully removed; one stent unraveled during its extraction, but was otherwise accomplished without adverse effects. A second series of patients ($n = 16$) with postliver transplant bile leaks underwent first-line treatment with placement of a fcSEMS (Viabil) [44]. Endoscopic removal was accomplished in all 13 patients in whom it was attempted. However, stent-related complications included a secondary stricture (one patient), internal migration (one), and postprocedure pain that required a short hospitalization (one). Balloon dilation of the biliary orifice was required at the time of endoscopic removal in five cases.

fcSEMS offer the potential for at least comparable if not superior efficacy compared with standard plastic stent therapy for the treatment of benign biliary strictures. Ironically, these newer and more expensive devices may be cost-effective compared with standard stent therapy by reducing the number of ERCPs required to successfully treat a stricture. SEMS-specific complications, including stent-induced strictures, cholecystitis and migration were highlighted in a retrospective analysis of 396 patients who underwent partially covered SEMS, 149 of whom were for benign indications [45]. These risks have greater significance among patients with benign diseases and an unlimited life expectancy. Therefore, a randomized clinical trial comparing fully covered SEMS with conventional plastic stent therapy is warranted.

Conclusion

The role of purely diagnostic ERCP is limited, with further advances in alternative imaging modalities such as MRCP and EUS. Minimizing injections of the pancreatic duct, WGC and prophylactic pancreatic duct

stents remain the most important technical maneuvers to minimize the risk of PEP. Preliminary studies using fcSEMS for benign biliary disease appear promising, though randomized clinical trials comparing these to current approaches are needed. Advances in endoscope and device technology are likely to further enhance the utility of therapeutic ERCP in the years to come.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 521–522).

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