ADVANCES IN ENDOSCOPY

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Medications and Methods for the Prevention of Post-ERCP Pancreatitis

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G&H How commonly does pancreatitis occur as a complication of endoscopic retrograde cholangiopancreatography?

AW The overall incidence of post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis has been reported to be approximately 3% to 10% in systematic reviews. However, in patients who are at elevated risk for post-ERCP pancreatitis, the incidence can be 15% or greater. I tell my patients who are at average risk that the incidence of post-ERCP pancreatitis typically ranges from 2% to 7%. Of note, these percentages depend heavily on patient- and procedure-related risks (Table).

G&H Which pharmacologic agents can help prevent the incidence of post-ERCP pancreatitis?

AW Nonsteroidal anti-inflammatory drugs (NSAIDs) work by inhibiting cyclooxygenase, prostaglandins, and phospholipase A2. A 2012 landmark study by Dr B. Joseph Elmunzer and colleagues brought to the forefront the use of indomethacin given by rectum. In this multicenter, placebo-controlled, double-blinded study, patients who were at increased risk for post-ERCP pancreatitis were given two 50-mg rectal suppositories of indomethacin following ERCP. The rates of post-ERCP pancreatitis were significantly lower in patients who were administered indomethacin vs placebo (9.2% vs 16.9%, respectively). However, a prospective, placebo-controlled, double-blinded study that was published in 2016 found that per rectal indomethacin did not prevent post-ERCP pancreatitis in consecutive patients (not all of whom were at increased risk) who underwent ERCP. These 2 contrasting studies highlight that per rectal indomethacin should not be considered a panacea for obviating the risk of post-ERCP pancreatitis, and factors including performing ERCP for proper indications and using good technique cannot be underemphasized. It is also important to keep in mind that these studies had varying patient populations, and further studies will help to elucidate this area of interest.

Administration of intravenous fluid is another method that may reduce patients' risk of post-ERCP pancreatitis, as giving patients more fluid than they might normally receive during the procedure has been shown to be potentially effective. This was highlighted in a 2014 pilot study by Dr James Buxbaum and colleagues in which patients were administered intravenous fluids either aggressively or at a standard rate in the 8 hours following ERCP. Of the patients who received standard hydration, 17% developed post-ERCP pancreatitis, compared to 0% of those who received aggressive hydration. A 2017 double-blinded, randomized, controlled trial by Dr Jun-Ho Choi and colleagues found that vigorous periprocedural intravenous hydration with lactated Ringer solution also reduced the incidence and severity of post-ERCP pancreatitis. A prospective, randomized, double-blinded, placebo-controlled study by Mok and colleagues looked at the use of 1 L of lactated Ringer solution infused over 30 minutes before

Table. Risk Factors Associated With Post-ERCP Pancreatitis

Significant Risk	Potential Risk	Inconsistent or Insignificant Risk
Female sex	Common bile duct stone absent	Small common bile duct diameter
Younger age	Normal serum bilirubin	Periampullary diverticulum
Suspected sphincter of Oddi dysfunction	Chronic pancreatitis absent	Pancreas divisum
Prior post-ERCP pancreatitis	Pancreatic brush cytology	Allergy to contrast media
Recurrent pancreatitis	Pain during ERCP	Prior failed ERCP
Pancreatic duct injection	Pancreatic acinarization	Therapeutic vs diagnostic
Pancreatic sphincterotomy	Low-volume endoscopist	Intramural contrast injection
Difficult or failed cannulation	Trainee participation	Biliary sphincterotomy
Precut (access) sphincterotomy	Balloon dilation (of intact biliary sphincter)[a]	Sphincter of Oddi manometry
Failed prophylactic pancreatic duct stenting		

ERCP, endoscopic retrograde cholangiopancreatography.

[a]Conflicting prospective randomized studies.

Adapted from Wang AY, Strand DS, Shami VM. Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: medications and techniques. *Clin Gastroenterol Hepatol*. 2016;14(11):1521-1532.e3 with permission from Elsevier.

ERCP in combination with rectal indomethacin for prevention of post-ERCP pancreatitis in high-risk patients. This study found that patients who were treated with lactated Ringer solution and indomethacin had a statistically significant reduced rate of post-ERCP pancreatitis compared to patients who received saline and placebo. Overall, these studies demonstrate that intravenous fluid hydration can play a role in reducing the risk of post-ERCP pancreatitis, which might be complementary to the use of per rectal indomethacin.

G&H What side effects are associated with the use of NSAIDs and intravenous fluids?

AW In general, the risk profiles for NSAIDs and intravenous fluids are favorable and the risks are very low, as demonstrated by the aforementioned studies. However, NSAIDs should generally be avoided in patients who have a documented allergy or who are pregnant, as there can be cardiovascular effects on the fetus. Additionally, there is a potential risk of using NSAIDs in patients who have renal insufficiency, and use of rectal indomethacin in these patients should be individualized.

G&H What role do corticosteroids and medications that promote papillary sphincter relaxation play in the prevention of post-ERCP pancreatitis?

AW Similar to NSAIDs, corticosteroids can also inhibit phospholipase A2, and they have other powerful anti-inflammatory effects. However, large randomized studies have not shown much benefit with corticosteroids in reducing the risk of post-ERCP pancreatitis; therefore, their use for this purpose is not currently recommended. Likewise, studies regarding the use of medications that promote papillary sphincter relaxation as a means to reduce the risk of post-ERCP pancreatitis have not been conclusive, and their use is also not recommended.

G&H Is the use of regulatory hormones recommended?

AW Regulatory hormones have been an area of interest in this field, although there have been conflicting data regarding the use of somatostatin and octreotide. While large-scale studies might provide additional insight, at this time, using these agents to reduce the risk of post-ERCP pancreatitis is not recommended.

G&H What other therapies are available for post-ERCP pancreatitis prevention?

AW Protease inhibitors such as gabexate, ulinastatin, and nafamostat may have some utility in this field and have been used primarily in Asian countries. This is likely an area that would benefit from further study, but the

prophylactic use of these medications is not currently recommended.

G&H How do pancreatic duct stents prevent the risk and severity of post-ERCP pancreatitis?

AW It is not exactly known why pancreatic duct stents work so well in reducing the risk and probably severity of post-ERCP pancreatitis, although pancreatic duct stents likely provide mechanical benefit by maintaining pancreatic drainage when papillary swelling occurs during the course of ERCP. It is important to realize that, while the protective mechanism may not be completely clear, multiple studies have shown that pancreatic duct stents do significantly decrease the risk of post-ERCP pancreatitis, with some studies reporting a reduction in the risk of post-ERCP pancreatitis upwards of 80%. As such, the ability to place a small-caliber prophylactic pancreatic duct stent should be mandatory for any endoscopist who performs ERCP, and pancreatic duct stenting should be strongly considered in patients who are at increased risk for post-ERCP pancreatitis.

G&H What is the risk of post-ERCP pancreatitis due to failed stenting?

AW The risk of failed placement of a pancreatic duct stent is quite high and is associated with a markedly increased risk of post-ERCP pancreatitis. Various studies have shown an 8- to 16-fold increased odds of pancreatitis associated with failed pancreatic duct stenting. A 2015 study by Dr Neel Choksi and colleagues found that patients who had failed pancreatic duct stent placement and who did not receive indomethacin had up to a 34.7% rate of post-ERCP pancreatitis. These studies underscore that performing high-quality ERCP requires adequate training and experience, including in the placement of prophylactic pancreatic duct stents.

G&H Which stent size and designs are the most effective for preventing post-ERCP pancreatitis?

AW The optimal size and length of pancreatic duct stents to reduce the risk of post-ERCP pancreatitis has not been clearly determined. However, expert opinion generally is to use a small-caliber (5-French or smaller) pancreatic duct stent. These stents can be long if the guidewire can be easily passed to the tail of the pancreas. Many endoscopists prefer short pancreatic duct stents that do not cross the genu of the pancreas. Some experts advocate using stents made of softer materials. I generally use a 5-French, 4 cm–long pancreatic duct stent with a single pigtail that is left in the duodenum. Such a stent can be obtained from various manufacturers.

G&H Should NSAIDs be used in combination with prophylactic pancreatic duct stents?

AW A large multicenter, randomized, noninferiority trial, funded by the National Institutes of Health, is currently underway to explore the use of rectal indomethacin alone compared to indomethacin and pancreatic duct stenting for the prevention of post-ERCP pancreatitis in high-risk patients. The results from this study will likely be of great importance, but the study is still a few years away from concluding. In the absence of more conclusive data, I view the placement of prophylactic pancreatic duct stents and the use of rectal indomethacin as adjunctive and complementary means of potentially reducing the risk of post-ERCP pancreatitis, particularly in patients at increased risk for pancreatitis. Actually, as the risk associated with a single 100-mg dose of per rectal indomethacin is so low, a case could be made to use this medication in all patients, including those at average risk for post-ERCP pancreatitis, unless they have an absolute contraindication.

G&H How effective are guidewire cannulation and catheter cannulation with contrast opacification?

AW There have been more than 5 high-quality, randomized, controlled trials investigating guidewire cannulation vs catheter cannulation followed by contrast opacification. Two of these studies showed a statistically significant improvement in rates of biliary access, and 1 study showed reduction in rates of post-ERCP pancreatitis with guidewire cannulation. A Cochrane meta-analysis of 12 studies compared these 2 approaches. In an unweighted pooled analysis, the rate of post-ERCP pancreatitis was 3.5% in the guidewire cannulation group vs 6.7% in the group receiving catheter cannulation followed by contrast opacification, which equates to a number-needed-to-treat of 31 favoring use of guidewire cannulation.

While expert opinion on this subject is mixed, many pancreaticobiliary endoscopists advocate guidewire-assisted cannulation. The effectiveness of these techniques might also depend on who is passing the guidewire, as in some practices and when using long-wire devices it is the ERCP assistant rather than the endoscopist who controls guidewire passage. A 2016 study by Dr Buxbaum and colleagues showed that there was a lower rate of post-ERCP pancreatitis when an endoscopist directed the guidewire compared to an assistant (2.8% vs 9.3%, respectively). Thus, in situations in which an experienced

assistant is not available, having the endoscopist control the guidewire may be another way to reduce the risk of post-ERCP pancreatitis.

G&H What techniques are available to facilitate selective biliary cannulation?

AW There are various techniques that can be used to facilitate biliary access, particularly in difficult cases. In situations in which the pancreatic duct is inadvertently and/or repeatedly accessed, leaving a pancreatic guidewire or placing a small-caliber pancreatic duct stent can help direct a wire into the bile duct. There are various precutting methods, as well as endoscopic ultrasound–guided techniques for rendezvous biliary access or even direct biliary intervention. Given the breadth of this topic, it is probably best to say that various adjunctive methods are possible in cases of challenging biliary cannulation and that some techniques might be better suited to certain clinical situations than others. Some of these advanced access techniques can be associated with higher rates of adverse events; as a result, quite often, patients with difficult-to-access ducts are sent to high-volume referral centers.

G&H How else can post-ERCP pancreatitis be prevented?

AW The most important way to reduce the likelihood of post-ERCP pancreatitis is to use sound clinical judgment that involves performing ERCP only for appropriate indications (usually for therapeutic intent) and by using good endoscopic technique, which derives from proper training and sustained experience. To quote Dr Peter Cotton, "ERCP is most dangerous to those who need it the least."

In many instances, the outcome of an ERCP is also influenced by what is done before the procedure. When possible, preprocedural imaging such as magnetic resonance cholangiopancreatography can be helpful in planning a procedure and identifying variant pancreatic-biliary anatomy, such as pancreas divisum.

It is important to remember that even in careful and experienced hands, adverse events such as post-ERCP pancreatitis are certain to occur. Therefore, it is critical to review the possible risks and benefits of an ERCP or any endoscopic procedure with a patient and, if possible, with his or her family, beforehand and to document informed consent.

G&H What are the priorities of research?

AW ERCP is a cognitively and technically challenging procedure. In addition to studies that focus on improving procedural effectiveness and safety by refining techniques or using novel or improved devices, an important area in need of further study is that of ERCP training. Studies that evaluate issues such as how to assess for competency and what is required to maintain competency following training are needed.

It should also be emphasized that, in addition to being cognizant of ERCP best practices and the latest studies, it is important in clinical practice for doctors to follow their own outcomes and take note of whether the way in which they perform ERCP results in high clinical success and low, acceptable rates of adverse events.

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Suggested Reading

Adler DG, Lieb JG II, Cohen J, et al. Quality indicators for ERCP. *Gastrointest Endosc*. 2015;81(1):54-66.

Buxbaum J, Leonor P, Tung J, Lane C, Sahakian A, Laine L. Randomized trial of endoscopist-controlled vs. assistant-controlled wire-guided cannulation of the bile duct. *Am J Gastroenterol*. 2016;111(12):1841-1847.

Buxbaum J, Yan A, Yeh K, Lane C, Nguyen N, Laine L. Aggressive hydration with lactated Ringer's solution reduces pancreatitis after endoscopic retrograde cholangiopancreatography. *Clin Gastroenterol Hepatol*. 2014;12(2):303-307.e1.

Chandrasekhara V, Khashab MA, Muthusamy VR, et al; ASGE Standards of Practice Committee. Adverse events associated with ERCP. *Gastrointest Endosc*. 2017;85(1):32-47.

Choi JH, Kim HJ, Lee BU, Kim TH, Song IH. Vigorous periprocedural hydration with lactated Ringer's solution reduces the risk of pancreatitis after retrograde cholangiopancreatography in hospitalized patients. *Clin Gastroenterol Hepatol*. 2017;15(1):86-92.e1.

Choksi NS, Fogel EL, Cote GA, et al; United States Cooperative for Outcomes Research in Endoscopy. The risk of post-ERCP pancreatitis and the protective effect of rectal indomethacin in cases of attempted but unsuccessful prophylactic pancreatic stent placement. *Gastrointest Endosc*. 2015;81(1):150-155.

Elmunzer BJ, Scheiman JM, Lehman GA, et al; US Cooperative for Outcomes Research in Endoscopy (USCORE). A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med*. 2012;366(15):1414-1422.

Freeman ML. Use of prophylactic pancreatic stents for the prevention of post-ERCP pancreatitis. *Gastroenterol Hepatol (N Y)*. 2015;11(6):420-422.

Levenick JM, Gordon SR, Fadden LL, et al. Rectal indomethacin does not prevent post-ERCP pancreatitis in consecutive patients. *Gastroenterology*. 2016;150(4):911-917; quiz e19.

Mok SR, Ho HC, Shah P, Patel M, Gaughan JP, Elfant AB. Lactated Ringer's solution in combination with rectal indomethacin for prevention of post-ERCP pancreatitis and readmission: a prospective randomized, double-blinded, placebo-controlled trial [published online November 2, 2016]. *Gastrointest Endosc*. doi:10.1016/j.gie.2016.10.033.

Wang AY, Strand DS, Shami VM. Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: medications and techniques. *Clin Gastroenterol Hepatol*. 2016;14(11):1521-1532.e3.