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Raising the Bar on Risk Reduction in Post-ERCP Pancreatitis Prevention

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G&H What is the current incidence rate for pancreatitis after endoscopic retrograde cholangiopancreatography?

BJE The risk of post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis varies between procedures. Incidence can be as high as 10% to 15% in cases that are at high risk and about 5% or even less in cases at lower risk, depending on patient and procedural characteristics. The risk range factors into the decision-making around whether to perform ERCP, what kind of prophylactic interventions are indicated, whether the patient should be observed in the hospital after the procedure, and so on.

G&H What key patent-related and procedural factors increase the risk of post-ERCP pancreatitis?

BJE There are several characteristics and interventions that have been shown to be independent predictors of developing post-ERCP pancreatitis. From the patient point of view, for example, a prior history of post-ERCP pancreatitis is a strong risk factor. Young women with a history of recurrent pancreatitis, which typically means that their pancreas is irritable, so to speak, are at higher risk. Patients with suspicion of sphincter of Oddi dysfunction are also at higher risk. From a procedural point of view, there are several independent predictors. Difficult cannulation can cause trauma to the papilla that can lead to swelling, reduced flow of pancreatic juice, and build up of pressure in the pancreas, resulting in initiation of the inflammatory cascade. Performing a pancreatic sphincterotomy has been associated with post-ERCP pancreatitis, as has repeated injection of dye into the pancreas, particularly aggressively, all the way out to the tail. Inserting a wire in the pancreas, particularly when not aiming to do pancreatic work—when the endoscopist attempts to go into the bile duct and inserts a wire in the pancreas—is another predictive factor. Although there is still some controversy around whether a single wire passage vs repeated wire passages in the pancreas raise the risk, the evidence is mounting that inserting a wire in the pancreas is a significant risk factor for post-ERCP pancreatitis. Of course, there are other factors, both from a procedural and patient point of view, but these are the main ones.

G&H What is the most effective strategy for avoiding post-ERCP pancreatitis?

BJE The most important strategy for reducing the incidence of post-ERCP pancreatitis is thoughtful patient selection. The guiding principle is that ERCP should no longer be a diagnostic procedure but rather a near-exclusively therapeutic procedure restricted to patients in whom a therapeutic intervention is clearly indicated, and those are the people in whom the risk-benefit ratio is going to be most favorable. In this era of widespread access to dedicated pancreaticobiliary imaging technologies that provide highly accurate diagnostic information more safely, ERCP for diagnostic purposes is no longer indicated. These are, namely, magnetic resonance cholangiopancreatography and endoscopic ultrasound, as well as other noninvasive methods. The point is that endoscopists

should be extremely thoughtful about when to invoke ERCP. The transition from performing ERCP as a diagnostic procedure to performing ERCP in situations where there is a very high likelihood of delivering a therapeutic intervention, like removing a stone or placing a stent, and so forth, has been a huge paradigm shift over the course of the last two decades. The safer alternatives now available should be done first in most situations in order to determine whether ERCP is indicated. Again, the guiding principle is to avoid unnecessary diagnostic ERCPs by employing thoughtful patient selection and then, when performing ERCP, taking advantage of a combination of prophylactic interventions.

G&H Could you provide an update on pharmacologic prevention and what has been shown to work?

BJE For background, pharmacoprevention of postoperative pancreatitis was historically a failed enterprise in the sense that many agents had been tried over the course of decades in literally hundreds of clinical trials with very little movement in clinical practice until rectal nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs first came on the scene in the early to mid 2000s. Since our first randomized controlled trial published in *The New England Journal of Medicine* in 2012, there have been many additional randomized controlled trials and meta-analyses that consistently show the effectiveness of NSAIDs, either indomethacin or diclofenac, given around the time of ERCP, as a suppository. There has been ongoing debate as to whether giving NSAIDs intravenously or orally would work. There is reason to believe that rectal NSAIDs are perhaps unique in some way; however, the main rationale for giving NSAIDs rectally is because that is what the clinical trial evidence shows. Current evidence-based practice is to deliver NSAIDs rectally, and the benefit appears to be specific to indomethacin and diclofenac, probably because of their mechanisms of action and their unique impact on phospholipase A2. From a pharmacologic prevention point of view, there are several agents that either have shown promise or could conceptually work, but the evidence base currently only favors the use of rectal indomethacin or diclofenac.

G&H Are rectal NSAIDs for everyone (except those with contraindications) or only high-risk patients?

BJE Our original clinical trial in 2012 was restricted to patients at high risk. The reason for that is to make the sample size more manageable; the goal was to enrich the patient population with those who are more likely to have episodes of post-ERCP pancreatitis. The trial results were positive and brought rectal NSAIDs to the forefront. Of course, the initial assumption was that this medication does work but only in high-risk patients. Since then, there have been other clinical trials and several other lines of research suggesting that the medication is effective regardless of risk, although the impact may not be as substantial in patients at lower risk. The benefit appears to be in the range of about 40% to 60% in terms of reducing post-ERCP pancreatitis. Historically, the European guidelines have always recommended rectal NSAIDs for every patient undergoing ERCP. More recently, the American guidelines have followed suit and now recommend giving rectal NSAIDs to basically everybody who is at any risk for post-ERCP pancreatitis, but especially those who are at high risk for the complication.

G&H What is the benefit of placing pancreatic duct stents alone or with, for example, indomethacin, or should the approach vary depending on risk?

BJE Before rectal NSAIDs were an option, the only effective prophylactic intervention for post-ERCP pancreatitis was temporary placement of a pancreatic stent. These thin-caliber stents are placed at the time of ERCP and, in most cases, are expected to fall out spontaneously within a few days of the procedure. Essentially, their purpose is to ensure the flow of pancreatic juice into the small intestine in the face of possible blockage of the pancreatic opening because of swelling or injury related to ERCP; the stents reduce the likelihood of pressure building up in the pancreatic duct in those critical hours after the ERCP and therefore reduce the risk of post-ERCP pancreatitis. This is obviously not the only mechanism of post-ERCP pancreatitis because if that were the case, then stents would be universally effective; however, they are not. Just like NSAIDs, stents are effective in some patients, but people can still get pancreatitis despite prophylactic

> The results affirmed guideline recommendations that in high-risk patients, endoscopists should be placing prophylactic stents and giving rectal NSAIDs.

stenting. Over the years, it had been suggested through hypothesis-generating studies that patients who received rectal NSAIDs may not need a prophylactic stent. Our more recent clinical trial that was published in *The Lancet* in 2024 essentially asked the fundamental question of whether that hypothesis is true. If it was true, that would be advantageous because prophylactic stents, while they are beneficial, have several important disadvantages. One is that stents inherently require tampering with the pancreas when we try our best not to tamper with the pancreas, and they are sometimes difficult to place. Occasionally, when the endoscopist has difficulty placing a stent and tries too hard, it is possible to induce even more damage; attempting to place a stent and failing increases the risk even above baseline. Of course, stents are costly, and even though they are supposed to fall out on their own, they do not always, so every single patient requires an x-ray to make sure that the stents have spontaneously passed. In up to 15% or 20% of patients—depending on what kind of stent is used—the stent fails to pass, and another upper endoscopy is needed to retrieve the stent.

Regarding the question of whether—in this new era of NSAID pharmacoprevention—prophylactic stent placement is still needed in high-risk patients, our recent clinical trial showed that there clearly is a benefit to the combination of prophylactic stenting and rectal NSAIDs compared with rectal NSAIDs alone. This trial specifically looked at high-risk patients. The results affirmed guideline recommendations that in high-risk patients, endoscopists should be placing prophylactic stents and giving rectal NSAIDs. Again, the unique aspect of prophylactic stenting is that it can, if done traumatically, cause the very complication that it aims to prevent. Stenting always is a judgment call. The endoscopist must always consider the risks and benefits of placing a stent. In situations where there is already a wire in the pancreas and placing a stent is a straightforward process, and the patient is at high risk—that is a no-brainer. However, in other situations in which the endoscopist does not have easy access to the pancreas, and it is very difficult to get into the pancreas, there comes a point of diminishing returns where additional efforts will likely cause more harm than good. Unlike with rectal NSAIDs, which are safe, easy to administer, and could be used more universally, prophylactic stenting still requires real-time procedural and clinical judgment to decide where the risk-benefit equation stands. The reality is that patients may benefit from both and deciding when to use both can be more of an art than a science.

G&H What other prevention strategies can help reduce or eliminate this problem, and how successful are they?

BJE There is growing evidence in favor of aggressive intravenous (IV) fluid hydration around the time of ERCP. Preclinical data outside of the post-ERCP pancreatitis context, in acute non-ERCP pancreatitis, and several randomized controlled trials for post-ERCP pancreatitis indicate that aggressive IV fluids are beneficial for reducing the incidence of post-ERCP pancreatitis. For context, it is known that IV fluids are the mainstay of treating acute pancreatitis in general. However, there are several controversies regarding this intervention. One controversy is around how aggressive to be. Evidence in pancreatitis in general is showing that being overly aggressive could be causing more harm than good, but the opinion on this is evolving. Post-ERCP pancreatitis is uniquely positioned to benefit from aggressive IV fluids because it is the only situation in which we know the exact moment at which pancreatitis has started developing. For most patients who develop spontaneous pancreatitis at home, there is a delay from when their symptoms start to when they come to the hospital, and there is a missed opportunity to intervene. Whereas for patients with post-ERCP pancreatitis, particularly if they are already admitted to the hospital, IV fluids can be started immediately once symptoms start, taking full advantage of the window during which IV fluids are believed to be beneficial.

As mentioned, there is clinical trial evidence suggesting that aggressive hydration with IV fluids, specifically with lactated ringer solution, is beneficial. However, there are a few other important controversies around aggressive IV fluids. One is that it is not as clear if they work in combination with other prophylactic interventions. If the patient is already receiving NSAIDs and a stent, is giving aggressive IV fluids also necessary? Some studies suggest that in isolation, IV fluids are very effective, but once combined with another prophylactic intervention, they are not as effective, or maybe not necessary at all. Another controversy is how long to give IV fluids. The clinical trials have all employed a prolonged infusion of IV fluids for 8 or more hours, and that is not practical in the West, where most patients are not admitted to the hospital after ERCP. Typically, IV fluid data are extrapolated. Patients are given fluids around the time of the procedure and in recovery for a couple hours, and then we hope that is sufficient, but that is not evidence-based. Furthermore, we do not know how much IV fluid to give or what the proper IV flow rate should be because patients are very different. Some patients tolerate fluid better than others; some patients are at risk for fluid overload. There are different considerations in that decision-making. It is important to have a better understanding of what is the right dose that can be given over a limited amount of time in the recovery room in patients who are going to be discharged that day, especially in those receiving other

prophylactic measures. Despite these controversies, in a young, healthy patient who is not at risk for fluid overload but is at high risk for post-ERCP pancreatitis, I personally give a robust bolus of IV fluids in recovery, sometimes up to 3 liters, recognizing that this is controversial.

G&H How is early recognition/prediction of post-ERCP pancreatitis best achieved in individual patients?

BJE Prediction is important, as I mentioned earlier, in the sense that a clear understanding of a particular patient's risk for post-ERCP pancreatitis is essential because it will factor into many decisions, including, sometimes, whether or not to do the ERCP at all. Sometimes, if the patient is at really high risk and the indication is not very strong, or the symptoms are not that compelling, the decision may be that it is just not worth it. Risk stratification is important in deciding whether to do ERCP locally or send the patient to a tertiary or quaternary referral center. Risk stratification is central to the decision of placing a prophylactic stent and whether to give rectal NSAIDs, how aggressive to be with IV fluids, and whether to admit the patient to the hospital for observation after ERCP. For patients who convincingly are at very high risk and live in a place that is far away without great medical care, the endoscopist may, based on risk stratification and prediction, decide to observe them in the hospital after ERCP.

Early recognition is a slightly separate topic. Generally speaking, with all adverse events, but certainly with ERCP complications, early recognition is critically important because the ability to intervene sooner, in principle and in practice, should mitigate the severity of the complication. In pancreatitis, being able to take full advantage of that golden window during which IV fluids are likely to be most effective is key. Recognizing too late compromises IV fluid resuscitation or even triaging the patient to the right level of care, and so forth. Because pancreatitis is the most feared complication of ERCP, for endoscopists who perform ERCP, it is on their radar, and for a patient after ERCP who has pain, they must think of pancreatitis first because it is the best opportunity to intervene.

G&H How can endoscopists/future studies continue to raise the bar, so to speak, on risk reduction in post-ERCP pancreatitis?

BJE This is perhaps the most important question because, on one hand, great progress has been made in the last few decades in the prevention of post-ERCP pancreatitis relative to what had been a stagnant field of study before that. At the same time, there is evidence that the incidence and mortality of post-ERCP pancreatitis has not changed at all, and that is very disheartening. Some possible reasons for this are that the interventions are becoming more complex or that patients are sicker, older, and more challenging to treat. Another explanation is that endoscopists are not doing a great job applying and implementing these prophylactic interventions. One area of focus in terms of dissemination and implementation science will be on better utilization of the things that work in clinical practice. That I think will move the needle. There is plenty of evidence to suggest that rectal NSAIDs are underused, that prophylactic stenting is profoundly underutilized, that there are variable approaches to IV fluids, and, most importantly, that unnecessary ERCPs are being performed. We need to restrict ERCPs for clear therapeutic indications. Even with existing strategies of dissemination and implementation, post-ERCP pancreatitis will likely remain a major clinical problem until there is more research and development in pharmacologic solutions. Rectal NSAIDs have helped but not solved the problem. A re-energized focus on pharmacoprevention is needed. Although several drugs could possibly be repurposed for this indication, the ideal is to have a better understanding of the science and a bigger commitment on behalf of scientists and pharma to develop a drug that will either eliminate or near-eliminate this problem.

Disclosures

Dr Elmunzer has no relevant conflicts of interest to disclose.

Suggested Reading

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