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The Role of Capsule Endoscopy in Diagnosis and Management of Inflammatory Bowel Disease

Capsule endoscopy (CE) is emerging as an effective tool for the diagnosis and management of inflammatory bowel disease (IBD). In an article published in *Gastrointestinal Endoscopy Clinics of North America* in 2021, co-authors Josiah D. McCain, M.D., Shabana F. Pasha, M.D., and Jonathan A. Leighton, M.D., discuss the indications, strengths and limitations of CE in the diagnosis and management of IBD, as well as the current trends and future directions for the use of this tool. Drs. Pasha and Leighton are gastroenterologists at Mayo Clinic in Scottsdale, Arizona, and Dr. McCain is a Mayo Clinic gastroenterology fellow. In this Q and A, the co-authors answer key questions related to the use of CE in patients with IBD.

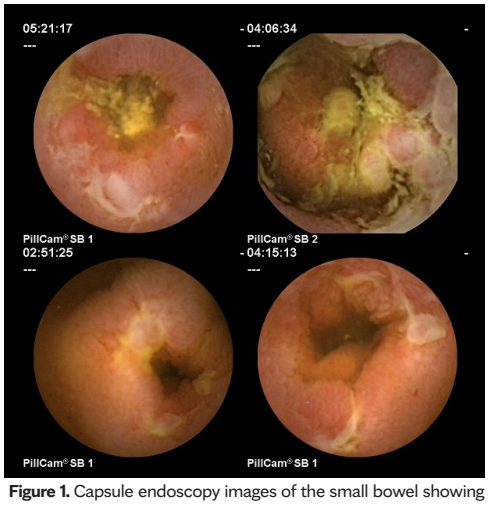

Figure 1. Capsule endoscopy images of the small bowel showing changes consistent with Crohn's disease.

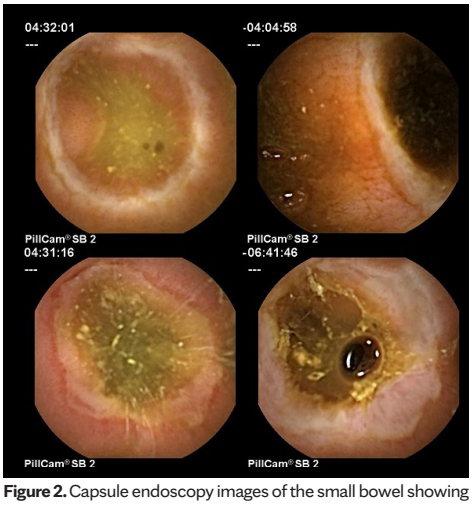

Figure 2. Capsule endoscopy images of the small bowel showing changes consistent with NSAID enteropathy.

What are some benefits associated with CE when compared with traditional endoscopy in patients with Crohn's disease?

Small bowel CE provides us with a well-tolerated, less invasive way to visualize the entire length of the small bowel in patients with Crohn's disease (CD). In most patients with suspected CD, ileocolonoscopy is still the most appropriate first evaluation. However, small bowel CE can be useful when ileocolonoscopy is negative, especially if small bowel cross-sectional imaging is also negative, and the index of suspicion for CD remains high. In patients with established CD, CE can help determine extent of disease, assess its severity in the small bowel and assist in monitoring response to therapy (Figures 1 and 2).

Can you explain CE's role in assessing mucosal healing and treat-to-target progress in patients with established CD?

Clinical symptoms do not consistently correlate with disease activity, and therefore endoscopic visualization of the mucosa is the most objective way to evaluate and document response to

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medical therapy in patients with CD. Mucosal healing in the small bowel after initiation of medical management is predictive of reduced activity in the future and overall better patient outcomes. Because CE can detect mucosal inflammation that might be missed by less sensitive modalities, it facilitates monitoring of disease activity more accurately, and it can thus guide management.

Cross-sectional studies such as computerized tomography (CT) or magnetic resonance (MR) enterography are also helpful to evaluate response to therapy. But CE may have a role in monitoring select patients with nonstricturing small bowel CD to confirm mucosal healing. Pan-enteric capsule endoscopy (PCE), in particular, might have a potential role in the future for assessment of patients with small bowel and colonic CD.

What role can CE play in diagnosing and managing UC?

While small bowel CE has been fairly well studied in CD, colon capsule endoscopy (CCE) for ulcerative colitis (UC) has not been as well studied. Therefore, the published evidence demonstrating the use of CCE in individuals with UC is still fairly limited. Small bowel CE is useful in ruling out small bowel CD in patients with IBD when there is not a clear diagnosis of UC.

Ileocolonoscopy is currently the diagnostic procedure of choice in patients with UC. Colon capsule endoscopy (CCE) has potential as a noninvasive tool for diagnosis and monitoring of UC. In our article we share available data from the literature showing that CCE has a fairly high degree of specificity and sensitivity, and substantial agreement with colonoscopy findings using the Mayo endoscopic score and the Ulcerative Colitis Endoscopic Index of Severity. In addition, CCE was both better tolerated and preferred by patients over colonoscopy. Further studies are needed to evaluate this role for CCE.

What more do we need to learn about using this tool in managing UC?

The precise role of CCE in UC remains to be defined. More research needs to be performed before we can determine the true diagnostic accuracy of this test in patients with this disease. If mucosal healing remains a primary endpoint of UC management, patients will need to undergo periodic endoscopic surveillance in addition to other noninvasive tests such as fecal calprotectin. CCE's advantages for this application include its tolerability and less invasive nature, its sensitivity, and the fact it requires less time away from work for patients.
It's important to acknowledge that CCE requires patients to undergo an extensive bowel prep with boosters. And unlike ileocolonoscopy, it does not allow for tissue sampling. We also need more data on the cost-effectiveness of CCE compared with ileocolonoscopy.

How significant is the risk of capsule retention?

In general, we have good evidence that CE is a very low-risk procedure with one major exception: potential retention of the video capsule. The risk of capsule retention in the general population is probably very low and estimates of its incidence range from 1.0% to 2.5%.

Capsule retention rates are higher (2.6%) when evaluating suspected CD. In patients with established CD, risk of capsule retention is much higher as patients may have strictures even in the absence of obstructive symptoms. It is recommended that patients with established CD be pre-screened to minimize risk of capsule retention. The risk can be significantly reduced by performing patency capsule or cross-sectional small bowel imaging prior to CE.

Can you share guidelines for management of capsule retention?

We recommend a conservative, observational approach as the first treatment for capsule retention, as many patients will pass the capsule spontaneously. If needed, medical therapy such as steroids or biologic agents can be helpful, especially for patients with Crohn's disease. Endoscopic or surgical retrieval of a capsule should only be performed in patients in whom observation and medical therapy have failed.

FOR MORE INFORMATION

McCain JD, et al. Role of capsule endoscopy in inflammatory bowel disease. *Gastrointestinal Endoscopy Clinics of North America*. 2021;31:345.

Examining the Clinical Presentation and Imaging Characteristics of Cryptogenic Multifocal Ulcerous Stenosing Enteritis

First described in the early 1960s, cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) is a rare illness with unknown etiology and pathophysiology. This condition is characterized by chronic or intermittent symptoms of obstruction caused by multiple fibrous strictures and shallow ulcers of the small bowel.

Because CMUSE shares some clinical and imaging features with Crohn's disease (CD), nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy, and other more-common causes of small bowel ulcerations and stenosis, making an accurate diagnosis requires integration of clinical, endoscopy, radiology and pathology data.

Seeking to gain a better understanding of CMUSE, researchers from Mayo Clinic Gastroenterology and Radiology in Rochester, Minnesota, conducted a multidisciplinary study for patients diagnosed with this illness. The results of the study, the largest single tertiary care center experience of adults with CMUSE in North America, were published in *Abdominal Radiology* in 2021. In their article, the authors discuss factors that may differentiate CMUSE from other more-common causes of intestinal ulcerations and potential interventions.

METHODS

According to gastroenterologist Guilherme (Gui) Piovezani Ramos, M.D., and radiologist David J. Bartlett, M.D., lead authors of the *Abdominal Radiology* article, the researchers reviewed electronic medical records from patients seen at Mayo Clinic and diagnosed with CMUSE during a 20-year period, and they abstracted clinical data and confirmed diagnosis using published criteria. Co-authors Shannon P. Sheedy, M.D., and Jeff L. Fidler, M.D., radiologists specializing in gastrointestinal disorders, reviewed the computerized tomography enterography (CTE) and magnetic resonance enterography (MRE) exams of patients diagnosed with CMUSE to characterize the disorder's imaging features.

RESULTS

Overall, the researchers identified 33 patients for whom CMUSE was considered as a diagnosis during initial clinical evaluation. After excluding 21 patients who were later diagnosed with a different condition and four patients who did not meet CMUSE diagnostic criteria, the researchers identified eight patients with clinically confirmed CMUSE for the study cohort. Image review from the eight patients included analysis of nine CTEs and one MRE.

Clinical presentation and imaging characteristics

The researchers note that the most common major morphologic feature observed in all patients diagnosed with CMUSE was short, multifocal small bowel strictures measuring less than 2 cm in length with circumferential luminal narrowing and stratified hyperenhancement. Listed below are some more-detailed findings that the researchers share in their article.

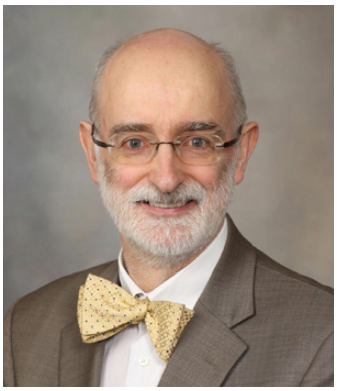
- Disease location: Eight (100%) patients had strictures located in the ileum; four (50%) had strictures located in the jejunum.
- Stricture quantity: Four (50%) patients with CMUSE had 10 or more strictures; three (37.5%) had from 5 to 10 strictures.
- Endoscopic findings: Six (75%) patients had circumferential ulcers; seven (87.5%) had well-demarcated ulcers.
- The median proximal small bowel dilation was 2.95 cm (range, 2.5 to 4.1 cm).
- No patients with CMUSE presented with penetrating disease (such as abscess or fistula).

Treatment and outcomes

Overall, the researchers noted that most of the patients diagnosed with CMUSE did not respond to their first treatment and had symptoms that were refractory to surgical intervention. Additional details about treatment and outcomes include the following findings:

- Budesonide or prednisone were the most common treatments, administered in seven (87.5%) patients.

Guilherme (Gui) Piovezani Ramos, M.D.



Joseph A. Murray, M.D.

- Biologic medications were administered in three (37.5%) patients; one received vedolizumab after a partial clinical response to methotrexate; one received vedolizumab after failed treatment with both budesonide and mesalamine; and one received treatment with a combination of adalimumab and azathioprine combination therapy after experiencing an adverse event during treatment with infliximab.
- Recurrence to medical therapy (median of four months after treatment) occurred in six (85.7%) patients.
- Surgery for refractory intestinal obstruction was performed in four (50%) patients; and 50% of patients who underwent surgery experienced a postoperative recurrence of ulcerating disease.
- The three (37.5%) patients treated with endoscopic balloon dilation experienced recurrence(s) of obstructive symptoms during study follow-up.

DISCUSSION AND CONCLUSIONS

The Mayo Clinic researchers note that differential diagnosis of short, multifocal small bowel strictures should always include CD, NSAID-induced enteropathy and CMUSE. According to the research team, this retrospective review demonstrated that CTE and MRE are invaluable tools in the multidisciplinary diagnostic evaluation of CMUSE.

"We know that differentiating between Crohn's disease, drug-induced enteropathy and CMUSE is challenging because of their overlapping characteristics," explains Dr. Piovezani Ramos. "Some of the characteristics and imaging features we noted in our study cohort can improve our ability to distinguish between these diagnoses. For example, enterography studies showing disease involvement in multiple long small bowel segments, especially those that are patchy and asymmetric, are more indicative of Crohn's disease. In contrast, although some CMUSE lesions may have subtle asymmetry, a higher proportion of lesions in our study subjects diagnosed with CMUSE were circumferential."

"It's also helpful to note that when we can identify penetrating disease such as a fistula, abscess or perianal disease, we can exclude a diagnosis of CMUSE and NSAID-induced enteropathy," explains Mayo Clinic gastroenterologist Joseph A. Murray, M.D., the study's corresponding author. "Disease location is another significant feature. Involvement of the colon, duodenum, stomach or esophagus, and extra-enteric complications — such as primary sclerosing cholangitis and sacroiliitis — can also serve as differentiating signs for a diagnosis of Crohn's disease. Additionally, sequela of mesenteric vein thrombosis, fibrofatty proliferation and pseudosacculations are all suggestive of Crohn's disease."

The research team acknowledges that the study has limitations, including its small sample size and retrospective design. The team is hopeful, however, that the data yielded by this investigation will increase clinicians' awareness and identification of this rare condition, and encourage additional research that focuses on therapeutic options and how to position CMUSE alongside other more-common types of inflammatory bowel disease.

FOR MORE INFORMATION

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Diagnosis and Management of Patients With Gastroparesis

Gastroparesis is characterized by a delay in gastric emptying associated with upper gastrointestinal symptoms and no evidence of a mechanical obstruction. Symptoms include nausea, vomiting, early satiety and postprandial fullness.

Often, idiopathic gastroparesis may develop postoperatively or after an infection. Other conditions and factors associated with gastroparesis include type 1 and type 2 diabetes mellitus, medications that impair gastric emptying (most notably opioids, GLP-1 agonists used for

diabetes and tricyclic antidepressants at high doses), neurological disorders, and autoimmune disorders.

Published in 2021, the United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on gastroparesis presents statements on symptom characteristics, pathophysiology, diagnosis and management for this condition.

In a commentary published in *Neurogastroenterology & Motility* in 2021, Mayo Clinic gastroenterology researchers begin their article by congratulating the ESNM and UEG members for developing comprehensive recommendations on gastroparesis, noting the strength of the systematic literature reviews, and the consensus and grading processes. The commentary's lead author, Michael Camilleri, M.D., is a gastroenterologist at Mayo Clinic in Rochester, Minnesota. Dr. Camilleri's research team focuses on disorders of gastrointestinal motility and function.

Dr. Camilleri and co-authors note that they were in agreement with many of the endorsed statements. However, because the ESNM work group's literature search ended in 2019, the commentary from the Mayo Clinic researchers includes updates of the current state of knowledge related to gastroparesis. Their primary goal was to identify and elaborate on topics where recently published literature provides additional insights that may not have been available while the ESNM document was produced. To achieve this objective, the Mayo Clinic researchers conducted an extensive review of currently available published literature related to each of the ESNM's consensus statement topics.

In this article, Dr. Camilleri and commentary co-author Ting Zheng, M.D., a gastroenterology fellow at Mayo Clinic, elaborate on a few of the updated perspectives discussed in their commentary.

DEFINITIONS AND SYMPTOMS: PAIN

Addressing the ESNM's statement about whether abdominal pain is considered a symptom of gastroparesis, Mayo Clinic authors shared findings from the National Institutes of Health gastroparesis consortium published in 2020, in which 90% of patients with either diabetic or idiopathic gastroparesis reported abdominal pain. Consequently, the Mayo Clinic authors suggest that even though pain is not a predominant symptom of gastroparesis, it is a frequent component of the symptoms of patients with this condition.

EPIDEMIOLOGY

Mayo Clinic commentary authors are in agreement that the epidemiological characteristics of gastroparesis are not yet well understood. They note that two objective testing methods (upper gastrointestinal endoscopy and gastric emptying scintigraphy, respectively), to exclude upper gastrointestinal obstruction and to document delayed gastric emptying, are not widely used to confirm the diagnosis upon which the epidemiology is based. Hence, the authors assert that it is essential for future studies to incorporate those objective measures to gain better insights about the epidemiology of gastroparesis.

PATHOPHYSIOLOGY

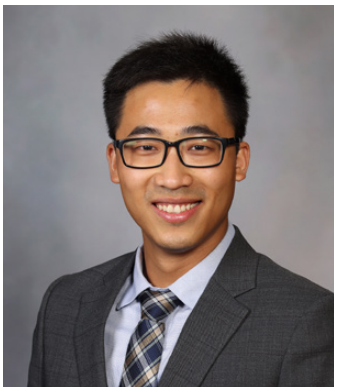
The Mayo Clinic commentary authors observe that although multiple factors are likely to be responsible for the etiology of gastroparesis symptoms, delayed gastric emptying plays an essential role and should be considered mandatory for the diagnosis of gastroparesis. They note that multiple studies summarized in Mayo Clinic publications in 2019 and 2020 have demonstrated a positive association between optimally measured gastric emptying and symptoms, as well as documenting improvement in upper gastrointestinal symptoms with acceleration of gastric emptying.

TREATMENT

Treatment of gastroparesis continues to require a multidisciplinary approach that includes dietary adjustments, nutritional support, prokinetic agents and pyloric interventions. Dr. Camilleri comments that some of the recently introduced therapeutic strategies are very encouraging.

"Within the U.S., no new drugs have been approved by the Food and Drug Administration for several decades. But I do believe we are on course to having more to offer our patients. So, I am optimistic that we are on the right track."

Michael Camilleri, M.D.



Ting Zheng, M.D.

Dietary adjustments
Mayo Clinic commentary authors agree with ESNM statements related to dietary adjustments. "Small portion, frequent meals consisting of food with high carbohydrate, low-fat, low-fiber content is the first step in the management of gastroparesis," explains Dr. Zheng. "Homogenized food and liquid nutrition tend to be well tolerated. In patients with refractory nausea and vomiting, oral or percutaneous jejunal nutrition may be necessary. Parenteral nutrition is associated with high risk of complications and should be reserved for patients with more-severe disease and intolerance of enteral feeding."

Proton pump inhibitors
In their commentary, Mayo Clinic authors observe that gastroesophageal reflux disease commonly coexists with gastroparesis, for which proton pump inhibitors may be helpful.

Prokinetics
Dr. Zheng adds that "prokinetics and anti-emetics are the first line pharmacological treatments in patients with gastroparesis. While the correlation between symptomatic improvement and the enhancement of gastric emptying rate remains controversial, recent evidence based on studies with optimal measurement of gastric emptying (based on emptying of solids over at least three hours) demonstrates clinical efficacy of prokinetics that are associated with accelerated gastric emptying."

NK1 antagonists
Recent study data suggest the efficacy of NK1 antagonists, such as aprepitant and the experimental medication tradipitant, for at least some of the cardinal symptoms of gastroparesis such as nausea and vomiting.

Gastric peroral endoscopic pyloromyotomy (G-POEM)
Interventions directed at the pylorus have gained popularity in recent years based on many open-label trials. Sham-controlled trials are required.

CONCLUSIONS

In closing their commentary, Dr. Camilleri and co-authors commend the ESNM work group's extensive literature review and identify five high-priority areas that require the attention of researchers in gastroparesis to advance the field.

- Consensus endorsement of delayed gastric emptying, measured at least three hours after ingestion of a solid meal, to facilitate consistent diagnosis
- Performance of epidemiological studies using optimal gastric emptying measurement (more feasible using Food and Drug Administration-approved stable isotope breath test, which was originally validated at Mayo Clinic) as the basis for diagnosis
- Further research including gastric biopsies to address intrinsic etiopathologic mechanisms
- Discovery of effective and safe prokinetics as well as optimized placebo-controlled trials to define the role of prokinetics and other treatments
- Investigation of standardized predictors of success with pyloric interventions, whether performed by endoscopy or laparoscopy

FOR MORE INFORMATION

Schol J, et al. United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on gastroparesis. *United European Gastroenterology Journal*. 2021;9:287.

Camilleri M, et al. A North American perspective on the ESNM consensus statement on gastroparesis. *Neurogastroenterology & Motility*. 2021;33:e14174.

Use of Antispasmodics for the Treatment of Abdominal Pain

Abdominal pain is one of the most common gastrointestinal (GI) problems causing individuals to seek medical care within the United States. Functional GI disorders, also known as disorders of gut-brain interaction (DGBI), are common underlying causes of abdominal pain in many patients. This highly prevalent category of GI disorders includes irritable bowel syndrome (IBS), functional dyspepsia (FD) and centrally mediated abdominal pain syndrome (CAPS).

Clinicians frequently prescribe antispasmodic agents to treat symptoms of abdominal pain, including spasms and cramps, in patients with DGBI. Within the U.S., the number of prescriptions for these medications is estimated to exceed 3 million a year.

In a review article published in *The American Journal of Gastroenterology* in 2021, co-authors Darren M. Brenner, M.D., and Brian E. Lacy, M.D., Ph.D., examine the published data related to the use of antispasmodic agents available in North America for the treatment of abdominal pain in patients with DGBI. Dr. Lacy is a gastroenterologist at Mayo Clinic in Jacksonville, Florida, and a co-author of the American College of Gastroenterology (ACG) clinical guideline for the management of IBS published in 2021.

Currently, three categories of antispasmodics are available in North America, each of which has a different mechanism of action:

- Anticholinergic and anti-muscarinic agents, which inhibit GI smooth muscle contraction
- Calcium channel inhibitors, which inhibit calcium transport into GI smooth muscle
- Direct smooth muscle relaxants, which inhibit sodium and calcium transport (Table)

METHODS

Seeking to examine the efficacy and safety of these medications more closely, the co-authors conducted a review of available randomized, placebo-controlled, parallel or crossover studies of antispasmodics currently available in North America (United States, Canada and Mexico) that involved adults with abdominal pain related to IBS, dyspepsia or FD, and CAPS.

Anticholinergic and anti-muscarinic antispasmodics
- Dicyclomine
- Hyoscine
- Hyoscyamine
- Otilonium

Direct smooth muscle relaxants
- Dicyclomine
- Hyoscine
- Mebeverine

Calcium channel inhibitors
- Alverine
- Otilonium
- Pinaverium
- Trimebutine

Table. Antispasmodics available in North America grouped by mechanism of action.

The co-authors' database search identified a total of 26 studies, including 23 focused on IBS, one on FD and two on recurrent abdominal pain with cramping. The search did not identify any studies evaluating antispasmodics in patients with CAPS. The co-authors then analyzed each study's patient population, treatment regimen, efficacy outcomes and safety outcomes.

Brian E. Lacy, M.D., Ph.D.

DISCUSSION AND RESULTS

The co-authors provide detailed information and charts summarizing the available data related to each of the specific medications that are currently available in North America for the treatment of chronic abdominal pain related to DGBI. After performing this analysis, Drs. Lacy and Brennan concluded that data supporting the use of antispasmodics for the treatment of chronic abdominal pain in patients with DGBI, including IBS and FD, are limited. They note that many of the trials included in this analysis have limited sample size, short duration of therapy, heterogeneity in outcomes and concerns related to study design bias.

"The antispasmodics studied were found to vary dramatically in efficacy and safety. This makes it difficult to recommend these agents for clinical use, especially after comparing the data sets available from large, randomized, controlled trials evaluating the performance of IBS medications currently approved for use in the United States," explains Dr. Lacy.

"Our research also highlights the need to use other approved therapies to treat chronic abdominal pain, such as neuromodulators and cognitive behavioral therapy, and to engage in additional research to develop and test agents to treat this debilitating disorder," says Dr. Lacy. Researchers at Mayo Clinic in Jacksonville, Florida, are evaluating the use of virtual reality to treat abdominal pain symptoms in patients with functional dyspepsia. Preliminary results were shared at the 2021 meeting of the American College of Gastroenterology in Las Vegas.

FOR MORE INFORMATION

Brenner DM, et al. Antispasmodics for chronic abdominal pain: Analysis of North American treatment options. *The American Journal of Gastroenterology.* 2021;116:1587.

Lacy BE, et al. ACG clinical guideline: Management of irritable bowel syndrome. *The American Journal of Gastroenterology.* 2021;116:17.

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This course addresses new approaches to the diagnosis and management of patients with gastrointestinal and liver diseases, including general gastroenterology, inflammatory bowel disease, colorectal neoplasia, esophageal diseases, motility, nutrition, pancreaticobiliary disorders, endoscopy and hepatology.

Innovations in Management of Pancreatic Conditions and Therapies: The Mayo Clinic IMPACT Course — LIVESTREAM
April 22, 2022
This one-day course with pancreas experts highlights the recent innovations in the management of pancreatic conditions and the therapies that can be incorporated into clinical practice.

Gastroenterology & Hepatology Board Review 2022
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This comprehensive review helps prepare candidates for the initial and maintenance of certification examinations. It includes case-based content delivered by Mayo Clinic faculty who deliver up-to-date, practical information.

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Cover image:
Desmoplasia in pancreatic cancer, light micrograph

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