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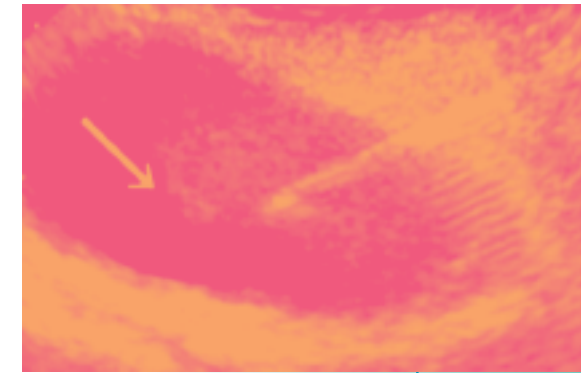
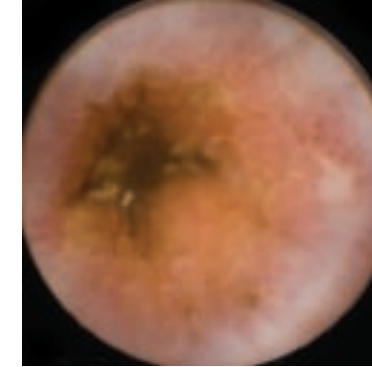
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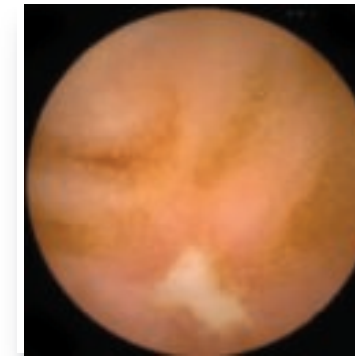
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Mount Sinai Digest



Capsule Endoscopy in Crohn's Disease

Blair S. Lewis, MD, Clinical Professor of Medicine



Capsule endoscopy (CE) initially marketed in 2001 has quickly gained a reputation as providing state-of-the-art imaging of the small intestine. Routinely used in the evaluation of obscure gastrointestinal bleeding after colonoscopy and

Crohn's disease was diagnosed in 12 of the 17 by capsule endoscopy. Selective criteria are needed and the following algorithm can be applied (Figure 1). Capsule endoscopy yield in the diagnosis of Crohn's disease is enhanced if extraintestinal manifestations, inflammatory markers or abnormal imaging studies are present.

Finding a Common Language: Capsule Scoring Index

Lack of a standardized terminology to describe the extent and severity of small bowel inflammatory lesions has limited CE's clinical utility. Until recently, no severity scale of mucosal disease activity or even a threshold for disease diagnosis had been agreed upon akin to the Crohn's disease activity (CDAI) or the Harvey-Bradshaw index. Prior to CE, there had been no consistent measure of mucosal disease activity in the small intestine. Current clinical indices are based on clinical symptoms and some laboratory parameters. A recently developed scoring index to assess mucosal inflammatory disease in the small bowel based on three capsule endoscopic variables (villous appearance, ulcerations and stenosis) detected by CE is now part of capsule endoscopy software (Figure 2). The score provides a common language to quantify mucosal changes. The index does not diagnose or measure a disease, or have the discriminatory ability to differentiate these illnesses; it measures mucosal change. This scoring index combined with the patient's history, presentation and laboratory values may help establish the diagnosis of small bowel Crohn's disease and document mucosal healing in response to therapy. Finally, the CE score could become an indispensable common language shared by treating physicians and clinical researchers to assess therapies and outcomes.

Table 1. The incremental yield of capsule endoscopy over other testing

	Total yield CE (%)	Total yield other modality (%)	% IY for CE (95% CI)
Small bowel series	66	24	42 (0.30-0.54)
Ileoscopy	61	46	15 (0.02-0.27)
CT Enterography	75	37	38 (0.23-0.54)
Push Enteroscopy	51	7	44 (0.31-0.57)
Small bowel MRI	60	40	20 (0.41-0.81)

upper endoscopy, capsule endoscopy has demonstrated utility in assessing patients with suspected and established Crohn's disease. CE has a low miss rate for ulcers of 0.5%. Compared to other imaging modalities of the small bowel for inflammatory bowel disease CE has an incremental diagnostic yield of 25-40% over barium studies and CT scanning (Table 1). A recent International Conference on Capsule Endoscopy (ICCE) concluded that capsule endoscopy identifies small-bowel mucosal lesions not seen with other imaging modalities and may play an important diagnostic role in the evaluation and monitoring of patients with known or suspected Crohn's disease. Further, the conference concluded that capsule endoscopy may have a unique role in assessing mucosal healing after medical therapy and for assessing early post-operative recurrence and in guiding therapy, and finally that capsule endoscopy may serve as a sub-clinical marker in asymptomatic family members and contribute to the understanding of the natural history IBD.

Capsule Endoscopy in Suspected Crohn's disease

Suspicion of Crohn's disease was previously left to the discretion of the physician treating a patient complaining of abdominal pain or persistent diarrhea. Yields of capsule endoscopy are low when performed in patients with abdominal pain alone or in patients with abdominal pain and diarrhea alone. Signs or symptoms of inflammation including elevated erythrocyte sedimentation rate, C-reactive protein, thrombocytosis and leukocytosis increases the yield of capsule endoscopy. In one study, a group of patients with long term symptoms of abdominal pain, diarrhea, anemia, and weight loss and normal colonoscopies, upper endoscopies and small bowel series

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The Mount Sinai Digest is a quarterly newsletter published by the Mount Sinai School of Medicine, Dr. Henry D. Janowitz Division of Gastroenterology.

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Mount Sinai Digest

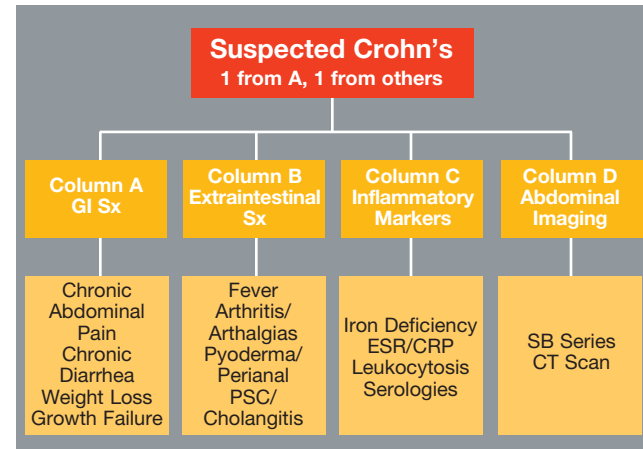
Update from the Dr. Henry D. Janowitz
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Inflammatory Bowel Disease (IBD) has come to encompass a wide variety of clinical scenarios since the original modern description of "regional ileitis" by Crohn, Ginzburg and Oppenheimer in 1932 here at Mount Sinai. While our understanding of IBD has deepened with the advances in basic science, medicine and surgery over the last 75 years there is still much we do not know. In this issue our contributors review three clinical challenges often encountered in patients with IBD where these gaps in our understanding can seem most stark; treating the pregnant patient, how to interpret capsule enteroscopy results, and incidental findings found on the CAT scans performed (some might argue too often) on IBD patients.

Reviewing these somewhat vexing cases we have Dr. Blair Lewis who has led the way in the standardizing the interpretation of capsule enteroscopy in Crohn's disease, Dr. Adam Steinlauf who has written and spoken widely on that state of the art of managing pregnancy issues seen in IBD and finally Dr. Michelle Kim, Director of our Endoscopic Ultrasound unit, who has demonstrated the utility of these newer tools in assessing IBD patients.

James F. Marion MD
Editor

Figure 1. Criteria for suspected Crohn's disease



The Future of Capsule Endoscopy in IBD

Capsule endoscopy has the potential to propel a coming paradigm shift in the treatment of Crohn's disease. Incredibly, the average time between the onset of a patient's symptoms until diagnosis historically remains an average of 35 months. Capsule endoscopy identifies the earliest changes of inflammatory change in the small bowel and has the potential to shorten this long lag time. Does earlier diagnosis and thus earlier intervention change the natural history of the disease? This is not known; though studies in children with fistulous disease had greater response to therapy the earlier they were diagnosed. Earlier diagnosis will bring earlier treatment and may bring improved outcomes. Another paradigm shift in the making is the method of assessing disease activity. Previously, physicians have used patients' symptoms to guide treatment.

Unfortunately high placebo response rates by symptoms can cloud clinical trial results. Remission when defined as symptom improvement using the CDAI does not correlate with mucosal healing. Prior to capsule endoscopy there was no reliable method to determine the extent or severity of the disease in the small bowel. Perhaps in the future patient management decisions may be based on measures of mucosal healing rather than merely symptom response.

Figure 2. Parameters and Weightings for the Capsule Endoscopy Scoring Index

First Tertile			
Parameters	Number	Longitudinal Extent	Descriptors
Villous Appearance	Normal – 0	Short Segment – 8	Single – 1
	Edematous – 1	Long Segment – 12	Patchy -14
		Whole tertile – 20	Diffuse – 17
Ulcer	None – 0	Short Segment – 5	<1/4 – 9
	Single – 3	Long Segment – 10	1/4-1/2 – 12
	Few – 5	Whole tertile – 15	>1/2 – 18
	Multiple – 10		

In summary, capsule endoscopy has been shown to detect small bowel inflammatory changes better than any other imaging modality. A common language has been developed. It is envisioned that the manner in which we treat Crohn's disease in the future will change, based on earlier diagnosis and treatment aimed at mucosal healing rather than symptom improvement.

Figure 3. Examples of endoscopic findings of Crohn's disease at capsule endoscopy

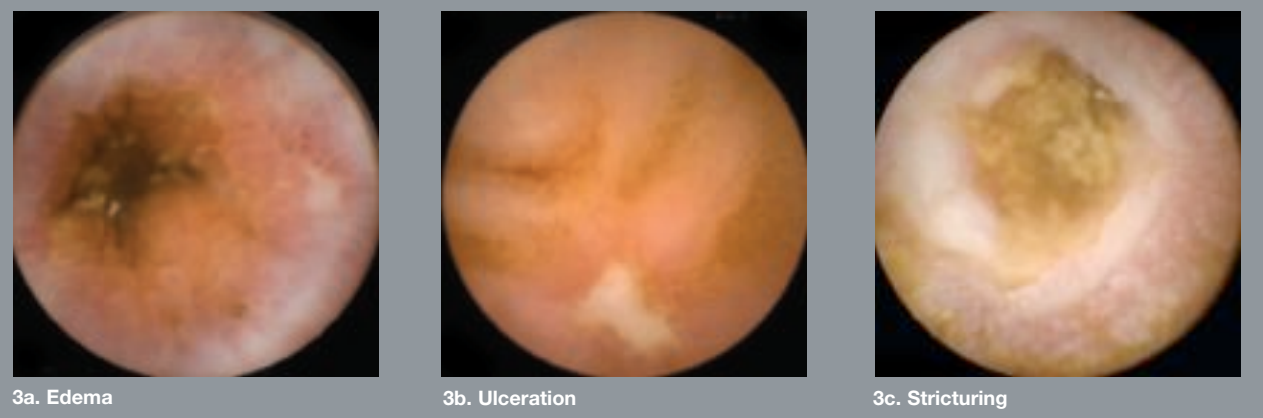


Table 1. From Triester. Figure 1. Mergener K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, Seidman E, Cellier C, Murray J, de Franchis R, Rosch T, Lewis B. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Endoscopy 2007;39:895-909. Figure 2. From Gralnek.

The Pregnant Patient with Inflammatory Bowel Disease

Adam F. Steinlauf, MD, Assistant Clinical Professor of Medicine

Inflammatory Bowel Disease often affects young people of childbearing age. The medical management of this challenging population can intimidate even experienced gastroenterologists and obstetrician/gynecologists. Effective management of such patients requires assisting the patient through all phases of their family planning.



Counseling Prospective Parents

The treating physician must be fully informed in order to effectively counsel these patients. "Will my child have IBD too?" is frequently heard in the consultation room.

Our understanding of the genetics of IBD has greatly improved in the last several years but large gaps persist. The susceptibility of developing IBD in an individual cannot be explained using a simple Mendelian model. For Crohn's disease (CD), there is a concordance rate of only 44-50% in monozygotic twins whereas the rate in dizygotic twins is 0-3%. For ulcerative colitis (UC), the corresponding rates are 6-14% and 0-5%, respectively. In general, a child has a 5-8% chance of developing IBD if one parent has CD and a 2-4% chance if the parent has UC. If both parents have IBD, the chance increases to 35%-50%. As we learn more about the specific gene risk factors involved in IBD, such as CARD 15, we will soon be able to better predict which patients are at risk.

Infertility rates in patients with IBD are similar to that of the general population. Patients with IBD do seem to have fewer children than expected due to voluntary reasons or inappropriate medical advice. Crohn's disease can transiently effect fertility when active, but less so when inactive. IBD per se does not appear to effect male fertility.

The Effects of Pregnancy on Inflammatory Bowel Disease

When a woman conceives at a time of disease remission, her chances of suffering a flare of her disease during her pregnancy are 33%, similar to those of non-pregnant women. If conception occurs during disease activity, the disease will persist or worsen in 66% of patients. Women should be advised if at all possible to refrain from pregnancy until the disease is controlled.

The Effects of IBD on Pregnancy

Many patients and physicians believe that pregnant patients with IBD should avoid most medications during pregnancy. When advising patients, it is important to convey the risks of active IBD in-and-of itself on the developing fetus versus the risks of treatment. Inactive UC has little effect on the course of pregnancy in terms of congenital abnormalities, spontaneous abortions and stillbirths. Active UC can result in poor maternal health, which can ultimately lead to prematurity and low birth weight, congenital malformations and an increased combined abortion-still birth rate. Fulminant UC requiring surgery carries a combined abortion-still birth rate which is substantially higher. CD demonstrates a similar pattern. Active disease has been shown to increase the incidence of fetal loss, still births, pre-term delivery, low birth weight and developmental defects. The risk appears to be related to disease activity rather than the medications used to treat the disease. Fetal mortality increases when surgery is indicated.

The Effects of Medications Used to Treat IBD on Pregnancy

When treating a pregnant woman with IBD, the physician must keep two basic facts in mind: a) underlying IBD may pose a greater risk to a developing fetus than the medications used to treat IBD and b) pregnant women should essentially be treated in a similar fashion as those who are not pregnant. Some patients stop their maintenance medications before conception based on either personal beliefs or inappropriate medical advice. Although it is important to inform couples contemplating pregnancy regarding drug risks and warnings, it is equally important to educate and counsel them with regard to the experience and safety of most of these medications during pregnancy. Mesalamine and corticosteroids are safe and well tolerated. Antibiotics such as metronidazole and ciprofloxacin have also proven to be safe for short courses. Mercaptopurine (6-MP) and azathioprine (AZA) also appear to be safe in a landmark study from Mount Sinai physicians. The Mount Sinai study reported on 325 pregnancies in 155 patients (female and male), and found that 6-MP was not associated with prematurity, spontaneous abortion, congenital abnormalities, or neonatal and childhood infections. Indeed, recent studies suggest that discontinuing these medicines prior to conception may increase the chances of fetal loss. Infliximab postmarketing data has shown no difference in terms of live births, miscarriages and therapeutic terminations compared to mothers not exposed to the drug.



Medication	FDA Pregnancy Category	Recent Safety Data During Pregnancy
5-ASA Azulfidine Mesalamine Balsalazide	B B B	All shown to be safe. Folate supplements required with sulfasalazine. Kernicterus is a potential but rare concern with sulfasalazine. Very high doses of 5-ASA should be used with caution.
Antibiotics Metronidazole Quinolones Penicillins Cephalosporins Erythromycin	B C B B	Short courses of metronidazole appear safe when used for trichomonas. Ciprofloxacin appears safe. Possible arthropathogenicity with ciprofloxacin, but not seen in two major studies.
Corticosteroids Prednisone Prednisolone Solucortef Solumedrol Budesonide	C C C C	Generally well tolerated and safe in pregnancy. Topicals are safe until third trimester unless miscarriage or preterm delivery a concern. Budesonide was teratogenic and embryocidal in rats and rabbits, but safe during pregnancy when inhaled.
Purine Analogues Mercaptopurine Azathioprine	D D	Appears safe for use during pregnancy.
Anti-TNF Infliximab Thalidomide	B X	Infliximab appears safe in murine models and post-marketing safety database which demonstrates outcomes consistent with those in healthy women. Thalidomide associated with fetal abnormalities and a high mortality rate.
Immuno-Suppressives Cyclosporine Tacrolimus	C C	Cyclosporine appears safe for use during pregnancy. Associated with low birth weight and prematurity, but high survival. Tacrolimus appears safe. It compares favorably to other immunosuppressives with regard to congenital malformations, birth weight and neonatal problems.
Antimetabolites Methotrexate	X	Teratogenic and embryotoxic in animals, resulting in chromosomal damage and miscarriage. Used as an abortifacient in tubal pregnancies. Should be avoided.

The Effects of Surgery for Inflammatory Bowel Disease on Pregnancy

Decreased fecundity may occur after ileal pouch-anal anastomosis in UC likely secondary to tubal occlusion from adhesions and pelvic nerve dissection. With improved fertility techniques, these patients can now conceive at rates similar to those of the general population.

Performing surgery during pregnancy has been associated with a high rate of spontaneous abortions and stillbirths. In spite of this, surgery has been performed successfully during pregnancy when absolutely indicated. Surgical procedures such as these should be reserved for surgeons who are vastly experienced in handling such patients. Our surgical staff at Mount Sinai has this degree of experience.

Approach to Delivery

Patients with UC can expect normal labor and vaginal delivery. If the patient has a J-pouch, she probably can deliver safely vaginally. Patients with CD and active perineal involvement should undergo a C-section. If vaginal delivery can not be avoided, all attempts should be made to avoid an episiotomy. If an episiotomy is required, a mediolateral approach is preferable. In patients without perineal involvement, vaginal delivery can be attempted; however, there

may be an increased chance of developing perineal disease afterwards. An experienced obstetrician should be consulted throughout the entire pregnancy period.

Summary

The complete care of the pregnant patient with IBD requires an informed patient and a team of gastroenterologists, surgeons and obstetricians who are experienced and comfortable with treating such challenging patients.

1. Steinlauf AF, Present DH. Medical management of the pregnant patient with inflammatory bowel disease. *Gastroenterology Clinics of North America* 2004; 33:361-85.
2. Francella A, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. *Gastroenterology* 2003; 124: 9-17.

Approach to the “Incidentaloma” in an IBD Patient

Michelle Kang Kim, MD, MSc, Director, Endoscopic Ultrasound, Assistant Professor of Medicine

Evaluation and treatment of inflammatory bowel disease frequently entails using many different imaging techniques. CT and MR have become increasingly available and sophisticated, frequently generating unexpected findings in need of further evaluation. Pancreatic cysts represent such common “incidentalomas.” These findings present difficult clinical dilemmas; as evidence of this, there has been an explosion of literature to attempt to clarify what these lesions are and how they should be managed.

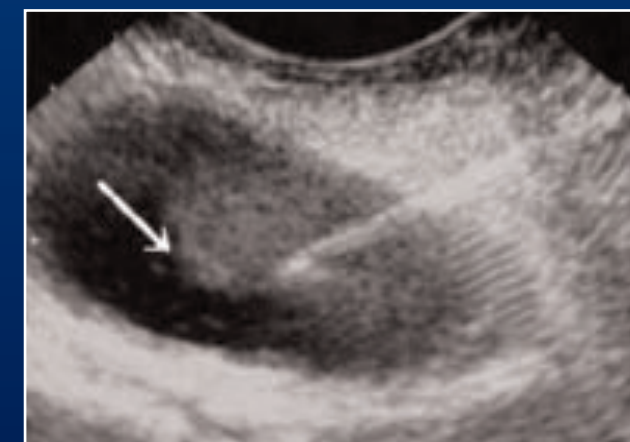
Pancreatic cysts have long been waved off as benign simple cysts or pseudocysts. Most pancreatic cysts are neither homogeneous nor benign. The differential is lengthy and includes premalignant lesions, such as mucinous cystadenomas and intraductal papillary mucinous neoplasms (IPMNs), as well as frankly malignant entities like mucinous cystadenocarcinomas and islet cell carcinomas. Serous cystadenoma, as well as pseudocysts and simple cysts, comprise the most common benign entities.

The clinical challenge in managing pancreatic cysts lies in discriminating between benign and potentially malignant cysts. Basically, we need to be able to distinguish mucinous cysts from nonmucinous cysts. That such lesions can call for surgical resection of the pancreatic cyst, a procedure that may have significant morbidity and mortality, only raises the stakes. There is great heterogeneity in the biologic behavior of pancreatic cysts; mucinous cysts may behave indolently, while an IPMN with malignant transformation may behave more aggressively. Although CT and MR may provide important morphologic information of cysts, they are not frequently diagnostic. Imaging frequently fails to clarify whether a cyst is benign or malignant.

Endoscopic Ultrasound

Combining endoscopy and ultrasound greatly improves our access to the pathology of these incidentalomas. Endoscopic Ultrasound (EUS) has rapidly evolved from a solely diagnostic tool to a more therapeutic one. With the use of fine needle aspirate (FNA), EUS is increasingly able to make meaningful contributions to clinical management. In Nonoperative treatments such as ethanol lavage and cyst ablation are currently under review.

While EUS alone may allow descriptive evaluation of a cyst such as presence of septations or mural nodules, the addition of FNA allows for aspiration of cyst fluid and determination of important information such as cytology, chemistries such as amylase and CEA, and mucin stain. The Cooperative Pancreatic Cyst study demonstrated



Courtesy of DAVE Project. EUS-FNA of mucinous cystic lesion. The needle is visible within the cyst, as is mucoid material within the cyst (indicated by the white arrow).

that a CEA level of 192 ng/mL was the most accurate cutoff for differentiation between mucinous lesions and nonmucinous cysts. In a more recent study, k-ras and loss of heterozygosity appeared to be predictive of malignant mucinous cysts. Such analysis of pancreatic cyst fluid is instrumental in clarifying which cysts have malignant potential. In this way, physicians and their patients can achieve clarity about the risks and benefits of surveillance or surgical resection.

Decision Algorithm

Patients who are symptomatic from their pancreatic cyst should be referred to a pancreatic surgeon for consideration for surgical resection. In those who are asymptomatic and in whom the diagnosis remains unclear, an endoscopic ultrasound with fine needle aspirate should be performed. Because many cystic neoplasms may be indolent, the decision to operate should be based on a combination of patient’s comorbidities, life expectancy, and malignant potential of the cyst. While many pancreatic cysts can be observed and do not warrant surgical resection, it is important to identify those lesions with malignant potential and to survey them. In some, patient preference may also be a factor; to some patients, a definitive surgical resection may well be preferable to the uncertainty and possibility of decades of surveillance.

Pancreatic cysts continue to challenge many physicians. Although current tools such as EUS-FNA have good accuracy in clarifying cyst pathology, further study is needed to define its optimal management. Study of molecular markers remains a topic of active investigation.