Utility of Intestinal Ultrasound as a Diagnostic Tool for the Evaluation of Pouchitis and Other Outcomes After Ileal Pouch-Anal Anastomosis: A Prospective Pilot Study

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IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

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Study Title: Utility of Intestinal Ultrasound as a Diagnostic Tool for the Evaluation of Pouchitis and Other Outcomes After Ileal Pouch-Anal Anastomosis: A Prospective Pilot Study

Protocol version number and date: Version three and date June 1, 2024

Research Question and Aims

Background: (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.)

Intestinal ultrasound (IUS) has been studied in the evaluation of inflammatory bowel disease (IBD) and is increasingly used as a non-invasive, easy to use, cost-effective tool for point-of-care to assess disease activity and more recently to predict response to treatment.[1-4] However, there is a paucity of data on the use of IUS specifically for ulcerative colitis (UC) patients with an ileal pouch-anal anastomosis (IPAA). Pouchitis is a common complication occurring in up to 60% of patients.[5] The use of IUS for assessing inflammation of the ileoanal pouch, the pre-pouch ileum, and the cuff is not well known. In addition, the accuracy of IUS for diagnosing pouchitis and other pouch outcomes (Crohn's like disease of the pouch) is not well-studied. IUS

may be a valuable diagnostic modality to distinguish pouchitis from non-inflammatory disorders of the pouch (e.g., irritable pouch syndrome).

Aims, purpose, or objectives:

1) Establish normal sonographic parameters in patients with an IPAA and normal pouch function.
2) Evaluate the feasibility of IUS for diagnosing pouchitis and other outcomes and compare its performance with the current gold standard of pouchoscopy with biopsies.
3) Evaluate patient satisfaction with intestinal ultrasound (through survey methodology).
4) Investigate the cost-effectiveness of IUS compared to pouchoscopy for diagnosing pouchitis and other pouch disorders.

Hypothesis: Intestinal ultrasound in ulcerative colitis (UC) patients will have a high accuracy for diagnosing pouchitis and other pouch outcomes in those with an ileal pouch-anal anastomosis (IPAA)

Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol.*

Adults (age ≥ 18 years) with UC who have undergone IPAA (completed all stages) will be consecutively enrolled March 1st, 2024 - March 1st, 2025, from the outpatient IBD and colorectal surgery clinics at Mayo Clinic in Rochester, MN. Participants will be recruited via phone or electronically through the portal. Pediatric patients, pregnant patients, those with a history of indeterminate colitis, and any patients who underwent IPAA for familial adenomatous polyposis will be excluded. Additionally, patients with inability to provide informed consent will be excluded. The first nine subjects enrolled in the study will not be assigned to one of the groups (normal pouch endoscopy or pouchitis) . Since this is the first time ultrasound is being used to scan patients with an IPAA, the first nine subjects enrolled will be to confirm the ultrasound standard operating procedure collects the information that will be needed. In aim one, 50 patients will be recruited to serve as controls (normal pouch endoscopy) and aim two will include 50 patients with endoscopic evidence of pouchitis. Transabdominal and transperineal ultrasounds of the pouch will be performed by an experienced sonographer for each patient and interpreted by a board-certified radiologist specializing in IUS. The IUS will be performed within 7 days before/after endoscopic evaluation of the pouch and before starting treatment (determined by clinician). Except for the first nine subjects enrolled, these subjects will only need to have a confirmed IPAA. The sonographers and radiologist will be blinded to the patients' clinical history and endoscopic findings. Patients will additionally be sent a brief questionnaire evaluating their experience with IUS compared to conventional evaluation with pouchoscopy. The questionnaire may be completed in-person or via regular mail (paper), or electronically via REDCap.

Documentation of informed consent will involve the use of the Remote Electronic Consent technology. The subject may print or electronically save the form through the Mayo Clinic-designated electronic consent technology or from their patient portal or the subject may contact the study team to provide a copy of the form. Note: If the subject or their representative or parent/guardian prefers not to use the Electronic Consent technology, the study team will provide a paper consent form for signature.

Pouchitis diagnosis will be determined based on a combined assessment of patient symptoms, endoscopy/histology showing acute/chronic inflammation, and exclusion of alternate etiologies (infection). Crohn's-like disease of the pouch will be determined based on the presence of inflammation involving the pre-pouch ileum, strictures (involving pouch, afferent limb, or small bowel), and/or fistulizing disease. IUS parameters will be collected on i) quality of view (good, partial, or poor), ii) pouch wall thickness (mm), iii) sonographic features of inflammation in pre-pouch ileum, pouch, and cuff, iv) hyperemia using color doppler signal, v) presence of lymphadenopathy and vi) presence of mesenteric fat,.[6-8] Area under the curve (AUC) for receiver operating characteristic (ROC) analysis will assess the diagnostic performance of both transabdominal and transperineal IUS.

Pouchitis will be defined *a priori* based on 1) duration (acute versus chronic), 2) disease pattern (infrequent, relapsing), and 3) response to antibiotics (responsive, dependent, and refractory). Acute pouchitis will be defined by symptom duration ≤ 4 weeks and chronic as > 4 weeks. Infrequent pouchitis will be defined as < 3 episodes annually, relapsing pouchitis in those with ≥ 3 episodes annually (or recurrence of pouchitis within 3 months of discontinuing effective therapy). Antibiotic-dependent patients will be defined as those necessitating ongoing antibiotic therapy for disease remission, whereas antibiotic refractory patients are those not responding to ≥ 4 weeks of antibiotic treatment.

Minimal Risk:

Patients will only come for a one-time intestinal ultrasound visit and will complete a survey questionnaire afterwards. Subjects will receive the option of,, a one-day parking pass to help cover the cost of parking the day, or a meal card to the Mayo Clinic patient cafeteria, both of equal value.. There will be no additional patient contact and the appropriate treatment plan for pouchitis or other conditions of the pouch will be determined by the clinic provider and patient. The IUS results will not be clinically used by providers for diagnosis or management and will only be utilized for research study purposes exclusively. There will be minimal risk to patients (ultrasound imaging procedure) with no collection of biospecimens (blood draws/ tissue samples). The ultrasound images will be stored in the patient's medical record.

References:

1. Maaser C, Petersen F, Helwig U, et al. Intestinal Ultrasound for Monitoring Therapeutic Response in Patients with Ulcerative Colitis: Results from the TRUST&UC Study. Gut. 2020;69(9):1629-36.

2. De Voogd F, van Wassenaer EA, Mookhoek A, et al. Intestinal Ultrasound is Accurate to Determine Endoscopic Response and Remission in patients with Moderate to Severe Ulcerative Colitis: A Longitudinal Prospective Cohort Study. Gastroenterology. 2022;163(6):1569-81.

3. Ilvemark JFKF, Hansen T, Goodsall TM, et al. Defining Transabdominal Intestinal Ultrasound Treatment Response and Remission in Inflammatory Bowel Disease: Systematic Review and Expert Consensus Statement. J Crohns Colitis. 2022;16(4):554-580.

4. Kucharzik T, Wittig BM, Helwig U, et al; TRUST Study Group. Use of Intestinal Ultrasound to Monitor Crohn's Disease Activity. Clin Gastroenterol Hepatol. 2017;15(4):535-542.e2.

5. Barnes EL, Allin KH, Iversen AT, et al. Increasing Incidence of Pouchitis Between 1996 and 2018: A Population-Based Danish Cohort Study. Clin Gastroenterol Hepatol. 2023;21(1):192-199.e7.

6. Maaser C, Sturm A, Vavricka SR, et al; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019;13(2):144-164.

7. Calabrese E, Maaser C, Zorzi F, et al. Bowel Ultrasonography in the Management of Crohn's Disease. A Review with Recommendations of an International Panel of Experts. Inflamm Bowel Dis. 2016;22(5):1168-83.

8. Bryant RV, Friedman AB, Wright EK, et al. Gastrointestinal Ultrasound in Inflammatory Bowel Disease: An Underused Resource with Potential Paradigm-Changing Application. Gut. 2018;67(5):973-985.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 109 patients with UC who underwent IPAA surgery (completion of all stages). Single-center prospective pilot study in Rochester, MN at Mayo Clinic.

Subject population (children, adults, groups): Adults (age ≥ 18 years) with UC who have undergone IPAA will be consecutively enrolled March 1st, 2024- July 1st, 2025, from the outpatient IBD and colorectal surgery clinics at Mayo Clinic in Rochester, MN.

Inclusion Criteria:
Adult patients (≥ 18 years of age)
Ulcerative colitis diagnosis (confirmed on endoscopy/histology)
Underwent ileal pouch-anal anastomosis (IPAA) surgery (completed all stages)

Exclusion Criteria:
Pediatric patients (< 18 years of age)
Indeterminate colitis
Patients with familial adenomatous polyposis (FAP)
Pregnant
Unable to provide informed consent (dementia, cognitive abilities)
BMI >30 kg/m^2 (will impact ability to perform intestinal ultrasound)

Patients with decompensated cirrhosis (Patients with Primary Sclerosing Cholangitis (PSC) without decompensated cirrhosis may be enrolled)
Patients taking NSAIDS >3 times a week
<12 months from completion of the IPAA

Biospecimens

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____N/A_____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) ___N/A_____

Prospective collection of biological specimens other than blood: _____N/A_____

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

X The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____N/A_____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement: Not applicable; this is a pilot study

Data Analysis Plan:

Continuous variables will be reported as means with standard deviation (SD) and categorical variables as frequency (percentages) or median (range). Univariate regression followed by multivariable regression will be used to identify sonographic parameters that are predictive of a diagnosis of pouchitis and other pouch outcomes. The AUROC (Area Under the Receiver Operating Characteristic curve) will be calculated and summarized using a point-estimate and corresponding 95% confidence interval. ACUROC will be used to determine the diagnostic performance of intestinal ultrasound in UC patients with an IPAA. All tests will be considered statistically significant at $p \leq 0.05$. Lastly, cost effectiveness analysis will be performed to compare intestinal ultrasound vs. pouchoscopy for diagnosing pouchitis and other pouch disorders (based on CPT and APC codes estimating financial costs of respective interventions).

Endpoints
Primary:

- Ultrasound parameters (e.g., bowel wall thickness, vascularity) in patients with normal pouch function [Aim 1]
- Accuracy of IUS for diagnosing pouchitis and other pouch disorders compared to conventional evaluation (pouchoscopy/biopsies) [Aim 2]

Secondary:

- Patient satisfaction with IUS (assessed via survey questionnaire) [Aim 3]
- Cost-effectiveness of IUS compared to pouchoscopy for diagnosing pouchitis and other pouch disorders [Aim 4]