Study Title: Multicenter Analysis of Pouchitis Classification, Diagnosis, and Treatment Outcomes in Italian Patients with Ileal Pouch-Anal Anastomosis for Inflammatory Bowel Disease: An IG- IBD Initiative

Study Acronym: POUCH-CARE – ***Pouchitis Classification, Assessment, Response, and Evaluation in Patients with Inflammatory Bowel Disease***

Protocol version: 1.0 **Date: 10.02.25**

Sponsor: Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

STUDY SYNOPSIS

Study Title	Multicenter Analysis of Pouchitis Classification, Diagnosis, and Treatment Outcomes in Italian Patients with Ileal Pouch-Anal Anastomosis for Inflammatory Bowel Disease: An IG- IBD Initiative
Sponsor	Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)
Principal Investigator	Dr. Luisa Bertin Prof. Edoardo Vincenzo Savarino Prof. Paolo Gionchetti
Protocol Version and Date	Protocol Version: 1.0 Date: 10.02.25
Background and rationale	Pouchitis is the most common long-term complication following ileal pouch-anal anastomosis (IPAA) in ulcerative colitis (UC) patients, significantly affecting quality of life. Despite recent advances, there remains a lack of standardized classification, diagnostic criteria, and treatment protocols. This study aims to analyze pouchitis subtypes, evaluate diagnostic accuracy, and assess treatment outcomes in an Italian cohort.
Study objectives	Primary Objective: • To systematically classify pouchitis subtypes (acute, chronic, antibiotic-responsive, refractory) in post-IPAA patients with IBD and evaluate their clinical characteristics. Secondary Objectives: • Identify clinical, demographic, and microbiological factors associated with refractory and recurrent pouchitis. • Evaluate treatment outcomes, including remission rates and recurrence, based on individualized therapeutic regimens over 12 months. • Assess postoperative complications, including pouch failure, and their correlation with pouchitis subtypes and treatment approaches.
Study design	• **Type:** Observational, retrospective, multicenter cohort study • **Setting:** Multiple Italian IBD centers affiliated with IG-IBD • **Time Frame:** Data collection spanning 1995-2022 • **Sample Size:** A representative cohort of patients who underwent IPAA for IBD

Study popolation	Adults patients (≥18 years) who underwent IPAA surgery for IBD from 1995-2022; confirmed pouchitis diagnosis based on International Ileal Pouch Consortium (IIPC) criteria; minimum 12-month post-diagnosis follow-up
Methodology	1. Data Collection & Screening (Months 1-6): Retrospective chart review of patient demographics, clinical history, surgical details, pouchitis classification, treatments, and outcomes. 2. Data Analysis (Months 7-12): 3. Dissemination of Findings (Months 12-18):
Statistical plan	Descriptive Analysis: Mean, standard deviation, median for baseline characteristics; Comparative Analysis through Chi-square/Fisher's exact test for categorical data and T-tests/Mann-Whitney U test for continuous data. Multivariate Logistic Regression: Identify factors influencing refractory pouchitis and recurrence ($p<0.05$ significance level).Risk Factor Analysis will assess how demographic, surgical, and clinical factors influence complications. Software: IBM SPSS Statistics, Version 29
Ethical considerations	Compliance: Study will adhere to the Declaration of Helsinki, ICH-GCP guidelines, and national regulatory requirements. Ethical Review: Protocol will be approved by an Independent Ethics Committee (IEC). Confidentiality: All patient data anonymized and stored securely, in accordance with GDPR regulations.
Stusdy timeline	Project Start Date: 20.03.2025 Completion of Patient Enrollment: Month 6 Data Collection Completion: Month 12 Data Analysis: Month 12-18 Presentation of Scientific Report: Month 18+

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Authorizations and Signatures

AGREEMENT

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This document, however, can be made known to the designated Ethics Committee, or representatives authorized by the Investigator or the Health Authority provided that they are bound to its confidentiality.

The Principal Investigator's signature below confirms his agreement to this protocol and provides the necessary guarantees that:

1.This study will be conducted following all the clauses of the protocol and in accordance with the Helsinki declaration (Edinburgh 2000 with Explanatory note paragraph 29 from Washington 2002 and paragraph 30 from Tokyo 2004) and current legislation regarding clinical studies.

2. No partial or final data (written or verbal) will be published without prior agreement between the Investigator and the IgIBD

PRINCIPAL INVESTIGATOR SIGNATURE

Printed name:

Institution:

Signature _____ Date

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Institution:

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Institution:

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TITLE: Multicenter Analysis of Pouchitis Classification, Diagnosis, and Treatment Outcomes in Italian Patients with Ileal Pouch-Anal Anastomosis for Inflammatory Bowel Disease: An IG- IBD Initiative

Abstract

Pouchitis is the most frequent long-term complication post-ileal pouch-anal anastomosis (IPAA) in patients with ulcerative colitis (UC), presenting a range of clinical features and responses to therapy. This multicenter study, conducted by the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD), aims to classify pouchitis subtypes, evaluate diagnostic approaches, and analyze treatment outcomes in Italian UC patients post-IPAA. By including multiple Italian IBD centers, this cohort study examines the prevalence and classification of acute, chronic, antibiotic-responsive, and refractory pouchitis. Clinical data will document outcomes, diagnostic timelines, and responses to standard therapies including antibiotics, corticosteroids, immunomodulators, and biologics. Advanced imaging, endoscopy, and histology will also be evaluated for their diagnostic value in distinguishing pouchitis from similar pouch conditions. The study aims to identify factors linked to refractory cases and assess long-term outcomes. The findings will enhance the clinical framework for pouchitis management, contributing to personalized treatment protocols in inflammatory bowel disease.

Background and Scientific Rationale

Despite advancements in medical therapy, colectomy remains necessary for patients with medically refractory ulcerative colitis (UC), poor medication tolerance, or colitis-associated neoplasia, affecting approximately 20% of patients [1–3]. The standard surgical procedure is restorative proctocolectomy (RPC), which involves a total proctocolectomy with ileal pouch-anal anastomosis (IPAA). This procedure is also utilized for familial adenomatous polyposis and, occasionally, for Crohn's Disease (CD), either intentionally or inadvertently [4]. IPAA is preferred among surgical options because it preserves the natural route of defecation and avoids a permanent stoma, significantly improving patients' health-related quality of life [4].

This reconstructive surgery can lead to various short- and long-term complications, classified into structural, inflammatory, or functional disorders of the pouch, as well as neoplasia [6]. Factors such as the underlying disease, surgical aspects, and anatomical changes contribute to these adverse effects [7]. A significant post-surgical issue is pouch failure which can result from such

complications [8].

Pouchitis is the most common inflammatory and long-term complication following pouch surgery for UC [9]. It is defined as a non-specific inflammation of the ileal reservoir. The cause of acute pouchitis is likely influenced in part by the gut microbiota. In contrast, the development of chronic pouchitis involves complex interactions among genetic predisposition, fecal stasis, the gut microbiota, dysregulated host immunity, surgical techniques, ischemia, and mesentery-related factors [10]. Pouchitis can be classified as idiopathic (primary) or secondary [11]. It affects approximately 48% of patients within the first two years post-surgery, and up to 80% experience symptoms at some point after the procedure [5,9,12–17]. Diagnosis of pouchitis is based on a combination of clinical symptoms and endoscopic findings [26]. Histology can further support the diagnosis by identifying inflammation in the pouch body. Fecal markers, such as fecal calprotectin, can be used as adjunct measures to further quantify pouch inflammation.

Multiple strategies are used in the treatment and prevention of pouchitis, including antibiotics, probiotics, corticosteroids, biologic therapy and oral small molecule drugs with the primary goal of clinical remission. Significant advances are being made in the field, such as the development of scoring systems to better characterize patient-reported outcomes and endoscopic findings [27–29] other than the Pouchitis Disease Activity Index (PDAI) [30,31].

Pouchitis can be classified clinically into acute or chronic, with an arbitrary cutoff of 4 weeks based on the duration of persistent symptoms despite therapy. It can also be considered chronic if there are more than 3-4 acute episodes per 12 months. Chronic pouchitis rates are lower, affecting about 17% of the population [32,33].

Pouchitis can also be classified into antibiotic-responsive, antibiotic-dependent, or antibiotic-refractory phenotypes based on the response to commonly used antibiotics. Chronic antibiotic therapy is recommended for recurrent pouchitis that relapses shortly after stopping antibiotics, known as chronic antibiotic-dependent pouchitis (CADP). Advanced immunosuppressive therapies, like biologics, may be used for chronic antibiotic-refractory pouchitis (CARP) [34]. The recent randomized controlled trial (RCT) comparing vedolizumab with placebo in the treatment of patients with CARP (EARNEST trial) led to the approval of vedolizumab with this indication [35].

Crohn's disease of the pouch (CDP) or Crohn's-like inflammation of the pouch (CDLPI) can develop post-IPAA, affecting approximately 10% of patients [32,33]. Although CDP and CDLPI have been used interchangeably, there is a distinction. When Crohn's colitis is the pre-colectomy diagnosis, the condition in the pouch is considered true CDP. Conversely, if the preoperative or

perioperative diagnosis was UC or indeterminate colitis, and CD is identified later, this condition is described as CDLPI.

Current literature, including findings from the RESERVO study, points to varying therapeutic needs across inflammatory pouch disorders [36,37]. A lack of standardization in classification and management protocols continues to challenge optimal patient outcomes. This study will examine and classify pouchitis subtypes, such as acute, chronic, recurrent, antibiotic-dependent, and refractory, and compare them with CDP and cuffitis in terms of long-term therapeutic needs, advancing the goal of more refined and individualized management strategies for patients with inflammatory pouch disorders.

Objectives and Hypotheses

Primary Objective

1. To systematically classify and characterize subtypes of pouchitis (acute, chronic, antibiotic-responsive, and refractory) in IBD following IPAA, with an emphasis on understanding the clinical presentation and progression of each subtype.

Secondary Objectives

1. To identify clinical, demographic, and microbiological factors associated with refractory and recurrent pouchitis, utilizing multivariate analysis to determine their impact on treatment outcomes.
2. To monitor treatment outcomes, including rates of symptom remission and recurrence, in patients with pouchitis, specifically focusing on the effectiveness of individualized treatment regimens over a defined follow-up period of 12 months.
3. To compile and analyse detailed postoperative complication data, including the incidence of pouch failure, and examine their correlation with specific pouchitis subtypes and treatment approaches, thereby informing risk stratification and management strategies for affected patients.

Hypotheses

- Distinct pouchitis subtypes exist with varied treatment outcomes.

- Antibiotics effectively treat acute cases, while chronic/refractory cases respond better to advanced therapies.
- Longitudinal monitoring of treatment responses will reveal trends in pouchitis management and highlight effective strategies for improving patient quality of life.
- Comprehensive data collection on complications will provide insights into the long-term risks associated with pouch surgeries and their management.

Methodology

Study Design

This is an observational, retrospective, and multicenter cohort study conducted across multiple Italian centers associated with IG-IBD. Data collection will focus on IBD patients aged 18+ who underwent IPAA between 1995 and 2022. Surgery related details will be collected including: Year of surgery; Type of procedure performed; High-volume vs. low-volume center classification (centers with ≥10 cases per year vs <10 cases per year); Number of surgical stages; Reported surgical complications. Patients with confirmed pouchitis based on International Ileal Pouch Consortium guidelines (IIPC) will be eligible [26]. Those with in-situ defunctioning or insufficient follow-up (<12 months post-pouchitis diagnosis) will be excluded.

Patient Population

Inclusion criteria:

- Patients aged ≥18 years with IPAA surgery for IBD from 1995 to 2022.
- Confirmed diagnosis of pouchitis, defined as inflammation of the ileal pouch confirmed by clinical symptoms, endoscopic findings (e.g., erythema, ulceration), and histological evidence of inflammation, excluding other conditions like cuffitis or Crohn's disease of the pouch (per IIPC criteria).
- Minimum follow-up of 12 months.

Exclusion criteria:

- Other pouch procedures (e.g., Kock pouch).
- No inflammatory pouch disorder or insufficient follow-up.

Study Phases and Timelines

1. Data Collection and Screening (Months 1-6):

- Retrospective data extraction from medical records, covering patient demographics, clinical history, surgical outcomes and complications, pouchitis classification, treatment regimens, and adverse events. Data regarding clinical, endoscopic, histological data will be collected after induction and after 1 year of each treatment. Data regarding adverse events will be collected as well.

2. Data Analysis (Months 7-12):

- Classification of pouchitis (acute, chronic, antibiotic-dependent, refractory), assessment of diagnostic tools, and treatment efficacy.

3. Dissemination of Findings (Months 12-18):

- Preparation of a report with actionable insights and recommendations for publication.

Diagnostic and Classification Criteria

Pouchitis cases will be classified according to IIPC criteria:

- **Duration:** Acute (<4 weeks) vs. Chronic (>4 weeks).
- **Recurrence:** Recurrent (>3 episodes/year) vs. episodic.
- **Antibiotic Response:** Responsive, antibiotic-dependent, and refractory types.

Treatment Evaluation

Therapies analysed will include antibiotics, probiotics, mesalamine, corticosteroids, immunosuppressants (e.g., thiopurines), and biologics (e.g., infliximab, vedolizumab) and small molecules (e.g. tofacitinib, upadacitinib). Treatment outcomes, adverse events, and therapy duration will be recorded, along with endoscopic and surgical interventions where applicable.

Statistical Analysis Plan

Descriptive statistics (mean, standard deviation, median) will be used for patient characteristics and baseline disease features. Comparative analysis will assess demographic, diagnostic, and

therapeutic variables across pouchitis subtypes. Statistical tests:

- **Chi-square/Fisher's exact test** for categorical data.
- **T-tests/Mann-Whitney U test** for continuous variables.
- **Multivariate logistic regression** for factors associated with refractory and recurrent pouchitis (significance level set at $p < 0.05$).
- **Risk Factor Analysis**: A comprehensive analysis of potential risk factors associated with complications will be performed. Factors such as age, sex, comorbidities, previous surgeries, and specific surgical techniques will be considered to identify patterns that may predispose patients to complications.

Data analysis will utilize IBM SPSS Statistics, version 29.

Significance of the Study

This study will provide critical insights into the management of pouchitis in Italian IBD patients post-IPAA, filling a gap in literature specific to the Italian patient population. Improved understanding of pouchitis subtypes, diagnostic criteria, and treatment responses will lead to optimized clinical management, reducing disease burden and enhancing patient quality of life. By focusing on antibiotic-refractory and chronic cases, we aim to guide therapy decisions for patients requiring advanced treatment approaches, such as biologics and surgical options.

The multicenter approach, aligned with previous GETECCU findings, strengthens the study's generalizability and potential impact on international guidelines for pouchitis care. By integrating insights on diagnostic and therapeutic variability, this research will also aid in defining optimal management protocols, ultimately contributing to advancements in the management of IBD and its complications.

Potential Challenges and Mitigation Strategies

1. **Data Completeness and Standardization:**
    - Use standardized forms for data collection across centers.
    - Regular monitoring and quality checks on data entries.

2. **Heterogeneity in Diagnostic and Treatment Protocols:**
    - Stratify analysis based on centre-specific protocols.
    - Adjust for variability in statistical modelling.
3. **Patient Retention and Longitudinal Follow-up:**
    - Establish minimum follow-up requirements for all included patients.
    - Engage centres to ensure retention of patients until data collection completion.

REGULATORY AND ETHICAL CONSIDERATIONS

Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country.

The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice. The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

Subject identification – Personal Data protection

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. The PI, the co-investigators and the personnel involved in the trial will comply with the GCP principles about storage, elaboration and divulgation of sensitive data.

Patient names will be kept confidential. Only the patient number and initials will be recorded in theeCRF (IGIBD RedCap). Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the sponsor, IEC or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the trial are published, the patient's identity will remain confidential. The investigators will maintain a list to enable patients' records to be identified. Data storage will be under the responsibility of the PI.

Informed consent

All patients will be informed of the aims of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Data Center. This will be done in accordance with the national and local regulatory requirements.

The informed consent procedure will conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

DATA OWNERSHIP

According to the ICH Guidelines on Good Clinical Practice the Sponsor of this study will be the owner of the data resulting therefrom. All centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Institution's prior express consent.

PUBLICATION POLICY

After completion of the study, the project coordinator will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be derived to the co-authors for comments and after revision will be sent to a major scientific journal.

All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by the Principal Investigator and the Sponsor for coordination and homogeneity purposes.

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