



Development of pouchitis following ileal pouch-anal anastomosis (IPAA) for ulcerative colitis: A role for serological markers and microbial pattern recognition receptor genes [☆]

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KEYWORDS

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Abstract

Background and Aims: Pouchitis, the most common complication after proctocolectomy with ileal pouch-anal anastomosis (IPAA) for ulcerative colitis, has been attributed to altered composition of faecal flora. We investigated the role of antimicrobial and antiglycan antibodies and polymorphisms in microbial pattern recognition receptor genes.

Methods: Clinical charts of all 184 patients with ulcerative colitis who underwent IPAA between 1990–2004 were reviewed for pre- and post-operative disease course.

Results: Follow-up data were available in 172 patients [67 female, median age at proctocolectomy 39.1 years]. During a median follow-up of 6.7 (interquartile range 3.7–10.5) years, 80 patients (47%) developed at least one episode of pouchitis. Cox proportional-hazard regression identified extra-intestinal manifestations [HR 1.78 (95%CI 1.10–2.88), $p=0.020$], a

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Abbreviations: ACCA, anti-chitobioside antibodies; ALCA, anti-laminaribioside antibodies; AMCA, anti-mannobioside antibodies; CARD15, caspase recruitment domain 15; CD, Crohn's disease; CD14, cluster of differentiation 14; EIM, extra-intestinal manifestations; EU, Elisa units; gASCA, glycominds anti-*Saccharomyces cerevisiae* antibodies; HLA-B27, human leucocyte antigen B27; HR, hazard ratio; IBDU, inflammatory bowel disease type unclassified; IC, indeterminate colitis; IIF, indirect immunofluorescence; IL-1RA, interleukin-1 receptor antagonist; IPAA, ileal pouch-anal anastomosis; IQR, interquartile range; Omp, outer-membrane porin; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; SNP, single nucleotide polymorphism; TLR, toll-like receptor; TNF, tumor necrosis factor; UC, ulcerative colitis; 95%CI, 95% confidence interval.

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GT/TT genotype at Toll-like-receptor-1 S87I [HR 1.64 (1.01–2.66), $p=0.047$], anti-chitobioside carbohydrate antibodies [HR 2.03 (1.11–3.70), $p=0.021$] and young age at diagnosis [$p=0.003$] to be independently associated with pouchitis. Factors associated with chronic pouchitis, diagnosed in 33 patients (19%), were extra-intestinal manifestations [HR 2.45 (1.07–5.62), $p=0.034$], backwash ileitis [HR 3.15 (1.10–9.00), $p=0.032$], outer-membrane porin antibodies [HR 2.67 (1.20–5.94), $p=0.016$] and young age at proctocolectomy [$p=0.008$].

Conclusions: The reported association with antibodies and Toll-like-receptor-1 supports the pathophysiological role of the faecal flora in the development of pouchitis.

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1. Introduction

Up to 30% of patients suffering from ulcerative colitis (UC) will ultimately need to undergo a total colectomy.¹ The most frequent indications for colectomy include intractable disease and the occurrence of dysplasia or cancer in case of long-standing colitis. A total proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become the surgery of choice for the "definitive" management of UC, since it avoids a permanent stoma while removing all diseased colonic mucosa.²

Although the mortality rate after IPAA is acceptable (less than 1%)^{2,3}, short term morbidity is seen in approximately 30% of patients, including post-operative bleeding, pouch leakage, pelvic abscess and fistula.^{2–5} On the long term, patients with a pouch can also be troubled by small bowel obstruction, faecal incontinence, sexual dysfunction and infertility.^{2–8} Pouch failure is seen in approximately 5% of patients.^{2,3,9}

The most frequent long-term complication is the occurrence of pouchitis¹⁰, with cumulative incidence rates varying significantly between studies (7 to 59%). Besides differences in length and type of follow-up, an important reason for this variation is a lack of universally accepted diagnostic criteria for pouchitis.¹¹ From a clinical perspective, different types of pouchitis exist.¹² Patients can present with one single episode of acute pouchitis, while others have acute relapsing pouchitis or a chronic unremitting course. In our own experience, 25% of patients developed pouchitis (proven by endoscopy and histology) within the first year after closure of ileostomy.⁹ During a median follow-up of 6.5 years, 46% of patient developed pouchitis, and more than half of them suffered from acute relapsing on chronic pouchitis.⁹

The aetiology of pouchitis is not entirely understood. Bacterial overgrowth, altered balance of luminal bacteria, mucosal ischemia, nutritional deficiencies, lack of short-chain fatty acids and faecal bile acids toxicity have all been suggested as possible etiological factors.¹¹ Factors that support the role of the microbial flora, are the fact that pouchitis is only seen after restoration of the faecal stream and can be treated successfully by use of antibiotics.^{11,12}

Bearing in mind the high cumulative incidence rate of pouchitis, several investigators have tried to define predictive factors which could help in selecting these patients in need for more intensive post-operative follow-up or post-operative prophylaxis. Established risk factors are non-smoking^{13,14} and the presence of extra-intestinal manifestations, especially primary sclerosing cholangitis.^{9,14–17} Possible risk factors might be the extent of colitis and presence of backwash ileitis prior to surgery^{17,18}, a young age at diagnosis or surgery^{9,14}, dysplasia as indication for surgery¹³, pre-operative use of steroids¹⁹ and the regular

use of NSAIDs in the postoperative phase.^{13,17} More recently, an association was found between pouchitis and variations in the interleukin 1 receptor antagonist (IL-1RA) and tumor necrosis factor (TNF) genes.^{20,21} Finally, pre-operative pANCA levels seem to be higher in patients who develop chronic pouchitis compared to patients who do not.²²

The primary aim of our study was to look for factors associated with pouchitis in patients who underwent a restorative proctocolectomy with IPAA for ulcerative colitis or IBD type unclassified (IBDU). Given presumed role of bacteria as main trigger in the onset of pouchitis, we were especially interested in the role of antimicrobial and antiglycan antibodies and polymorphisms in microbial pattern recognition receptor genes.

2. Material and methods

2.1. Patients

All patients who underwent a proctocolectomy with IPAA for ulcerative colitis (UC) or IBD type unclassified (IBDU) at the University Hospital Gasthuisberg in Leuven (tertiary referral centre) between January 1990 and December 2004 were identified through the surgical database. A total of 184 consecutive patients [113 male/71 female; median (interquartile range, IQR) age at diagnosis 29.5 (23.8–38.8) years; median (IQR) age at proctocolectomy 39.0 (30.4–47.7) years] were identified. However, we were unable to trace 11 out of 184 patients (5%) who had moved house without leaving updated contact details. The ileostomy could be closed in all but one patient. This patient was excluded for further analysis.

Clinical charts of all remaining 172 patients were reviewed to trace clinical, endoscopical and histological characteristics, including gender, age at diagnosis, age at proctocolectomy, age at closure of ileostomy, duration of disease prior to proctocolectomy, duration of follow-up after closure of ileostomy, diagnosis prior to proctocolectomy, diagnosis after proctocolectomy, familial history, extra-intestinal manifestations, smoking behaviour, therapy at proctocolectomy, extent of disease prior to proctocolectomy, presence of back-wash ileitis. Surgical characteristics included type of surgery (laparoscopic vs. laparotomy), type of anastomosis (stapled without mucosectomy vs. handsewn with mucosectomy), type of pouch (J-pouch or S-pouch), number of stages (1-, 2- or 3-stage surgery), construction of the pouch at time of proctocolectomy. The main clinical and surgical characteristics are enlisted in [Table 1](#).

The clinical charts were also reviewed to trace the occurrence of first pouchitis and the occurrence of chronic

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