How to deal with pouchitis
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How to deal with pouchitis

Disclosures

• Marc Ferrante
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How to deal with pouchitis

Introduction

• Do you follow patients with ulcerative colitis?
• Do you have patients with ulcerative colitis who are refractory to multiple therapies?
• Do you have patients with ulcerative colitis who develop dysplasia or cancer?
• Do you have patients with ulcerative colitis who underwent a colectomy?
• Do you have patients with an ileal-pouch anal anastomosis?
How to deal with pouchitis

Overview

• What is pouchitis?
• How frequent is pouchitis?
• What is the cause of pouchitis?
• Can we treat (chronic) pouchitis?
• Can we prevent (recurrent) pouchitis?
How to deal with pouchitis
What is pouchitis?

- Proctocolectomy with ileal pouch anal anastomosis (IPAA) is the procedure of choice for most patients with ulcerative colitis (UC) requiring colectomy.
How to deal with pouchitis
What is pouchitis?

• Proctocolectomy with ileal pouch anal anastomosis (IPAA) is the procedure of choice for most patients with ulcerative colitis (UC) requiring colectomy.
• Pouchitis is a non-specific inflammation of the ileal reservoir and is the most common complication after IPAA for UC.

Magro F, J Crohn’s Colitis 2017
How to deal with pouchitis
What is pouchitis?

• Normal pouch function:
  – 6-8 bowel movements per 24 hours
  – 1-2 bowel movements per night (50% of patients)
  – Loose or semi-formed stools
  – Able to defer for at least half an hour
  – Occasional seepage at night
  
  – Pouch function stabilizes 1 year after surgery
How to deal with pouchitis
What is pouchitis?

• Symptoms of pouchitis:
  – Increased stool frequency and liquidity
  – Abdominal cramping pain
  – Urgency and incontinence
  – Tenesmus
  – Pelvic discomfort
  – Less frequent: rectal bleeding, fever, extra-intestinal manifestations

  – But diagnosis should be confirmed through endoscopy +/- biopsies
    • Differential diagnosis: cuffitis, irritable pouch syndrome, Crohn’s disease of the pouch, small pouch, pouch inlet/outlet obstruction, functional outlet obstruction, pelvic collection, sphincter defect, ...
How to deal with pouchitis
What is pouchitis?

• Endoscopic findings of pouchitis:
  – Diffuse or patchy erythema
  – Edema
  – Granularity
  – Friability
  – Spontaneous or contact bleeding
  – Loss of vascular pattern
  – Mucous exudates
  – Erosions and ulcerations

  – Progression into the afferent limb should always be attempted
  – Biopsies should be taken from pouch and from the afferent limb but not along the staple or suture lines
How to deal with pouchitis
What is pouchitis?

- Pouchitis disease activity index (PDAI)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>Stool frequency</td>
<td></td>
</tr>
<tr>
<td>Usual postoperative stool frequency</td>
<td>0</td>
</tr>
<tr>
<td>1–2 stool/day &gt; postoperative usual</td>
<td>1</td>
</tr>
<tr>
<td>3 or more stool/day &gt; postoperative usual</td>
<td>2</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
</tr>
<tr>
<td>None or rare</td>
<td>0</td>
</tr>
<tr>
<td>Present daily</td>
<td>1</td>
</tr>
<tr>
<td>Faecal urgency or abdominal cramps</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Occasional</td>
<td>1</td>
</tr>
<tr>
<td>Usual</td>
<td>2</td>
</tr>
<tr>
<td>Fever (temperature &gt; 37.8 °C)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>

Active pouchitis: PDAI ≥7
mPDAI ≥5

Shen B, Dis Colon Rectum 2003
How to deal with pouchitis
What is pouchitis?

• Patterns of pouchitis
  – Based on the **duration of symptoms** into acute (≤ 4 weeks) versus chronic (> 4 weeks).
  – Based on **response to antibiotics** into antibiotic-responsive versus antibiotic-dependent (ie, requiring ongoing antibiotic therapy to keep disease in remission) versus antibiotic-refractory (ie, not responding to a standard course of antibiotic therapy).
  – Based on the **frequency of flares** into infrequent pouchitis (less than three episodes per year) versus relapsing pouchitis (three or more episodes per year).
  – Based on the **disease extent** into pouchitis versus pouchitis concurrent with prepouch ileitis/enteritis.
  – Based on the **etiology** into idiopathic versus secondary.
How to deal with pouchitis
How frequent is pouchitis?

• Reported frequency rates are highly variable, but mainly depend on the type and duration of follow-up.

IBD Leuven cohort 2008
172 UC IPAA patients
Median follow up: 6.5 years
Year 1: 25%
Year 2: 32%
Year 3: 36%
Year 4: 40%
Year 5: 45%

Note: 19% developed chronic refractory pouchitis

Magro F, J Crohn’s Colitis 2017
Ferrante M, Inflamm Bowel Dis 2008
How to deal with pouchitis
How frequent is pouchitis?

• Reported frequency rates are highly variable, but mainly depend on the type and duration of follow-up.

• Cumulative incidence of pouchitis seems to be much lower in patients with IPAA for familial adenomatous polyposis
  – Most reports in literature: 0 to 10%
  – Suggesting genetic/systemic factors

Magro F, *J Crohn’s Colitis* 2017
How to deal with pouchitis
What is the cause of pouchitis?

• Pathogenesis

Genetics

Gut microbiome

Mucosal immunity

More frequently in UC than in FAP
Association with polymorphisms in IL1R antagonist, NOD2/CARD15, TLR9, CD14, ...
Association with lower ABCB1 expression (xenobiotic efflux) suggesting a role of barrier dysfunction

Colonic metaplasia due to fecal stasis
Aberrant expression of Toll-like receptors
Increased production of antimicrobial peptides, such as human defensins
Increased proliferation of immature plasma cells
Production of pro-inflammatory mediators including TNF, cell adhesion molecules, ...

Magro F, J Crohn’s Colitis 2017
How to deal with pouchitis
What is the cause of pouchitis?

• Changes in gut microbiota
  – The construction of an IPAA promotes fecal stasis with bacterial overload and mucosal adaptive changes from small bowel mucosa to colon-like mucosa
  – A gradual shift from ileum- to colon-like bacterial community
  – Several species have been implicated in pouch inflammation including Lachnospiracea, *Incertae Sedis XIV*, Clostridiaceae spp, Bacteriodaceae spp, ...

How to deal with pouchitis
What is the cause of pouchitis?

• Predictive value of the pre-colectomy microbial composition

Machiels K, Gut 2017

Cumulative incidence of pouchitis

1 year follow-up + - pouchitis

m0 m1 m3 m6 m12

10% 21% 32% 42%

8/19 patients developed pouchitis within one year

Machiels K, Gut 2017
How to deal with pouchitis
What is the cause of pouchitis?

• Predictive value of the pre-colectomy microbial composition

Machiels K, Gut 2017
**How to deal with pouchitis**

**What is the cause of pouchitis?**

- Predictive value of the pre-colectomy microbial composition

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Pouchitis rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td>42.1</td>
<td>/</td>
<td>0 (0/3)</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>27.3</td>
<td>50</td>
<td>100</td>
<td>0 (0/4)</td>
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<tr>
<td>2</td>
<td>100</td>
<td>63.6</td>
<td>66.7</td>
<td>100</td>
<td>33.3 (2/6)</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>100</td>
<td>89.5</td>
<td>84.6</td>
<td>100 (1/1)</td>
</tr>
<tr>
<td>4</td>
<td>62.5</td>
<td>100</td>
<td>100</td>
<td>78.6</td>
<td>100 (3/3)</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>100</td>
<td>100</td>
<td>64.7</td>
<td>100 (2/2)</td>
</tr>
</tbody>
</table>

*The percentage of patients developing pouchitis after one-year of follow-up (number of patients showing pouchitis/total number of patients, for each risk score) NPV, negative predictive value; PPV, positive predictive value

Confirmed in an independent validation cohort

Machiels K, *Gut* 2017
How to deal with pouchitis
Can we treat pouchitis?

• Initial management of acute pouchitis
  – Ciprofloxacin 1 g/d for 2 weeks
  – Metronidazole 15-20 mg/kg/d for 2 weeks

ECCO statement 10B

The majority of patients respond to metronidazole or ciprofloxacin, although the optimum modality of treatment is not clearly defined [EL2]. Side effects are less frequent using ciprofloxacin [EL2]. Antidiarrhoeal drugs may reduce the number of daily liquid stools, independently of pouchitis [EL5]

Magro F, J Crohn’s Colitis 2017
How to deal with pouchitis
Can we treat pouchitis?

• Initial management of acute pouchitis
  – Ciprofloxacin 1 g/d for 2 weeks
  – Metronidazole 15-20 mg/kg/d for 2 weeks

  – A small study suggested equal efficacy for budesonide enema’s compared to oral metronidazole
  – In a small open label study, the highly concentrated probiotic preparation VSL#3 was shown to be effective for mildly active pouchitis
  – No significant benefit of rifaximin or Lactobacillus plantarum GG in comparison to placebo in small randomized trials
  – Even weaker evidence for tinidazole, amoxicillin-clavulanic acid, carbon microsphere agents, ...

Magro F, J Crohn’s Colitis 2017
How to deal with pouchitis
Can we treat pouchitis?

• Management of subsequent pouchitis
  – Ciprofloxacin 1 g/d for 2-4 weeks
  – Metronidazole 15-20 mg/kg/d for 2-4 weeks
  – Combination therapies
  – Longer maintenance therapies (e.g. ciprofloxacin 250-500 mg/d)
  – Suggested alternatives may be:
    • Rifaximin 1100mg daily (Targexan®, 11 Euro per day)
    • Tinidazole 1000mg daily (Fasigyn®, 4 Euro per day)
How to deal with pouchitis
Can we treat pouchitis?

• Chronic antibiotic refractory pouchitis
  – Evaluate and treat secondary causes
    • Discontinue nonsteroidal anti-inflammatory drugs
    • Systemic estrogen agents should be avoided
    • Concurrent pouch surgery-associated mechanical complications require multidisciplinary care
    • Treatment of infectious etiologies such as Clostridium difficile and CMV
    • Cuffitis: topical +/- oral 5ASA
How to deal with pouchitis
Can we treat pouchitis?

- Management of chronic antibiotic refractory pouchitis
  - Pick your drug...
    - Oral budesonide / beclomethasone dipropionate
    - Topical hydrocortisone or budesonide
  - Pick another drug...
    - Thiopurines (or methotrexate)
    - Biologics: anti-TNF agents, anti-adhesion molecules, anti-IL23/23 antibodies
    - Small molecules: tofacitinib
  - Limited evidence
    - Tacrolimus
    - Hyperbaric oxygen therapy
    - Apheresis
    - Fecal microbiota transplantation

Magro F, J Crohn’s Colitis 2017
How to deal with pouchitis
Can we treat pouchitis?

• Infliximab for chronic antibiotic refractory pouchitis (BIRD)

Ferrante M, Inflamm Bowel Dis 2010
How to deal with pouchitis
Can we treat pouchitis?

- Adalimumab for chronic antibiotic refractory pouchitis
  - Multicenter GETECCU study
  - 8 patients with chronic refractory pouchitis
  - All patients had been treated with infliximab
  - Start ADM induction with 160/80 mg

Barreiro-de Acosta M, *Eur J Gastroenterol Hepatol* 2012
How to deal with pouchitis
Can we treat pouchitis?

• Management of chronic antibiotic refractory pouchitis

Figure 2 | Results for antibiotics for chronic pouchitis.

Figure 3 | Results for biologics for chronic pouchitis.

Segal JP, Aliment Pharmacol Ther 2017
Antibiotic refractory pouchitis

60 patients with ulcerative colitis initiated biological therapy after colectomy

1 patient without baseline disease activity

13 patients with histological features of Crohn’s disease after revision of the colectomy specimen

3 patients with CD-related complications of the pouch

6 patients referred back to their treating gastroenterologist

4 patients included in randomized controlled trials for pouchitis

33 unique patients included

23 patients infliximab

13 patients adalimumab

15 patients vedolizumab

Proportion of patients in clinically relevant remission

Verstockt B, United European Gastroenterol J in press
Fecal microbiota transplantation for chronic antibiotic refractory pouchitis

- British pilot study including 8 patients
- Healthy donors included relatives, partners, unrelated donors
- One single nasogastric infusion of donor feces
- Variable shifts in fecal and mucosal microbiota composition and, in some patients, changes in proportional abundance of species suggestive of “healthier” pouch microbiota were observed
- After 4 weeks, none of the patients achieved clinical remission

Landy L, Sci Rep 2015
How to deal with pouchitis
Can we treat pouchitis?

• Fecal microbiota transplantation for chronic antibiotic refractory pouchitis
  – German pilot study including 5 patients
  – Two unrelated healthy donors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of FMT</th>
<th>PDAI</th>
<th>Calprotectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>1</td>
<td>10 → 5</td>
<td>566 → 47</td>
</tr>
<tr>
<td>Patient 2</td>
<td>3</td>
<td>12 → 2</td>
<td>479 → &lt;15</td>
</tr>
<tr>
<td>Patient 3</td>
<td>3</td>
<td>9 → 3</td>
<td>849 → 150</td>
</tr>
<tr>
<td>Patient 4</td>
<td>3</td>
<td>9 → 2</td>
<td>Not done</td>
</tr>
<tr>
<td>Patient 5</td>
<td>7</td>
<td>14 → 7</td>
<td>Not done</td>
</tr>
</tbody>
</table>

Stallmach A, Am J Gastroenterol 2016
How to deal with pouchitis
Can we prevent recurrent pouchitis?

• Treatment with the concentrated probiotic mixture VSL#3 may help to maintain remission
  – Per gram: 450 billion bacteria of eight different strains
  – But guidelines based on one single old and underpowered trial

Magro F, J Crohn’s Colitis 2017
Gionchetti, Gastroenterology 2003
How to deal with pouchitis
Can we prevent recurrent pouchitis?

• Treatment with the concentrated probiotic mixture VSL#3 may help to maintain remission
  – Per gram: 450 billion bacteria of eight different strains
  – But guidelines based on one single old and underpowered trial
  – VSL#3 available through Ferring
  – But is it still VSL#3?

• Anti-TNF therapies, vedolizumab (and ustekinumab) will probably be more efficacious therapies to prevent recurrent pouchitis

Magro F, J Crohn’s Colitis 2017
Gionchetti, Gastroenterology 2000
How to deal with pouchitis
And what if all medical therapies fail?

- Permanent ileostomy +/- pouchectomy

FIGURE 1. Kaplan–Meier curves showing the probability of pouch success with time following ileal pouch–anal anastomosis (IPAA) in patients with the eventual diagnosis of chronic ulcerative colitis (CUC), indeterminate colitis (IC) or Crohn’s disease.

Lightner AL, Inflamm Bowel Dis 2017
How to deal with pouchitis
Can we prevent pouchitis?

• VSL#3 vs. placebo
  – 20 patients in each arm

Figure 2. Kaplan–Meier estimates of cumulative rates of pouchitis during treatment with (A) VSL#3 or (B) placebo.

Magro F, J Crohn's Colitis 2017
Gionchetti, Gastroenterology 2003
How to deal with pouchitis
Can we prevent pouchitis?

• VSL#3 vs. placebo

• Limited evidence for
  – *Lactobacillus rhamnosus* GG
  – Tinidazole
  – Salazopyrine

Gosselink MP, *Dis Colon Rectum* 2004
Ha CY, *Digestive Disease Week* 2010
Scaioli E, *Dig Dis Sci* 2017
How to deal with pouchitis

Summary

- Pouchitis remains a **frequent and debilitating complication**
- The **etiolog**y of pouchitis remains unclear, but a close interaction between host genetics, immune response and microbiota plays a relevant role
- The pre-colectomy microbiome may predict patients at risk for pouchitis, but **preventive measures** are lacking
- Although evidence is far from strong, ciprofloxacin and metronidazole form the mainstay of treatment for **acute pouchitis**
- In case of **chronic refractory pouchitis**, an individualized therapy may include (topical) steroids, thiopurines, biologicals, ...
How to deal with pouchitis

Thank you