

# Acute pouchitis: the condition that time forgot about

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The ileoanal pouch offers patients with medically refractory ulcerative colitis the opportunity to avoid a permanent ostomy and utilize their own bowel as a reservoir allowing a more 'natural defaecation'.<sup>1</sup> However, medical complications from inflammatory (pouchitis, pre-pouch ileitis and cuffitis) and non-inflammatory (irritable pouch syndrome) are common and negatively impact the quality of life (QoL).<sup>2</sup>

Of the different medical complications, pouchitis (idiopathic) is the most common, with an overall incidence rate of 18% in population-based studies<sup>3</sup> and prevalence rate of up to 50% 10 years after a pouch is functional.<sup>4</sup> Currently, our understanding of the drivers responsible for pouchitis is limited. It is thought that pouchitis is driven by microbial perturbations and their interaction with the immune system; however, studies have been inconsistent, heterogenous and associative to date.<sup>5</sup> Despite this, early studies exploring treatments for pouchitis were based on microbial manipulation using antibiotics and probiotics.

To date, there are five randomized-controlled studies (RCTs) that have explored the efficacy of different treatments for acute pouchitis with a total of 103 patients evaluated. In placebo-controlled studies, Van Assche *et al.*<sup>6</sup> showed that 2/12 (16%) achieved clinical remission in those taking octreotide compared with 2/11 (18%) in the placebo group. Isaacs *et al.*<sup>7</sup> found that 2/8 (25%) achieved clinical remission in the rifaximin group compared with 0/10 (0%) in the placebo group. Kuisma *et al.*<sup>8</sup> evaluated 10 patients who received *Lactobacillus rhamnosus* GG and 10 who received placebo, and showed that 5/10 (50%) in the *L. rhamnosus* GG had a reduction in the pouch disease activity index compared with 8/10 in the placebo group. The other two RCTs compared

metronidazole as the treatment arm. Sambuelli *et al.*<sup>9</sup> found that 7/12 (58%) achieved clinical remission in the budesonide group compared with 7/14 (50%) in the metronidazole group. Shen *et al.*<sup>10</sup> found that 7/7 (100%) achieved clinical remission in the ciprofloxacin group and 6/9 (66%) in the metronidazole group. From this, one can deduce that our evidence base to support the use of antibiotics is very limited and grossly underpowered.

These data and clinical experience have demonstrated that most episodes of pouchitis are acute and intermittent with a return to baseline pouch function after successful treatment with antibiotics.<sup>11</sup> However, empirically using antibiotics for managing every episode of symptomatic pouch is suboptimal, not cost-effective, potentially harmful, and risks patients with a symptomatic pouch being empirically treated with repeated courses of antibiotics before being appropriately investigated.

It follows, the repeated use of antibiotics is not risk free. The two most commonly used antibiotics, metronidazole and ciprofloxacin, can be associated with side effects. In an observational study of 39 patients, repeated use of these antibiotics was associated with adverse effects in 11 (28%).<sup>12</sup> Furthermore, prolonged use of antibiotics maybe associated with antibiotic resistance. In a study using shotgun metagenomics to analyse 234 faecal samples in 49 patients with an ileoanal pouch during, and in the absence of, a 2- to 4-week course of ciprofloxacin and metronidazole for acute and chronic pouchitis, antibiotics were found to select for non-virulent strains that demonstrated antibiotic resistance in 72% of the samples taken from patients while on antibiotics, compared with only a 14% resistant rate in the samples taken off antibiotics. Thus, even short courses of antibiotics appeared to select for resistance.<sup>13</sup>

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Furthermore, pouch-related symptoms are not specific to any inflammatory or non-inflammatory pouch disorder.<sup>14</sup> A purely clinical diagnosis based on clinical symptoms and response to antibiotics risks exposing 25–35% of symptomatic pouch patients unnecessarily to antibiotics and is not cost-effective.<sup>15</sup> Instead, diagnosing pouchitis is based on the combined assessment of symptoms and objective evidence of pouch inflammation. Pouchoscopy remains the gold standard objective tool for diagnosing or excluding inflammatory disorders of the pouch. More recently, faecal calprotectin and gastrointestinal ultrasound have also been shown to accurately assess symptomatic pouch for pouch inflammation and its location.<sup>16</sup> Significantly, symptoms of acute pouchitis can mimic other pouch disorders to include peri-pelvic sepsis<sup>17</sup> and hence in particular situations, cross-sectional imaging may also provide important information.

Two steps appear to be crucial to improving and progressing the management of symptomatic patients with acute pouchitis. The first is accurate and efficient diagnosis through acceptable means to the patients, which may include both invasive or non-invasive techniques. The second is a deeper understanding of the mechanisms that drive inflammation. A key factor in helping to achieve this will be longitudinal studies that map out the immune–microbial interactions in the pouch to capture all spectrums of inflammatory pouch conditions. In addition, it is important that future interventional studies are inclusive of patients with acute pouchitis and that these studies integrate genetic, immunological, microbiome and next-generation technologies. It is possible that by getting treatment of the acute phase right the first time, fewer patients will develop chronic pouchitis and pouch failure. As pouch-related symptoms are associated with poorer patient-reported outcomes,<sup>18</sup> early and accurate treatment may ultimately culminate in a better QoL.

In conclusion, progressing the management of the most common complication of an ileoanal pouch, acute pouchitis, is long overdue. Despite the pouch being over 40 years old, little therapeutic progress has been made in terms of acute pouchitis. The conventional approach of empirically treating a symptomatic pouch with antibiotics is deficient as outlined above and hinders our understanding of the condition, prevention and ultimately cure. An improved understanding of the

underlying mechanisms of acute pouchitis will potentially lead to earlier intervention with tailored therapies, which may allow for changes in the natural history of these pouch-related disorders.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

All authors have agreed on the final version of the manuscript.

### *Author contribution(s)*

**Jonathan P. Segal:** Conceptualization; Data curation; Formal analysis; Project administration; Supervision; Writing – original draft; Writing – review & editing.

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Not applicable.

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