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ECCO Topical Review

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ECCO Topical Review: Refractory Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease is a chronic disease with variable degrees of extent, severity, and activity. A proportion of patients will have disease that is refractory to licensed therapies, resulting in significant impairment in quality of life. The treatment of these patients involves a systematic approach by the entire multidisciplinary team, with particular consideration given to medical options including unlicensed therapies, surgical interventions, and dietetic and psychological support. The purpose of this review is to guide clinicians through this process and provide an accurate summary of the available evidence for different strategies.

Key Words: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; refractory; unlicensed medication.

1. Introduction

A patient newly diagnosed with inflammatory bowel disease [IBD] has an uncertain future. In the pivotal IBSEN cohort, some patients had a relatively quiescent disease course whereas a significant minority experienced either relentless, poorly controlled disease or a period of relative control followed by a sudden and apparently irreversible loss of control.[1,2] Assessment of similar outcome data from patients with Crohn's disease [CD] treated in the era of biologic therapies has shown remarkably similar outcome patterns, with approximately 30% of patients who never achieve good disease control.[3] For these patients and their clinicians, difficult decisions must be made about whether and how to change therapy. It is vital that a systematic approach is taken to confirm the diagnosis, review the evidence for active disease, consider all information about past and present treatment failures, and discuss with the patient all potential further therapeutic strategies. These may include, where appropriate, the use of drugs that have not been licensed for the treatment of IBD but nevertheless have some evidence for efficacy.

Major advances have been made in the treatment of IBD in recent years. One consequence of this progress is that the definitions of refractory disease may shift; some of the evidence in this review comes from studies conducted in an era before the widespread availability of the current range of IBD therapeutics. We must consider to what extent the profiles of patients participating in these studies align with contemporary definitions of refractory disease. Earlier studies in less 'refractory' populations may provide an overestimate of contemporary response rates, although advances in management may also mean that current patients have accrued less bowel damage, which would have been the result of long periods of uncontrolled disease. Ultimately, we cannot be certain without further randomised controlled trials [RCTs] in these refractory patients, which we are unlikely to see for most of the interventions we discuss. Additional complexity arises when considering the evolution of trial outcomes. It is unclear how to compare historical trials, that suggest clinical benefit but did not assess endoscopic responses, with more recent studies where endoscopic responses were assessed and found to be non-significantly different from those observed in patients administered placebo. The overall principle remains that for a patient for whom all licensed treatment options appear to be exhausted, any knowledge from previous studies remains of value and should be carefully reviewed by the responsible clinician.

2. Methods

The European Crohn's and Colitis Organisation [ECCO] organised a topical review consensus group. ECCO topical reviews are developed from expert opinion consensus, informed by literature reviews, and are endorsed by ECCO. A topical review is distinct from ECCO consensus guidelines and is intended to provide guidance in clinical areas where scientific evidence is lacking. From an open call to all ECCO members, 15 individuals were selected based on expertise in the topic, with representation from physicians and surgeons. Working group 1 focused on principles of the approach to the patient with refractory IBD; working group 2 focused on patients with refractory ulcerative colitis [UC]; and working group 3 focused on patients with refractory CD.

Working groups defined important questions within their topic and then performed a systematic literature search. Discussions of published evidence took place initially among working group members, before a meeting of all members in Vienna in February 2020 to discuss further 'Current Practice Positions'. These were accepted when 80% or more of the participants agreed. Position statements should be read in context, with qualifying comments, and not in isolation.

3. General Considerations

Current Practice Position 3.1: *Refractory IBD should be defined as disease not responding to or losing response to all classes of licensed immunosuppressive and biologic agents. Refractory CD should additionally not be considered amenable to surgery. Refractory perianal fistulising CD should be defined as failure of at least one surgical intervention and anti-tumour necrosis factor therapy*

IBDs, namely CD and UC, are chronic debilitating diseases that can critically affect quality of life [QoL]. Prevention of structural damage to the bowel wall and perianal area has emerged as among the most important therapeutic outcomes. Almost one-third of patients do not achieve acceptable long-term remission, despite effective available therapies. Thus, there are still unmet therapeutic needs for these difficult-to-treat patients.[4] Very few clinical trials have attempted to address the needs of this patient population. Notable exceptions include the ASTIC trial, which defined refractory CD as active disease that was not amenable to surgery and with impaired QoL despite treatment with at least three immunomodulators or biologic agents and corticosteroids.[5] The ADMIRE study of complex perianal fistulas in CD defined refractory perianal CD as patients with fistula drainage for at least 6 weeks which was refractory to antibiotics, immunomodulators, and anti-TNF therapies, or combinations thereof. However, this study still set limits on the number of fistula openings, thus excluding the most severely affected patients.[6] In a recent study of appendectomy as a salvage intervention before colectomy, refractory UC was defined as active disease despite adequate therapeutic trials of 5-acetylsalicylic acid [5-ASA], corticosteroids, immunomodulators, and approved biologics.[7] A potential problem with these definitions is that, as new agents are licensed, the definition of treatment-refractory disease will shift, and older studies may no longer include patient populations relevant to revised definitions of 'treatment-refractory' disease.

Current Practice Position 3.2: *We currently lack clinical predictors or biomarkers of refractory disease behaviour*

In CD, initial corticosteroid requirement, age at onset <40 years, perianal disease, and ileocolonic and upper gastrointestinal tract location are associated with severe disease.[8–14] Independent risk factors for surgery include jejunal, ileocolonic, and upper gastrointestinal tract involvement and penetrating and stricturing disease behaviour.[13,14] Smoking is associated with a complicated course, including stenosing/fistulising behaviour, the need for corticosteroids, and surgery.[15–17] Severe endoscopic lesions are associated with penetrating complications and an increased risk of surgery in patients with colonic disease[18] although, in the era of biologic treatment, radiological changes consistent with complex disease behaviour may be more important.[19] Circulating antibodies against bacterial antigens and *NOD2* gene mutations are also associated with complicated CD,[20–26] although genetic studies have yielded limited further insight into risk

for disease behaviour.[27,28] In contrast, transcriptomic signatures relating to peripheral T cell function appear to predict aggressive disease behaviour in both CD and UC.[29]

For UC, extensive disease at presentation and proximal disease extension after index presentation are associated with higher hospitalisation rates, corticosteroid requirement, and surgery.[30,31] Independent factors associated with proximal disease extension are younger age at diagnosis and presence of primary sclerosing cholangitis [PSC].[32,33] Risk factors for colectomy include younger age at diagnosis, male gender, extensive colitis, presence of PSC, longer disease duration, and steroid-dependent disease.[33–41] Non-smoking status has been reported as associated with increased risk of adverse outcomes in UC, but data are limited and inconsistent and a protective effect of smoking in established UC has not been identified in meta-analyses of high-quality cohort studies.[42]

Current Practice Position 3.3: *The assessment of the reason for treatment failure should include the exclusion of concomitant clinical conditions and the evaluation of disease complications. It is also important to assess patient adherence to therapy and any potential for treatment optimisation [incorporating therapeutic drug monitoring where relevant]*

In patients with apparently refractory disease, it is important to confirm disease activity using objective markers of inflammation including serum and faecal biomarkers and endoscopy, or transmural imaging, or both. These help exclude functional gastrointestinal disturbances, such as irritable bowel syndrome and pelvic floor dysfunction, as a cause of dysregulated bowel habits or abdominal pain that may typically co-exist in patients with IBD.[43] Re-evaluation of disease distribution with imaging and endoscopy is advisable [if this will affect management] and IBD-related complications [strictures, fistulae, malignancy] should be assessed.[44,45]

Organic conditions that can occur coincidentally should be considered, based upon patient history, and where relevant should be tested for and excluded. These include infections with bacteria [including *Clostridioides difficile*, *Salmonella*, *Yersinia*, *Campylobacter*], viruses (typically cytomegalovirus [CMV]), protozoa [e.g. *Giardia*, *Cryptosporidium*, *Entamoeba histolytica*], *Mycobacterium tuberculosis*, or helminths [e.g. *Strongyloides*, *Schistosoma*]. Sexually transmitted infections that may mimic IBD include rectal infection with *Chlamydia trachomatis* serovars L1, L2, or L3 or syphilis. Bowel ulceration or enteropathy may be associated with drug usage, including NSAIDs, mycophenolate, or cocaine. A history of exposure to radiotherapy or immunotherapy [with cell-cycle checkpoint inhibitors] should be considered. Ischaemic changes may occur due to vascular insufficiency or vasculitis, including Behçet's disease. Intestinal lymphoma, sarcoidosis, or coeliac disease can also cause symptoms and signs that mimic and overlap with active IBD.[46] Other common causes of gastrointestinal [GI] symptoms that may co-exist in patients with IBD include bile acid malabsorption and small bowel bacterial overgrowth [both more common in those with a history of resectional ileal surgery] and exocrine pancreatic insufficiency.

Clinicians should explore treatment adherence with patients in a non-judgemental manner. Medication non-adherence is not uncommon[47] and is associated with poor outcomes with both conventional therapy and biologics.[48,49] For thiopurines and biologics, therapeutic drug monitoring may provide not only further clues on adherence but also on pharmacokinetic failure of drugs.[50] Risk factors for primary non-response [PNR] to anti-TNF agents include reduced innate immunity,[51] genetic markers,[52–55] and inflammatory burden.[56–60] The presence of fibrosis is associated with the absence of response to infliximab.[61,62] Shedding of biologic agents into the faeces has also been shown in patients with refractory active colitis.[63] Risk factors associated with secondary loss of response [LOR] to anti-TNF agents include CMV reactivation,[64] intestinal microbial composition,[65] accelerated clearance,[66] increased body mass index,[67,68] low muscle mass,[69] and low serum albumin levels.[70] Addition of immunomodulators to anti-TNF therapies is associated with improved pharmacokinetics,[71] and addition of immunomodulators may rescue anti-TNF therapy for some patients developing low-titre anti-drug antibodies.[72,73]

Dose escalation can play a valuable role for many therapies in IBD. This may be guided by therapeutic drug monitoring [TDM] although empirical, clinically guided dose escalation may be equally appropriate.[74,75] In patients with limited alternative treatment options and evidence of partial response to a biologic therapy at a maximum licensed dose, it may be appropriate to attempt dose escalation to an unlicensed dose. For example, dose escalation to 4-weekly dosing was reported for a cohort of 100 patients with CD experiencing LOR to ustekinumab, with a clinical response observed in over half.[76] It should be noted that the pharmacokinetics of monoclonal antibody therapy would suggest that these strategies are safe and no clear safety signals have been reported, including in a cohort of patients with supra-maximal anti-TNF levels.[77] The narrower therapeutic index of current small-molecule therapies does not support unlicensed dose escalation for these therapies.[78]

Current Practice Position 3.4: *Clinicians should review the history and documentation of previous treatment attempts that have been recorded as 'failure'; in carefully selected patients, it may be appropriate to re-attempt treatment*

It is not uncommon for patients to be told that they have experienced 'treatment failure', with limited evidence of any attempts to confirm disease activity, optimise drug dosing, or obtain pharmacokinetic data to judge mechanisms of treatment failure. Another inappropriate use of the term 'failure' arises when a medical therapy is initiated too late in the disease course to reverse the significant bowel damage that has already occurred; in such patients, re-use of the same drug after surgery may still be appropriate.

For patients who have previously reported side effects while on a therapy, re-challenge may be appropriate. For thiopurine therapy, this may include careful re-challenge with lower doses, potentially with the use of allopurinol in the context of careful TDM.[79] For anti-TNF agents, a small number of retrospective studies have addressed the efficacy and safety of re-introducing drugs that were discontinued due to intolerance, PNR, or secondary LOR. These studies are limited to CD patients and have reported rates of clinical response of 40–60% on re-treatment with infliximab [including a large proportion of patients receiving dose-intensified infliximab] after previously documented failure of both infliximab and adalimumab treatment.[80–83]

Current Practice Position 3.5: *IBD patients with refractory disease, who have exhausted all available treatment options, should be offered referral to a clinical trial unit*

For patients with refractory disease, participation in a clinical trial can offer access to new, potentially beneficial treatments, although many will ultimately not be characterised as suitable candidates.[84] One option for this patient cohort may be treatment with novel combinations of licensed therapies, including combination biologic therapies. This has been much discussed in recent years, although outcome data from controlled studies are currently lacking.[85] Lessons from rheumatology suggest that potential efficacy gains may be limited, whereas safety concerns remain paramount.[86] Ultimately, the ideal combination therapy approach would be tailored to the immunopathology of the individual patient.[87,88]

Current Practice Position 3.6: *The involvement of a colorectal surgeon is important in the management of IBD. If hospitalised, these patients are best cared for jointly by a gastroenterologist and a colorectal surgeon. Refractory IBD patients are at specific risk of malnutrition and psychological complications. Close dietetic and psychological support should be available*

The management of IBD requires tight control of disease progression, based on an interdisciplinary, holistic approach.[89] This is particularly true for those patients hospitalised with IBD, where close collaboration between gastroenterologists and colorectal surgeons is mandatory.

Surgical interventions can and should be considered for patients at all stages of disease, but particularly for those with limited or no response to standard medical therapies. For patients with UC, it is important to offer patient-centred discussions regarding the appropriateness of proctocolectomy with ileo-anal pouch or end ileostomy, with due consideration given to management of the associated psychological burden. Another emerging surgical option for medically refractory UC may be appendectomy. In the PASSION prospective case series of 30 patients with treatment-refractory UC, laparoscopic appendectomy was associated with a clinical response after 12 months in 30%,[7] with evidence of continued benefit over subsequent follow-up.[90] Multicentre RCTs of this intervention are ongoing.[91] For patients with refractory CD, although surgery may not offer full relief of symptoms it may, nonetheless, play an important role in managing disease complications, decreasing overall morbidity, and restoring QoL.

Once the decision has been made to proceed with surgery, preoperative optimisation should commence, ideally through an enhanced recovery programme.[92] Medical optimisation includes correction of anaemia, smoking cessation counselling, and tapering of steroids where possible. Malnutrition, malabsorption, and sarcopenia are frequently present, all of which should be addressed in partnership with an appropriately trained dietician. Pre- and post-surgical nutritional support should be tailored to patient and disease characteristics, the type of surgical procedure, the length of the remaining functional gut, the presence of a stoma or a fistula, and postoperative complications. Dietary optimisation is associated with an improvement in quality of care and patient-reported outcomes and reduced health care costs, but high-quality RCTs to support perioperative dietary interventions in IBD are lacking.[93]

Septic foci are treated with antibiotics and percutaneous drainage.[94] Patients who may require a stoma should meet with an enterostomal therapist preoperatively.[95,96] Bowel- and continence-preserving surgical approaches should be used, regardless of the segment of bowel involved. This involves favouring strictureplasties over resections, segmental resections over extended resections, and temporary stomas over permanent stomas whenever possible.

For patients with obstruction refractory to medical therapy, endoscopic options may include balloon dilatation or emerging techniques such as endoscopic electro-incision or stenting.[97] Surgical options for upper tract and small bowel disease are most commonly needed in fibrostenotic CD. At surgery, attempts should be made to perform strictureplasties and to avoid small bowel resections, but sometimes a combination of both is required.[98,99] This includes strictures of the duodenum and jejunum, but occasionally a duodenojejunal or gastro-jejunal bypass may be required.[100]

For patients with refractory Crohn's colitis, emphasis is again on bowel and continence preservation, hence segmental colectomies may be performed when possible.[101] Care should be taken when more than two active sites of disease exist in Crohn's colitis [i.e. multiple segmental Crohn's colitis or proctitis +/- perianal disease], as these patients are likely to develop short-term postoperative recurrence and may be best served by a subtotal colectomy [with ileorectal anastomosis in the case of rectal sparing], or proctocolectomy [in the case of significant proctitis or perianal disease].[102,103]

CD patients who are refractory to all medical therapies are at increased risk of short-bowel syndrome and intestinal failure from repeated resection.[104,105] These patients should be referred to an intestinal failure unit for consideration of treatment with teduglutide, bowel-lengthening procedures [e.g. serial transverse enteroplasty],[106,107] or intestinal transplantation.[108]

The psychological morbidity of refractory IBD should be recognised; this is driven by the impact of multiple treatment failures, the realisation that disease outcome may be undesirable, frequent exposure to opioids, and the significant distress caused by fluctuating or unremitting symptomatology.[109] Long periods of time experienced living with active disease will inevitably have negative consequences on personal, familial, social, and professional life. In addition, patients will be required to engage with their medical team at a time of heightened anxiety and distress amid a background of undesirable feelings frequently experienced by both the patient and the treating medical team, including frustration, failure, and blame. Accordingly, all patients will require a compassionate and supportive approach from all professionals involved in their care. This is essential to avoid damaging feelings of being let down or abandoned, which will inevitably lead to loss of treatment compliance and a breakdown in the relationship with the team. Inclusion of an appropriately trained clinical psychologist in the IBD team may not only offer support for more complex cases directly but may also increase the understanding, skills, and confidence of all staff working with this patient group.[110,111]

4. Management of Refractory UC

Current Practice Position 4.1: *There is evidence supporting the use of calcineurin inhibitors [ciclosporin and tacrolimus] to achieve short-term clinical response in patients with UC. Topical tacrolimus can achieve short-term clinical remission in proctitis*

The use of intravenous [IV] ciclosporin as a rescue therapy for steroid-refractory acute severe UC is well established.[112–114] Nonetheless, a narrow therapeutic index and variable pharmacokinetics of oral dosing complicate use in an outpatient setting, and there is a lack of data outside rescue therapy.[115] Attempts to develop ST-0529, a colonic delivery formulation of ciclosporin, showed initial promise in early trials,[116] but a phase 2 placebo-controlled RCT was terminated for futility.[117]

Tacrolimus is a calcineurin inhibitor with potent inhibitory effects on activated T cells and a more favourable safety profile than ciclosporin. Two small RCTs reported the benefit of oral tacrolimus in patients with moderate/severe corticosteroid-dependent or refractory UC extending beyond the rectum.[118,119] A meta-analysis of pooled data from these two studies revealed clinical response after 2 weeks of therapy in 29/53 [55%] tacrolimus-treated patients and in 6/50 [12%] of those given placebo (risk ratio for response: 4.61; 95% confidence interval [CI]: 2.09–10.17).[120] Key questions concern the efficacy of tacrolimus over longer durations and in patients with previous failure of treatment with immunomodulators, biologics, or both. Thin *et al*. reported outcomes in 24 patients with UC, all of whom had failed earlier therapy with thiopurines and 90% of whom had a previous history of anti-TNF therapy failure.[121] The proportions achieving clinical response at 30 days and at 1 year were 58% and 17%, respectively. The cumulative risk of surgery was 67% at 2 years. Boschetti *et al*. reported outcomes for a cohort of 30 patients with UC who were refractory to steroids, immunomodulators, and anti-TNF therapy.[122] After 12 weeks of oral tacrolimus, remission was observed in 12 [40%] and improvement in a further six [20%]. By 12 months, eight patients [27%] remained in remission, with the remainder considered either treatment failures or having withdrawn therapy due to adverse events including tremor and urinary tract infections.

Topical application of tacrolimus has been reported in patients with disease confined to the rectum. A small RCT performed in a patient group refractory to steroids, immunomodulators, or both, reported Week-8 clinical response in 8/11 [73%] of patients treated with rectal tacrolimus and 1/10 [10%] of those treated with placebo [p = 0.01].[123] A larger recent RCT reported clinical response after 4 weeks of topical therapy in 22/35 [63%] of patients with disease refractory to or dependent on topical 5-ASA. This rate did not differ significantly from patients randomised to treatment with topical beclomethasone [response in 22/37, 59%; p = 0.8].[124] Patients in the first RCT were excluded if they had a history of biologic exposure, and rates of biologic exposure in the second study were <10%; thus, the role of tacrolimus in proctitis refractory to biologic therapy remains unclear.

Current Practice Position 4.2: *Trichuris suis ova are not recommended for the treatment of UC. There is no evidence to support the use of other helminths as therapy*

The apparent reverse correlation between the epidemiology of IBD and helminth infections, along with animal data on the effects of helminth infection on mucosal immune responses, has led to the proposal to use colonisation with helminths, for which humans are not the natural host, to treat UC. Summers *et al*. randomised patients with UC to treatment with repeated doses of the porcine whipworm *Trichuris suis* or placebo.[125] At Week 12, clinical response was seen in 13/30 [43%] patients treated with ova and 4/24 [17%] placebo-treated patients. No patients were on biologic therapy at baseline and only 18.5% of patients were on an immunomodulator. A separate, smaller, unpublished clinical trial did not show any benefit compared with placebo (Week-12 clinical response in 4/7 [57%] patients vs 6/12 [50%] placebo-treated patients). A meta-analysis of available data did not show benefit of *Trichuris suis* ova.[126] There are no trial data regarding the use of other helminths in UC.

Current Practice Position 4.3: *There is some evidence supporting the use of thalidomide in paediatric patients with UC, albeit with significant safety concerns*

Thalidomide has anti-inflammatory properties that impede production of pro-inflammatory cytokines, including TNF.[127,128] Most evidence in IBD is derived from retrospective studies in CD, primarily in paediatric populations.[128] In a recent study in paediatric UC patients [most with anti-TNF refractory disease] who were randomised to receive thalidomide or placebo, clinical remission at Week 8 was achieved by significantly more children treated with thalidomide (10/12 [83%] vs 2/11 [19%] on placebo; p <0.005). A recent systematic review included 38 UC patients treated with thalidomide; 66% achieved clinical response and 71% clinical remission.[128]

Significant safety concerns are associated with the use of thalidomide. It cannot be used during pregnancy due to severe fetal limb malformations.[129] The most common adverse events associated with thalidomide therapy are neurological [peripheral neuropathy], sedation, skin reactions [rash, seborrhoea], and gastroenterological disturbances.[128]

Current Practice Position 4.4: *Methotrexate and granulocyte and monocyte adsorptive apheresis are not recommended for the treatment of UC*

Current evidence does not support the use of methotrexate monotherapy in UC. Although some clinical effect was suggested by observational studies,[130–132] two well-performed RCTs did not show benefit. The METEOR trial demonstrated that parenteral methotrexate was not superior to placebo for induction of steroid-free remission (19/60 [32%] vs 10/51 [20%] given placebo; p = 0.15).[133] The MERIT-UC study showed that for patients achieving remission after induction therapy with a combination of corticosteroids and methotrexate, methotrexate was not superior to placebo in maintaining corticosteroid-free remission over 32 weeks (29/44 [66%] vs 24/40 [60%] given placebo; p = 0.75).[134]

Granulocyte and monocyte adsorptive apheresis [GMA] is a procedure by which activated neutrophils, monocytes, and platelets are selectively removed from the blood.[135] Although several studies had suggested comparable outcomes to licensed medical therapies,[136] two RCTs performed with a sham-control arm failed to demonstrate any benefit.[137,138] A recent RCT compared GMA plus oral prednisone with sham apheresis and prednisone in patients with active, steroid-dependent UC and revealed that the rate of steroid-free remission at Week 24 was similar in both groups.[138]

Current Practice Position 4.5: *Hyperbaric oxygen therapy may achieve clinical response in UC*

Hyperbaric oxygen therapy [HBOT] involves breathing pressurised 100% oxygen to increase tissue oxygen levels. HBOT may have effects on inflammatory processes, including regulation of pro-inflammatory cytokine production and hypoxia response pathways, shifts in host-microbiome metabolism, increased growth factor synthesis, and stem cell migration.[139,140] Case series have reported response rates in both UC and CD, but with a high degree of publication bias.[140] Two small RCTs in UC both randomised 10 patients to HBOT and eight to standard therapy. In the first, no differences in clinical outcomes between the groups were detected,[141] and in the second, which recruited inpatients with acute severe UC, a significantly higher proportion of HBOT-treated patients achieved clinical remission at study Day 5 [50% vs 0%; p = 0.04], with a lower in-hospital colectomy rate in the HBOT group compared with sham treatment [10% vs 63%; p = 0.04].[139]

Current practice position 4.6: *Faecal microbial transplantation may be effective in achieving remission in UC*

Alterations in the gut microbiota, with decreased diversity and stability of mucosa-associated and faecal bacteria in comparison with healthy controls, has repeatedly been described in patients with UC.[142,143] The composition of the faecal fungal and viral microbiota has similarly been shown to be altered in UC.[144,145] Four RCTs have assessed induction[146–149] and one RCT assessed maintenance[150] of remission using faecal microbiota transplantation [FMT] in patients with UC [Table 1]. A meta-analysis of the induction studies, consisting of a total of 140 FMT-treated patients with differing definitions of outcomes, demonstrated that FMT was significantly associated with clinical remission (odds ratio [OR]: 2.89; 95% CI: 1.36–6.13).[151] Endoscopic remission rates were 12–55% with FMT application compared with 5–17% in controls. The maintenance study was conducted in 31 UC patients who were in clinical remission after previous FMT, and did not show a significant difference in the primary endpoint of clinical remission at Week 48 [87% of FMT vs 66% of placebo-treated patients; $p = 0.11$].[150] Secondary endpoints showed significantly higher rates of endoscopic remission [FMT 58% vs 27%; $p = 0.026$] and histological remission [FMT 45% vs 17%; $p = 0.03$].

Several details of the optimal procedure remain to be determined, but use of pooled donor stool providing greater microbial diversity and repeated administration via the lower gastrointestinal tract seem favourable. These trials did not show an increased incidence of adverse or serious adverse events or disease worsening, although the studies were not specifically powered to assess safety signals.[151] With FMT in other indications, two cases have been reported of extended-spectrum beta-lactamase [ESBL]-producing *Escherichia coli* bacteraemia; one patient died.[152] Therefore, currently FMT should only be performed within an accredited FMT facility with strict protocols in place for donor screening and ideally within the context of a controlled clinical trial.

Current Practice Position 4.7: *There is limited evidence supporting the use of anti-TNF therapies in patients with pouchitis. There is very limited evidence for vedolizumab and ustekinumab*

Current Practice Position 4.8: *There is very limited evidence for the efficacy of tacrolimus enemas in pouchitis*

Among UC patients who have undergone an ileal pouch-anal anastomosis, pouch inflammation [pouchitis] is a commonly encountered complication with a wide reported incidence range between 15% and 53%.[153] After endoscopic and histological confirmation of the diagnosis, established treatments include combinations of antibiotics given for periods of up to 8 weeks.[154] These have been reported as effective in a series of studies including an RCT,[155] a case-control study,[156] and three case series.[157–159] A meta-analysis of 95 patients treated with antibiotics for chronic pouchitis revealed a 70% remission rate [95% CI: 50–90%].[160] High rates of antibiotic resistance have been reported in chronic pouchitis that is apparently refractory to antibiotic treatment. Success has been reported in treating 12/15 [80%] such patients with a tailored antibiotic regimen after antibiotic-resistance testing for faecal coliforms.[161]

The use of topically acting oral steroids [budesonide or beclomethasone] has also been reported to induce remission in chronic pouchitis. This is based on two case series that reported 75–80% remission rates after 8 weeks of steroids in a total of 30 patients.[162,163] An RCT comparing 6 weeks of therapy using budesonide enemas with oral metronidazole did not reveal a significant difference in clinical remission rates between treatment arms.[164]

The use of anti-TNF therapies in treatment-resistant pouchitis has been assessed in a meta-analysis.[165] Huguet *et al.* identified retrospective studies including 313 patients treated with either infliximab or adalimumab for inflammatory complications of the pouch and reported that half of the patients achieved clinical remission [95% CI: 0.37–0.63]. The authors analysed 210 patients where pouchitis could be differentiated into inflammation limited to the pouch as opposed to more extensive CD-like pouch complications. Although the rate of remission after anti-TNF induction therapy was numerically higher for CD-like pouch complications compared with refractory pouchitis [64% vs 10%; $p = 0.06$], no differences were observed during maintenance therapy. However, a subsequent small placebo-controlled RCT of adalimumab in antibiotic-refractory pouchitis showed clinical improvement in 3/6 [50%] of patients treated with adalimumab and in 3/7 [43%] of patients treated with placebo [$p > 0.5$].[166]

Evidence for other biologics in refractory pouchitis is limited to case series data only for vedolizumab[167–170] and ustekinumab.[171] Ongoing trials in this area include a placebo-controlled RCT of vedolizumab [EARNEST, NCT02790138] and an open-label trial of ustekinumab [SOCRATES, NCT04089345].

A case series of 10 patients treated with tacrolimus enemas revealed a significant reduction in disease-activity scores after 8 weeks.[172] Similar low-quality data originally suggested efficacy for bismuth enemas,[173] but this was not supported in a subsequent RCT.[174] Open-label alicaforsen, an antisense oligonucleotide targeted against ICAM-1, was tested in a case series of 12 patients and showed a significant reduction in disease scores between baseline and Week 6.[175] Glutamine or butyrate suppositories had low effectiveness in maintaining remission over 3 weeks.[176]

Current Practice Position 4.9: *The available data do not suggest efficacy for faecal microbiota transplantation in pouchitis. Manipulation of microbiota using a multistrain probiotic containing a combination of lactic acid bacteria, Streptococcus, and Bifidobacteria is more effective than placebo in maintaining remission*

FMT has been assessed in treatment-resistant pouchitis. Four case series reported a total of 35 patients, with low rates of remission and response.[177–180] A placebo-controlled RCT was stopped prematurely due to low remission rates.[181]

Probiotics have been used in treatment-resistant pouchitis as maintenance therapy after induction of remission with antibiotics. A Cochrane review pooled the data from two RCTs of maintenance treatment using a multistrain probiotic containing a combination of lactic acid bacteria, *Streptococcus*, and *Bifidobacteria*[182,183] and revealed that 34/40 [85%] of patients in active treatment maintained remission compared with 1/36 [3%] in the placebo arm (relative risk [RR]: 20.24; 95% CI: 4.28–95.81) over 9–12 months.[184]

5. Management of Refractory CD

Current Practice Position 5.1: *The use of cannabis, curcumin, prebiotics, probiotics, lenalidomide, or sargramostim are not recommended in the treatment of CD. There is some evidence supporting the use of thalidomide in paediatric patients with CD, albeit with significant safety concerns*

Table 1. Key aspects of randomised controlled trials of FMT in patients with UC.

Author	Number of patients [FMT/control]	Severity of UC	Donor	Placebo	Route	Dosage stool FMT	Frequency	Primary endpoint	Clinical remission	Clinical response	Endoscopic remission
Rossen *et al.*, 2015[146]	23/25	Mild-moderate [SCCAI 4–11]	Heterologous FMT, one healthy donor	Autologous FMT	Nasoduodenal	Minimum 60 g stool in 500 ml	*n* = 2 [WWeek 0 and Week 3]	Clinical remission and endoscopic improvement at Week 12, 7/23 [30%] vs 5/25 [20%], *p* = 0.51 [SCCAI ≤2 and ≥1 point drop in combined MES	7/23 [30%] vs 8/25 [32%], *p* = NS [SCCAI ≤2]	11/23 [48%] vs 13/25 [52%], p = NS [SCCAI drop ≥1.5]	NR
Moayeddi *et al.*, 2015[147]	38/37	Mild-severe, [Mayo 4–12]	FMT/one healthy donor	Water	Enema	50 g stool in 50-ml infusion	*n* = 6 [weekly]	Clinical and endoscopic remission at Week 7, 9/38 [24%] vs 2/37 [5%], *p* = 0.03 [Mayo ≤2 and MES = 0]	9/38 [24%] vs 2/37 [5%], *p* = 0.03 [Mayo ≤2]	15/38 [39%] vs 9/37 [24%], *p* = 0.16 [Mayo drop ≥3]	9/38 [24%] vs 2/37 [5%], *p* = 0.03 [MES = 0]
Paramsothy *et al.*, 2017[148]	41/40	Mild-moderate [Mayo 4–10]	FMT/ multidonor [3–7 healthy donors]	NaCl 0.9%	Colonoscopy followed by enemas	37.5 g stool in 150 ml saline infusion	*n* = 41 [One FMT colonoscopy; followed by 5/week enema for 8 weeks]	Steroid-free clinical remission and endoscopic improvement at Week 8, 11/41 [27%] vs 3/40 [8%], *p* = 0.02 [Mayo ≤2, all subscores ≤1, ≥1 point drop in endoscopy subscore, no steroids]	18/41 [44%] vs 8/40 [20%], *p* = 0.02 [Mayo subscore ≤1 for bleeding and stool frequency combined, no steroids]	22/41 [54%] vs 9/40 [23%], *p* = 0.01 [Drop in combined Mayo subscore for bleeding and stool frequency of ≥3 or 50%, no steroids]	5/41 [12%] vs 3/40 [8%], *p* = NS [MES= 0, no steroids]
Costello *et al.*, 2019[149]	38/35	Mild-moderate [Mayo 3–10]	Anaerobe FMT/ multidonors [3–4 healthy donors]	Autologous FMT	Colonoscopy followed by enemas	50 g stool in 200 ml	*n* = 3 [one FMT colonoscopy; followed by 2/ week enemas for 1 week]	Steroid-free remission at Week 8, 12/38 [32%] vs 3/35 [9%] at Week 8, *p* = 0.02, [Mayo ≤2, MES ≤1, no steroids]	19/38 [50%] vs 6/35 [17%], *p* <0.01 [SCCAI ≤2, no steroids]	21/38 [55%] vs 7/35 [20%], *p* <0.01 [Mayo drop ≥3, no steroids]	21/38 [55%] vs 6/35 [17%], *p* <0.01 [MES ≤1, no steroids]
Sood *et al.*, 2019[150]	31/30	Patients in clinical remission after add-on FMT [Mayo score ≤2, with each subscore ≤1]	FMT/one healthy donor	Saline	Colonoscopy	100 g stool in 200 ml	*n* = 7 [FMT colonoscopy at Weeks 0, 8, 16, 24, 32, 40, and 48]	Maintenance of steroid-free clinical remission, 27/31 [87%] vs 20/30 [66.7%] at Week 48, *p* = 0.111, [Mayo score ≤2, all subscores ≤1]	NR	NR	18/31 [58%] vs 8/30 [26%], *p* = 0.026, [MES = 0]

FMT, faecal microbiota transplantation; UC, ulcerative colitis; SCCAI, Simple Clinical Colitis Activity Index; MES, Mayo Endoscopic Score; NS, not significant; NR, not reported.

The use of cannabis, curcumin, and pre- and probiotics was recently reviewed in the ECCO topical review on complementary medicine and psychotherapy in IBD.[185] None of these were recommended and this remains the case for refractory CD. Although the use of cannabis may be associated with a reduction of some symptoms in CD, there is no evidence to show that it improves inflammation.[185,186] In a recent RCT, cannabis induced significant clinical and QoL improvement without significant changes in inflammatory parameters or endoscopic scores after 8 weeks.[187]

Recombinant granulocyte macrophage colony-stimulating factor [GM-CSF, sagramostim] has been used in three RCTs in active CD with no evidence of benefit for induction of clinical remission or improvement in active CD compared with placebo.[188–191]

Several case series have reported the apparently successful use of thalidomide in patients with active CD, including patients refractory to anti-TNF therapy. In an RCT performed in 56 children with active CD [mean age 15, all of whom had failed previous immunomodulator treatment and 37% of whom had previously been treated with infliximab], clinical remission at Week 8 was achieved by 13/28 treated with thalidomide [46%] vs 3/26 treated with placebo [11.5%; $p = 0.01$].[192] Remission rates in the subgroup of children receiving thalidomide after previous failure of infliximab therapy were 8/17 [48%] vs 0/11 [0%] receiving placebo [$p = 0.01$]. Thalidomide was associated with longer-term maintenance of remission in an open-label follow-up. In a recent systematic review including mostly uncontrolled studies, clinical response and remission were observed in 55% and 70% of CD patients [$n = 379$], respectively, with perianal fistula improvement [using highly variable definitions] documented in 49/81 [61%] patients.[128] As already discussed, safety concerns [in particular teratogenic effects and neurological adverse events] should be considered carefully. An additional note of caution comes from a well-performed RCT of the thalidomide analogue, lenalidomide, in adult patients with active CD. The overall clinical response rate at 12 weeks was not significantly different in either of the two lenalidomide dosing groups [6/23, 26%; 16/33, 49%] compared with placebo [11/28, 39%].[193]

Current Practice Position 5.2: *There is very limited evidence for the use of immunomodulators, including ciclosporin, tacrolimus, cyclophosphamide, mycophenolate mofetil, and thioguanine in patients with CD*

Three case series reported the effects of IV ciclosporin in a total of 34 patients with CD and suggested potential efficacy for both luminal and fistulising CD.[194–196] No RCTs have been performed using IV ciclosporin. Oral ciclosporin therapy did not show efficacy in one small paediatric and two larger adult RCTs.[197–199]

A systematic review identified 70 patients with luminal CD treated with either oral or IV tacrolimus across six case series. After variable follow-up periods, the aggregate remission rate was 31/70 [44%].[200] Treatment of perianal CD with systemic tacrolimus has also been reported in a case series, with fistula benefit reported in 33/49 [67%].[200] A placebo-controlled RCT revealed significantly better fistula improvement in patients treated for 10 weeks with oral tacrolimus than with placebo (9/21 [43%] vs 2/25 [8%]; $p = 0.004$). No difference in rates of fistula remission was observed.[201]

Four small cohort studies reported high rates of clinical response [87–100%] and remission [22–100%] after two to nine cycles of cyclophosphamide treatment. Notably, most patients received azathioprine or methotrexate during the maintenance phase.[202–206]

The use of mycophenolate mofetil [MMF] in IBD has been reported in several small case series with widely varying rates of reported success.[207] Many of these studies mixed both CD and UC patients. One trial randomised 70 patients with CD who were naïve to thiopurine therapy to receive either MMF with corticosteroids or azathioprine with corticosteroids. This study showed broadly similar outcomes, but was beset with methodological problems, including a lack of blinding, mismatched groups at baseline, and a lack of an intention-to-treat analysis despite loss to follow-up in the MMF with corticosteroid group.[208]

Tioguanine is a thiopurine that has been proposed as an alternative agent for use in IBD. A systematic review of studies evaluating tioguanine therapy in CD patients [a large majority of whom had a history of previous azathioprine/mercaptopurine failure or intolerance] revealed a clinically relevant decrease in disease activity according to physician global assessment or steroid tapering/discontinuation in 118/225 [52%] of patients.[209] A subsequent study reported tioguanine effectiveness in a large cohort that was predominantly intolerant to previous thiopurine therapy, with effectiveness reported in 121/186 [65%] of CD patients.[210] One safety concern around tioguanine relates to hepatic nodular regenerative hyperplasia, although this was less frequently observed in patients exposed to the lower doses used in more recent cohort studies.[209,210]

Current Practice Position 5.3: *Other than infliximab and adalimumab, alternative anti-TNF therapies with evidence in CD include certolizumab pegol [RCT] and golimumab [case series]*

For patients with a history of secondary LOR to licensed anti-TNF therapies, the use of other anti-TNF therapies with evidence in IBD may be considered. Certolizumab pegol is a Fab' fragment conjugated to polyethylene glycol to improve stability, which is approved for the treatment of CD in the USA and certain other jurisdictions but does not have European Medicines Agency approval for this indication. The phase 3 PRECiSE programme showed clinical benefit in terms of induction of response [but not remission], maintenance of response and remission, and benefits in a small subgroup of patients with perianal fistulising disease.[211] A post-hoc analysis confirmed benefit in the subgroup of patients with prevvious anti-TNF exposure, a finding supported by the open-label WELCOME induction study on patients with earlier secondary failure of infliximab treatment.[212]

Although golimumab is licensed for the treatment of UC, data in CD are limited to case series only.[213–216] Clinical response was reported in 63/115 [55%] of CD patients refractory to other anti-TNF agents in a French retrospective multicentre study, although median treatment duration was less than a year.[214] A Swedish registry study similarly identified relatively high drug discontinuation rates in a cohort of CD patients who had predominantly experienced previous anti-TNF therapy failure, with drug continuation in only 35% after a median follow-up duration of 89 weeks.[215]

An important point is that for patients who develop anti-drug antibodies to a first anti-TNF therapy, the use of an immunomodulator is essential to reduce the risk of treatment failure if using a subsequent anti-TNF therapy.[217] This has been shown for infliximab and adalimumab, and similar principles likely extend to certolizumab and golimumab, which have both been associated with the development of neutralising anti-drug antibodies.[218]

Current Practice Position 5.4: *Antibiotics do not provide sustained clinical benefit in the treatment of luminal, non-penetrating CD. There is currently insufficient evidence to support faecal microbial transplantation in CD*

Similar to UC, alterations in gut microbiota are a well-recognised feature of CD,[219] and consequently manipulation of the intestinal microbiota by FMT has attracted interest from investigators and patients alike.[220] In contrast to the evidence in UC, no RCT [or non-randomised studies with a sham-controlled arm] are currently available in CD.[221] Open-label pilot studies in active, luminal CD [paediatric and adult] suggest that FMT may be a safe, feasible, and efficient treatment strategy to induce clinical improvement [rates ranging from 58% to 87%].[222–226] However, other series did not reveal any clinical benefit.[227] Data during maintenance[228] and in penetrating disease[225] are limited. No data are available on ideal donor characteristics, if any, for FMT in CD, or on optimal route of administration.

A more direct manipulation of the microbiota may be achieved with antibiotic therapy. Use of antibiotics for short-term control of perianal sepsis in patients with complications of perianal CD is well established and not considered here.[45] For luminal CD, a recent Cochrane meta-analysis identified seven RCTs on antibiotics which revealed a modest reduction in failure to achieve clinical remission [RR: 0.86; 95% CI: 0.76–0.98].[229] However, these studies were all characterised by the recruitment of patients with relatively mild disease activity and little previous immunomodulator or biologic exposure. Furthermore, there was no evidence for benefit of antibiotics in maintaining remission.

Some interest has arisen around antimicrobial therapy directed at *Mycobacterium avium paratuberculosis* [MAP], an obligate intracellular pathogen proposed as an aetiological factor in CD.[230,231] Initial data on the efficacy of chemotherapy against MAP in CD showed mixed results.[232–236] A subsequent placebo-controlled RCT recruited 213 patients with active CD to evaluate anti-tuberculous antibiotic therapy given over 2 years. There was evidence of efficacy at 16 weeks [66% clinical remission in the treatment arm vs 50% in the placebo arm; $p = 0.02$], although interpretation is complicated by high remission rates likely due to patients receiving a course of prednisolone. There was no difference in the rate of relapse at 52 and 104 weeks.[237] A further RCT recruited 331 subjects but has not yet been published in the peer-reviewed literature. Abstract data suggest that again there was clinical benefit at early time points but no evidence of benefit as maintenance therapy over 1 year or of significant endoscopic improvement.[238] Thus, current data do not support the use of antimycobacterial therapy in the treatment of refractory CD.

As with UC, a meta-analysis of RCTs using *Trichuris suis* ova administration in patients with CD did not reveal any clinical benefit.[126]

Current Practice Position 5.5: *Dietary strategies, including exclusive enteral nutrition, may induce remission in patients with CD, but long-term acceptability and efficacy data are lacking*

Therapeutic dietary interventions represent an attractive strategy for patients and clinicians alike.[239] Most studies have focused on patients with relatively mild disease and there is a lack of data to guide recommendations for patients with refractory CD. Nonetheless, simple dietary recommendations, including the consumption of a well-balanced diet, prepared largely from fresh ingredients and avoiding emulsifiers and other additives, can be considered for all CD patients. In patients with symptomatic strictures, a low-residue diet should be recommended to avoid obstruction.

The most established dietary treatment in CD involves exclusive enteral nutrition [EEN], which is established in paediatric practice and induces clinical remission in up to 80% of patients.[240,241] Given the restrictive nature of this intervention and limited acceptability of prolonged use, a solid food diet based on the composition of EEN and mimicking its effect on the gut microbiome has been developed [CD-TREAT] and has demonstrated promise in open-label paediatric CD studies.[242] Alternatively, a CD exclusion diet coupled with partial enteral nutrition [aiming to reduce exposure to dietary components that have adverse effects on the microbiome and intestinal barrier][243] showed significant clinical benefit compared with EEN in paediatric patients with mild-to-moderate CD, but again remains to be tested in other populations.[244] Other diets tested in small series with different endpoints and designs include the Food and Crohn's Disease Exacerbation Study [FACES] trial,[245] a specific carbohydrate diet,[246] an anti-inflammatory diet,[247] and the low FODMAP diet.[248]

Current Practice Position 5.6: *Haematopoietic stem cell transplantation has shown benefit in some patients with CD, but significant associated morbidity and mortality suggest that this treatment should be reserved for highly selected patients or within the context of clinical trials*

5.6.1. Haematopoietic stem cell therapy

Autologous haematopoietic stem cell transplantation [HCST] eliminates dysregulated immune cells and replaces them with uncommitted stem cells, aiming to generate a more tolerogenic immune cell repertoire. The ASTIC trial randomised 45 patients with CD to autologous HSCT or control treatment with delayed autologous HSCT at 1 year. This study failed to reach the primary endpoint of clinical disease remission for 3 months, off all medication, with no evidence of endoscopic disease activity.[249] However, 8/23 [35%] patients in the HSCT arm achieved clinical and endoscopic remission compared with 2/22 controls [9%; $p = 0.05$]. As might be expected with an aggressive treatment in a highly refractory cohort, a large number of serious adverse events [SAE] were observed, although there was no significant difference between the two treatment arms. One death occurred in the HSCT arm. On subsequent analysis, an inflammatory phenotype, colonic disease location, and a high endoscopic disease score were associated with treatment response, whereas smoking and perianal disease were identified as risk factors for SAE.[5] A combined analysis of patients from the ASTIC trial who received HSCT initially with those who received HSCT after 1 year of conventional therapy revealed that 13/34 patients reached a post-hoc primary outcome of steroid-free clinical remission for 3 months.[5] However, a subsequent trial with a less intense conditioning regimen and refined exclusion criteria [ASTIClite][250] was terminated early for safety reasons.[251]

In autologous HSCT, any underlying genetic predisposition still exists for the patient. In contrast, allogeneic stem cell transplantation may be considered in monogenic very early onset CD, and is served by a separate set of recommendations.[252] It is interesting to note a report of a single patient, originally diagnosed with CD at the age of 11, with a coding variant in the *XIAP* gene [previously associated with early-onset IBD] identified through targeted exome sequencing of 503 adult patients with severe IBD.[253] This suggests that screening

for monogenic causes of IBD may have a role in severely affected patients outside the well-established role in early-onset IBD.

5.6.2. Mesenchymal stem cell therapy

Most studies that evaluated mesenchymal stem cells [MSC] for CD are focused on fistulising disease, where administration of an MSC preparation to a carefully prepared fistula tract is associated with increased rates of fistula healing compared with sham surgery alone.[6,254] A recent meta-analysis identified 13 RCTs of MSC and suggested both efficacy and safety.[255]

Two open-label studies of autologous bone marrow-derived MSC have been reported for luminal CD.[256,257] Safety and feasibility were demonstrated by these studies, without a robust efficacy signal. A further open-label study[258] and a case series[259] reported a reduction in clinical and endoscopic activity in patients with refractory CD treated with allogeneic bone marrow and cord blood-derived MSC. An RCT of placenta-derived MSC revealed clinical improvement following MSC administration.[260] However, significant rates of disease remission were not achieved. One of the major limitations of systemic MSC therapy is that the cells have a limited ability to migrate beyond the lungs following infusion and have a short *in vivo* lifespan.[261]

6. Conclusion

Refractory IBD represents a significant challenge to the clinician and an enormous burden to the patient. The treatment of refractory IBD requires the full input of the multidisciplinary team with a detailed review of disease history and previous therapies. These reviews may highlight past missed opportunities and suggest that improvements in quality of care and increased clinician education may begin to reduce the prevalence of truly refractory cases. An effective treatment plan for refractory disease must focus on identifying any remaining, potentially effective therapeutics, the avoidance of ineffective treatments and, where appropriate, judicious surgical intervention. This plan should be made in conjunction with the patient in a supportive [both physical and psychological] context. In such a manner, although words such as 'remission' may no longer be spoken, it frequently is possible to achieve improvements in QoL that can deliver welcome relief to patients and their loved ones.

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Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict-of-interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI disclosures are not only stored at the ECCO Office and the editorial office of *JCC*, but are also open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of the authors.

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