

## Supplementary 1

### **RESULTS – OTHER INDICATIONS**

*Key issue: Inflammatory Bowel Disease (IBD)*

#### **FMT for ulcerative colitis (UC)**

**Statement:** There is insufficient evidence to recommend FMT as a treatment for UC in clinical practice. To date, its use should be limited to the research setting.

**Quality of evidence:** moderate

**Strength of recommendation:** weak

**Comment:** Alterations in the intestinal microbiota associated with IBD are well supported by the literature and have been widely accepted by the research community.(1) This led to the development of therapeutic avenues for IBD based on microbial modulation, including antibiotics, probiotics, prebiotics, synbiotics, and faecal microbiota transplantation.(2) In a recent meta-analysis,(3) Shi *et al.* found 14 cohort studies (4-17), and two RCTs on FMT for UC.(18, 19, 3-16) Subsequently, another RCT has been recently published as an abstract.(17) Overall clinical response and remission rates of cohort studies were reported to amount to approximately 60% and 40% respectively. However, these studies are limited by possible publication bias as well as by the presence of considerable clinical heterogeneity, especially with regard to patient selection and preparation, route and dosing of administration, follow-up time, and definition of outcomes.(3) Among the RCTs, two were reported as positive with a small but statistically significant treatment effect. Moayyedi *et al.* reported clinical and endoscopic remission of 24% in the FMT group versus 5% in the placebo group.(intention-to-treat analysis) (19) Paramsothy *et al.* obtained clinical remission and endoscopic improvement in 27% of the FMT group versus 8% of the placebo group (intention-to-treat analysis).(17) Treatment effects of this order were previously reported in large randomised ACT1 and ACT2 and ULTRA trials with infliximab and adalimumab for UC.(20) It is worth noting that the primary endpoint assessment was established after 6-8 weeks of treatment

with weekly or daily faecal enemas, and in that sense both trials only reflect remission induction. In contrast, the RCT by Rossen *et al.* did not show a statistically significant difference in clinical remission at 3 months between patients treated with two donor faeces administrations by nasojejunal tube at 0 and 3 weeks (per-protocol, 41.2%) in comparison to those who were given autologous faecal microbiota (controls – per-protocol, 25%).(18)

Data on changes in the microbiota signature in responders versus non-responders are available from the Dutch and the Canadian study.(18, 19) Both showed that responders in the active treatment group had more similarity to their donors than non-reponders. The Australian RCT used donor faeces derived from multiple donors, which precludes assessment of gain in microbiota similarity.(20)

From these RCTs, it can be deduced that indeed there seems to be a treatment effect of FMT in UC, but it is clear that it is not ‘one size fits all’. Hence, more research needs to be done regarding dosing and route of administration to enhance engraftment of the donor microbiota, as well as with respect to the optimal composition of donor faeces.(21)

Adverse events both in the cohort studies as well as in the RCTs were reported as mild and self-resolving. Cost-effectiveness has not been studied so far.

### **FMT for Crohn’s disease (CD)**

**Statement:** There is insufficient evidence to suggest FMT as a treatment for CD in clinical practice. To date, its use should be limited to research setting.

**Quality of evidence:** low

**Strength of recommendation:** weak

**Comment:** Seven cohort studies have been published on FMT in CD, (21-28) including 2 cohort studies in a paediatric population.(22, 23) There are no available RCTs using FMT in CD. The 2 pooled cohort studies reported clinical remission rate at 6 months as 22/32 (69%).(22, 23) There

were 3 studies that reported outcomes at 4-8 weeks and the overall remission rate was 10/27 (34%). One study reported a significant improvement in quality of life at 4 weeks after FMT using the IBD Questionnaire.(28) Adverse events were mostly reported as self-resolving. However, in a study by Vermeire *et al.*, one patient had aspiration pneumonia after applying FMT via the upper gastrointestinal tract, and as a result of this adverse event the authors changed their protocol regarding the route of faecal administration.(21)

Available studies appear to be considerably heterogeneous with regard to patient selection and preparation, route and dosing of administration, follow-up time, as well as definition of outcomes. In addition, there is the possibility of publication bias.

### **FMT for chronic pouchitis**

**Statement:** There is insufficient evidence to suggest FMT as a treatment for chronic pouchitis in clinical practice. To date, its use should be limited to research setting.

**Quality of evidence:** low

**Strength of recommendation:** weak

**Comment:** There have been two fully published studies on the use of FMT in pouchitis.(29, 30) Both were cohort studies. Stallmach *et al.* studied 5 patients following treatment failure with 10 days of antibiotics.(29) They were then given FMT via gastroscopy: at 4 weeks after FMT, 4 (80%) patients had resolution of symptoms, and at 3 months, 3 (60%) patients achieved a sustained response. Landy *et al.* conducted a trial of FMT in 8 patients with chronic refractory pouchitis, performing a single faecal infusion via nasogastric tube.(30) At 4 weeks following FMT, none of the patients achieved clinical remission but 2 patients, whose pouchitis was previously resistant to ciprofloxacin, regained sensitivity to ciprofloxacin enabling treatment in a standard way. Following FMT, there were variable shifts in faecal and mucosal microbiota composition towards a greater similarity to donor stool and, in some patients, changes in proportional abundance of species

suggestive of a “healthier” pouch microbiota. Both studies did not report any safety issues associated with FMT. Landy *et al.* reported minor adverse events, which were transient, in 3 patients (nausea, vomiting, bloating and fever).(30)

*Key issue: Irritable Bowel Syndrome (IBS)*

**Statement:** There is insufficient evidence to suggest FMT as a treatment for IBS in clinical practice. To date, its use should be limited to research setting.

**Quality of evidence:** low

**Strength of recommendation:** weak

**Comment:** Growing scientific evidence has shown the potential role of gut microbiota in the pathogenesis/pathophysiology of IBS.(31-35) Moreover, at least a subset of IBS patients have a different composition of gut microbiota compared with healthy subjects, and in some studies an association between microbiota composition and symptom pattern and severity has also been found.(35-39) However, currently, it is still debated if the alteration of the gut microbiota has a pathogenic role in IBS or if it is a consequence of other factors (e.g., host immune system, diet, medication, gut motility).(40)

Currently, there are no published RCTs with proper blinding investigating the effect of FMT in IBS. Only few case reports and small, uncontrolled studies have investigated on this issue. Old reports have shown that FMT in subjects with IBS can induce relief of symptoms in 50% of the cases.(41-43) More recently, by examining 13 subjects with IBS, Pinn *et al.* have shown that FMT induces a resolution or improvement of the symptoms in 70% of them.(44) In another recent open-label study, FMT provided adequate relief of overall IBS symptoms and abdominal bloating in nine of 12 (75%) patients with refractory IBS.(45). No data are available on the effect of FMT in subjects stratified by IBS type. There is, however, one pilot study demonstrating that FMT was safe and may have the potential to improve symptoms in patients with slow transit constipation.(46)

*Key issue: Metabolic disorders*

**Statement:** Higher evidence is needed to assess FMT efficacy in metabolic disorders, before its use in clinical setting can be advocated. To date, its use should be limited to research setting.

**Quality of evidence:** low

**Strength of recommendation:** weak

**Comment:** The study of the effectiveness of FMT in metabolic disorders in humans is still in its infancy, with one RCT in MS subjects published and several others underway.(47) Many observational studies in humans have shown microbiota differences between healthy individuals on one hand and obese,(48) MS,(49) or type 2 diabetic subjects on the other.(50) Causality has been studied using FMT in various mouse models.(51, 52) Several correlations between specific bacterial strains and aspects of the MS spectrum (obesity, glucose intolerance/type 2 diabetes, atherosclerosis, adipose tissue inflammation and liver steatosis) have been laid.(53-56) Intervention trials to test some of these strains are currently being carried out.

However, the ideal donor microbiota is not yet elucidated, mechanisms of engraftment are still poorly understood and resultant microbiota after FMT is largely temporary. Lastly, donor-recipient microbiota match can be an important determinant of microbiota engraftment.(57)

*Key issue: FMT in pediatrics*

### **FMT for recurrent *Clostridium difficile* infection in pediatrics**

**Statement:** FMT may have a role for the treatment of rCDI infection in paediatric clinical practice.

**Quality of evidence:** low

**Strength of recommendation:** weak

**Comment:** No RCTs in children with rCDI have been published so far. Data on the efficacy and safety of FMT used in this setting only rely on small observational studies, with up to 10 children

enrolled and no comparison group. In those studies, the overall efficacy of FMT was high, with success rates of 90-100%.<sup>(58-65)</sup> FMT was delivered either to the upper GI tract by nasogastric or transpyloric tubes or to the lower one through colonoscopy. In addition, data in very young children (< 3 year-old) <sup>(58-62)</sup> reported an improvement of growth in children treated with FMT as well.<sup>(62)</sup> However, given the high carriage rate of *C. difficile* in this group of age,<sup>(66-69)</sup> the right selection of patients eligible to this therapy is important.

As far as the safety is concerned, only mild transient symptoms (i.e. vomiting, abdominal pain and diarrhea) have been reported in pediatric series.<sup>(62-65)</sup>

### **FMT for IBD in pediatrics**

**Statement:** There is insufficient evidence to suggest FMT for the management of pediatric IBD. To date, its use should be limited to research setting.

**Quality of evidence:** low

**Strength of recommendation:** weak

**Comment:** To date, no RCTs evaluating the role of FMT in children with IBD are available. A few case series reported conflicting results in terms of efficacy.<sup>(9, 10, 12, 13, 22, 23, 69)</sup> The largest pediatric series published so far reported a clinical response (defined as a decrease of Pediatric UC Activity Score >15) at 1 month in 6 of 9 children with UC treated with serial faecal enemas.<sup>(9)</sup> Smaller studies reported no clinical improvement after FMT delivered via nasogastric tube.<sup>(12)</sup> Recently, a transitory withdrawal of immunosuppressants has been reported in 3 children with UC treated with high frequency faecal infusions firstly delivered by colonoscopy and then by serial enemas.<sup>(12)</sup>

Mild-to-moderate side effects were relatively common,<sup>(9, 13)</sup> and a case of transitory systemic reaction (profuse sweating, vomiting, paleness, tachycardia and fever) was described.<sup>(69)</sup>

## **DONOR SELECTION**

*Key issue: collection of medical history*

### **Recommendations for specific situations**

**Statement:** Additional inclusion/exclusion criteria could be considered when FMT is performed for indications other than CDI in the context of research setting.

**Quality of evidence:** low

**Strength of recommendation:** weak

**Comment:** This statement basically leaves to investigators the chance to design a specific donor profile within a specific research protocol approved by the appropriate regulatory authorities. Specific characteristics of the donor may influence FMT outcomes, especially when FMT is performed to treat chronic, multifactorial disorders, such as IBD or MS. The application of a ‘one-size-fits-all’ approach should be discouraged, as each disorder potentially curable with FMT has its unique imbalance of microbiota composition. For example, temporal bacterial community dynamics may vary among UC patients after FMT,(19, 6) whereas obese/overweight donors were excluded with satisfactory results in MS.(47) Such evidence comes from small sample studies and it is not possible, yet, to identify specific inclusion or exclusion criteria for each particular indication of FMT. Additional studies are required to thoroughly address this issue.

*Key issue: Testing for donor selection*

**Statement:** Potential donors could undergo additional testing when FMT is performed for indications other than CDI in the context of research setting.

**Quality of evidence:** low

**Strength of recommendation:** weak

**Comment:** In case of some particular indications, beyond general testing, additional exams can be exploited to select donors. For instance, full lipid and glycemic profiles of donor should be investigated when FMT is performed for metabolic disorders.

Nevertheless, there is no evidence suggesting this approach for improving specific outcomes, nor definite exclusion criteria for each particular indication of FMT have been well identified.

Additional studies are required to address this issue.

## **PREPARATION OF FAECAL MATERIAL**

*Key issue: Microbiota analysis of donors and recipients*

**Statement:** Metagenomic and phylogenetic analysis of microbiota are suggested only for research purposes.

**Quality of evidence:** low

**Strength of recommendation:** weak

**Comment:** Considering the overall high success rates of FMT for the treatment of rCDI and that specific donor does not seem to affect the efficacy outcome,(70-72) analyses of microbiota do not seem to have a role for the treatment of rCDI in clinical setting. Having in mind a markedly lower microbiota diversity in infants compared to adults,(73, 74) assessment of microbiota in pediatrics and their long term follow up could be reasonable. Phylogenetic analyses based on the sequence of 16S/18S rRNA gene have been proven as a powerful tool for defining dysbiosis in various diseases but also in assessing the change of microbiota during the course of FMT in IBD and rCDI.(18, 75-77) Vermeire et al suggested a link between donor microbial diversity and FMT outcomes in IBD patients.(21) In research settings, beyond CDI treatment, the assessment of microbiota has a potential to improve our understanding of disease resolution process, to introduce criteria for donor selection and technical procedures in indications with lower success of FMT.



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