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TREATMENT CENTRE

For FMT requests and queries please email: [bhs-tr.fmt@nhs.net](mailto:bhs-tr.fmt@nhs.net)



# FMT for IBD

## Ready for prime time?

*Professor Tariq Iqbal*

*University of Birmingham*



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# Disclosures

- speaker fees from Vifor and Pharmacomos

# The idea

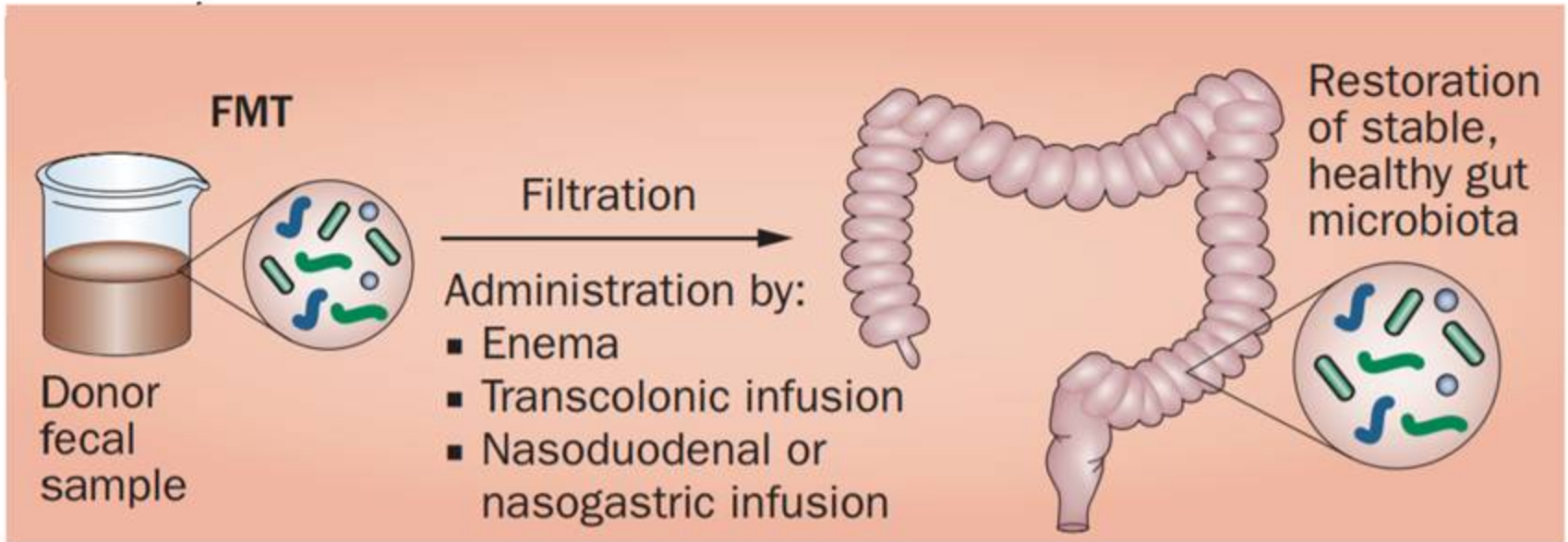
- Patients with “dysbiosis” have lost their healthy microbiota
- This can be corrected by transplantation of stool from healthy donors
  
- E.g. Dysbiosis in IBD
  - Reduced bacterial diversity/richness
  - Relative increase in Proteobacteria/reduction in Bacteroides and Firmicutes

# Specific differences

- Crohns
  - Reduced *F.prausnitzii*\*
  - Increased AIEC
  - Increased *R.torques*
- UC
  - Reduced *F.prausnitzii*\*
  - Reduced *Roseburia hominis*\*
  - Reduced *A.municipiphila*
  - Increased *R.gnavus*

*Manichanh C et al Gut 2006*  
*Joosens M et al Gut 2011*  
*Kostic AD Gastroenterology 2014*  
*Machiels K et al Gut 2014*  
*Gevers D et al Cell Host Microbe 2014*  
*Png CU et al Am.J.Gastro 2010*  
*Lloyd-Price J Nature May 2019*

# Faecal Microbiota Transplantation (FMT)



Borody and Khoruts, Nat Gastro Hep Rev. 2011



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## Problems with the concept of gut microbiota dysbiosis

- Cross sectional association studies underpowered
- Lack of inception cohorts
- No definition of eubiosis
- Confounding factors
- Plea for a more systematic approach with functional outcomes

## **TREATMENT OF ULCERATIVE COLITIS BY IMPLANTATION OF NORMAL COLONIC FLORA**

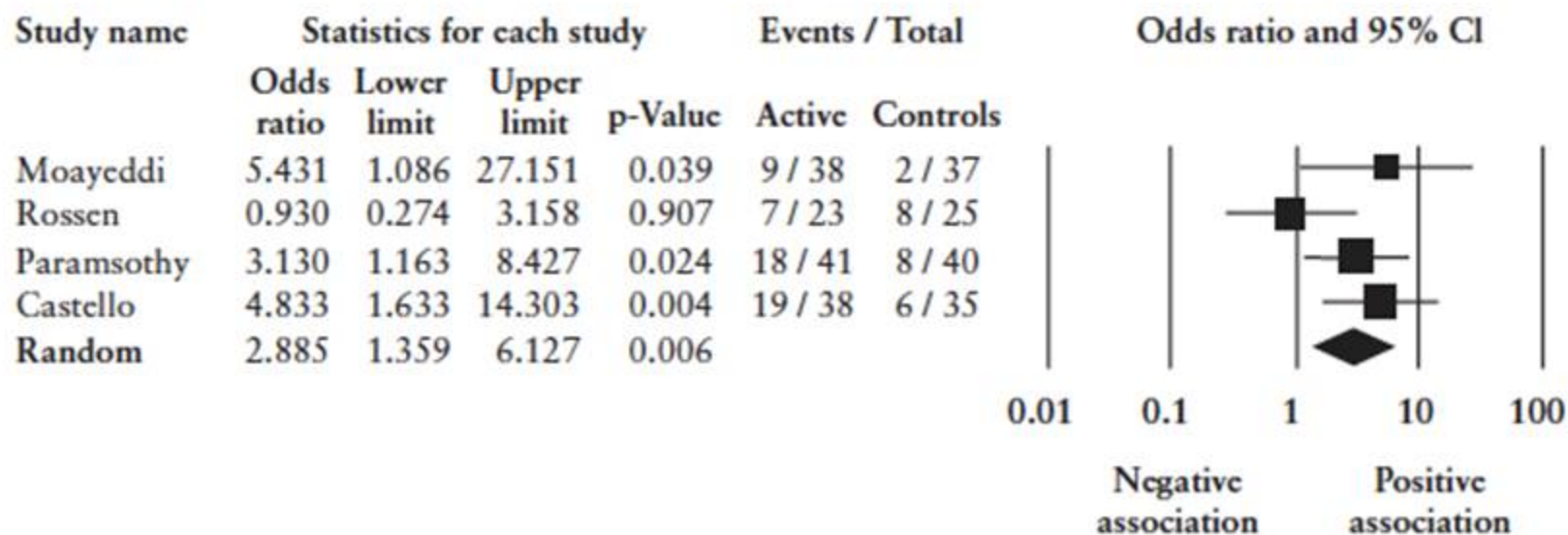
J. D. B. had continuously active, severe ulcerative colitis for 7 years, confirmed endoscopically and histologically.

recurrence of symptoms. It has now been six months since this implantation of “normal” flora, and J. D. B. has been symptom-free for the first time in 11 years without any medication.



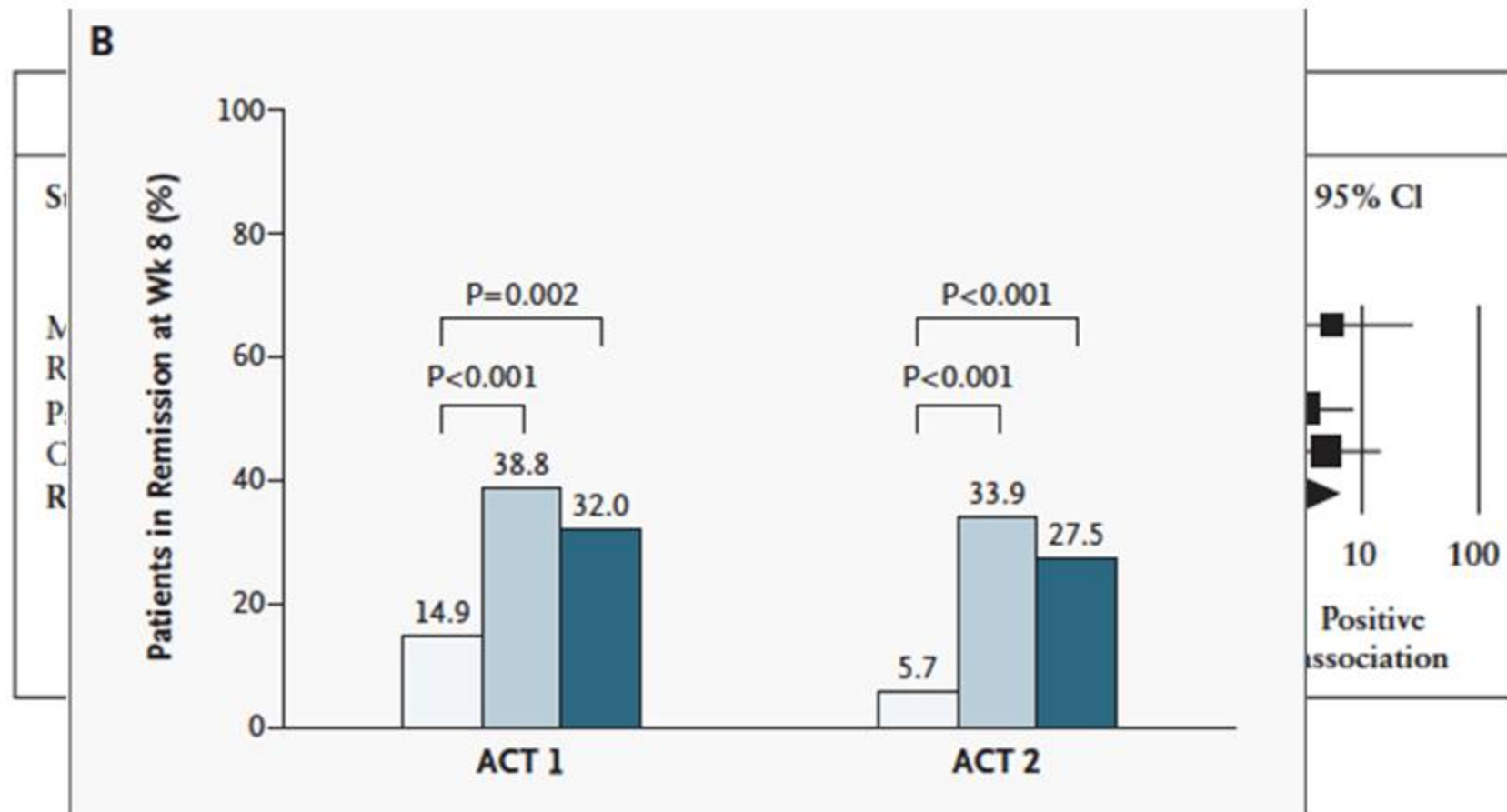
Remission induction donor FMT vs placebo	7/23 (30%) vs 5/25 (20%) P=.51	9/38 (24%) vs 2/37(5%) P=.03	11/41 (27%) vs 3/40 (8%) P=.02	12/38 (32%) vs 3/35 (9%) P<.01
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### FMT in Ulcerative Colitis RCTs - Clinical Remission



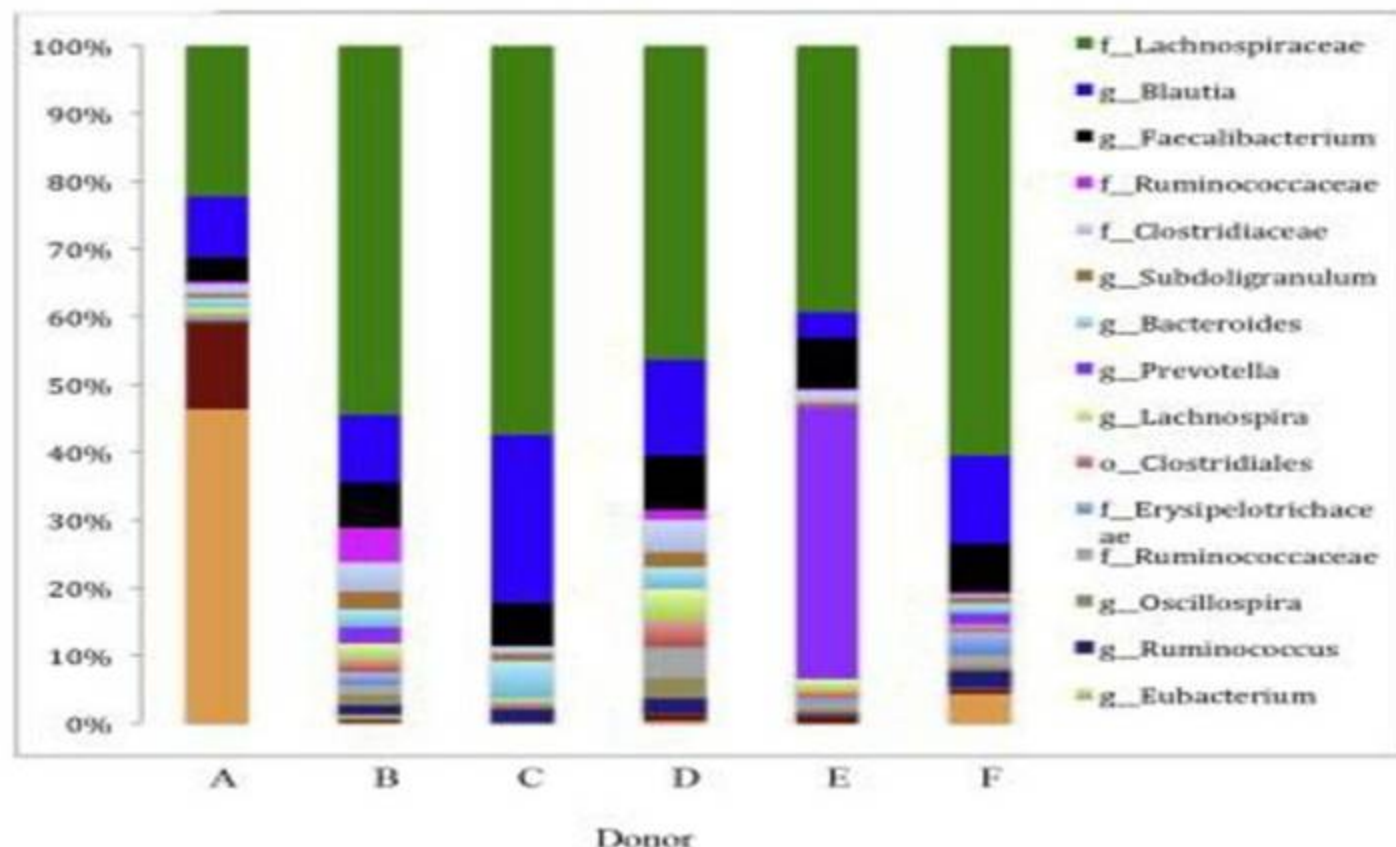


Remission induction donor FMT vs placebo	7/23 (30%) vs 5/25 (20%) P=.51	9/38 (24%) vs 2/37(5%) P=.03	11/41 (27%) vs 3/40 (8%) P=.02	12/38 (32%) vs 3/35 (9%) P<.01
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Paramsothy S et al JCC 2017

## Taxonomic profiles of donors used in the trial.



**\*\*Donor microflora matters\*\***

# Messages from UC trials

- There is a definite efficacy signal
- There are early signals relating to “donor effects”
  - Microbiota richness diversity
  - Clostridia cluster IV and XIVa
- Early mechanistic signals of effect in recipients
  - Microbiota diversity richness and diversity
  - Short chain fatty acid production

*Paramsothy S et al Gastroenterology 2019*

*Costello SP et al JAMA 2019*

*Kump P et al. APT 2018; 47:67-77*

*Vermiere S et al 2016; 10:387-394*

*Rossen Gastroenterology 2015; Moayyedi P Gastroenterology 2015*

# Things we don't know

- The best route of delivery
- What really makes a “super donation”
- Diet
- Is “engraftment” happening or even important?
- Host factors determining response
- Longevity of effect is a problem

# Investigational Medicinal Product



Investigational Medicinal Product  
(IMP) license for use of FMT in research / clinical trials



## STOP-Colitis

**NHS**  
National Institute for  
Health Research

Multicentre RCT investigating FMT for the treatment of active UC

Successfully supplied to STOP-Colitis pilot – completed recruitment April 2019

30 patients - total of over 360 FMT treatments

230 patient RCT to start end 2019

Keen to build collaborations around FMT research



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# STOP-Colitis – our first patient



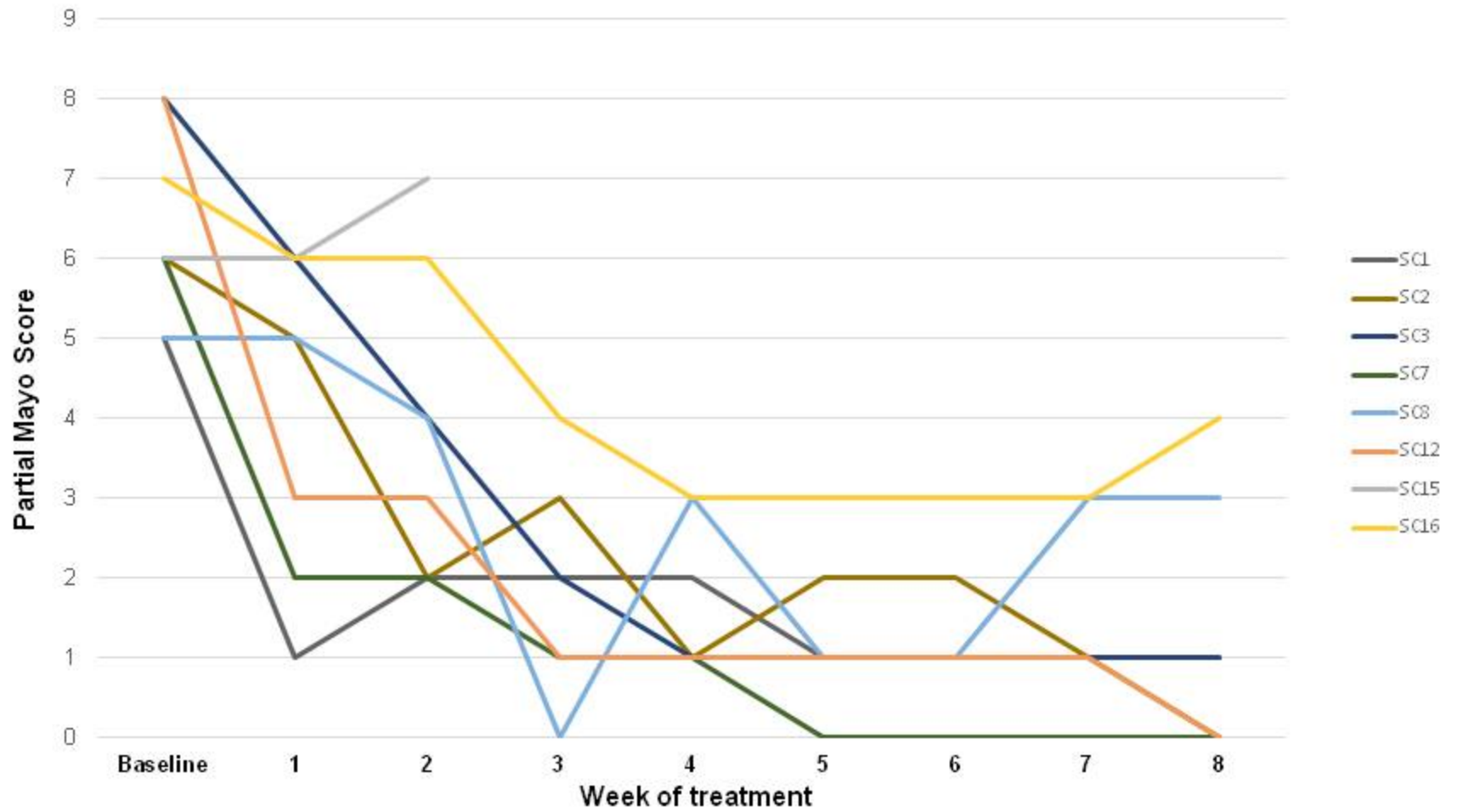
Baseline

Week 8

8 weeks of weekly FMT enemas

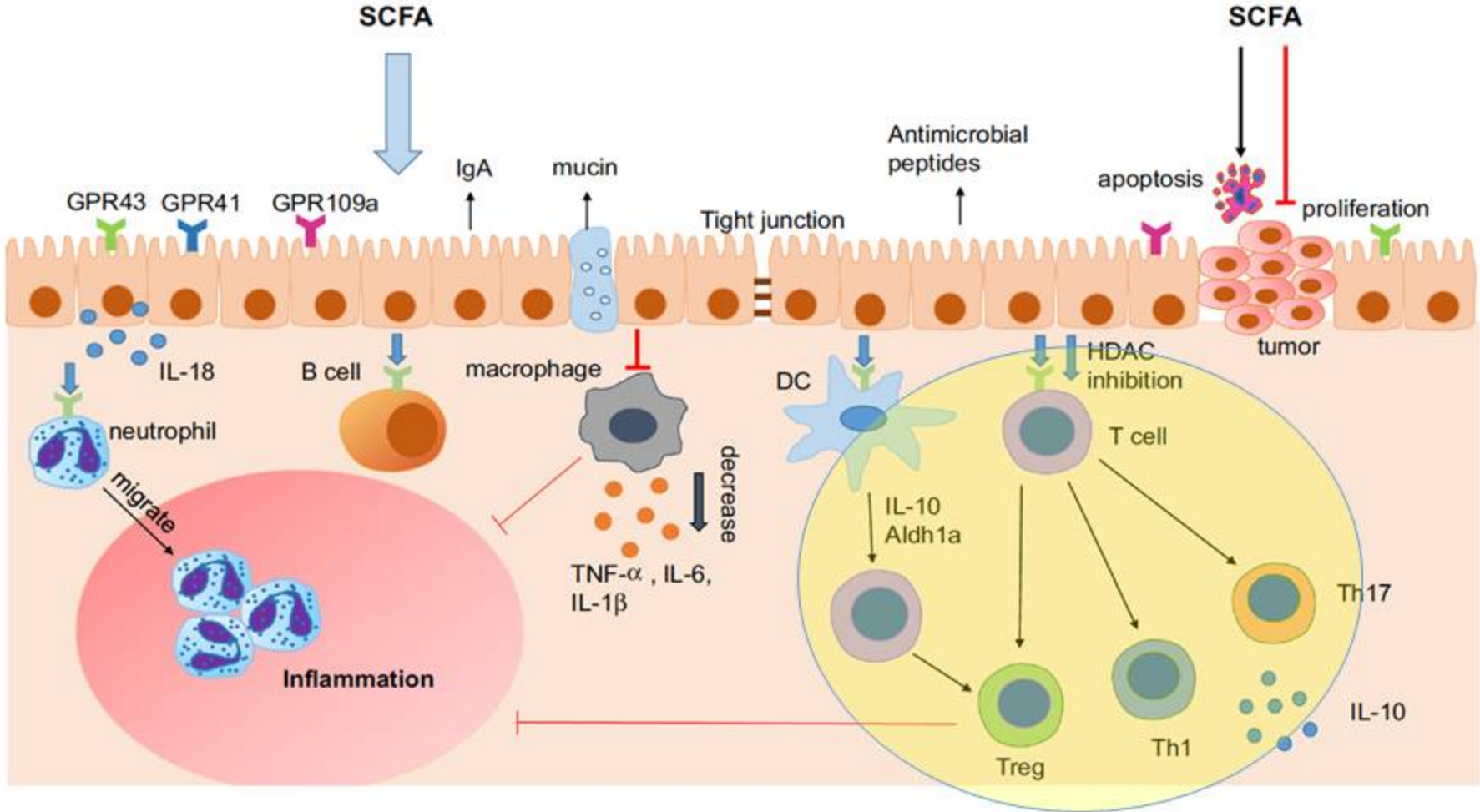


# Colonic Route



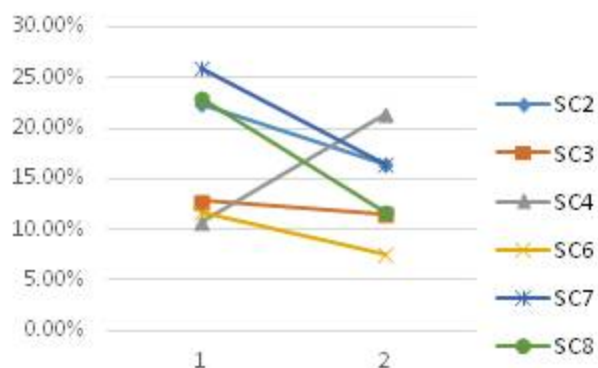


# SCFA signalling

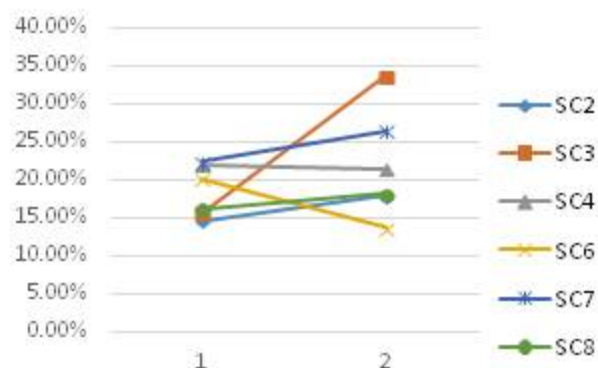


# Treg homing - LPMC

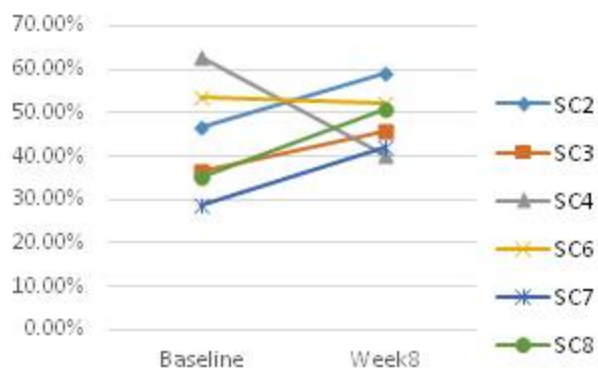
## Naive Tregs



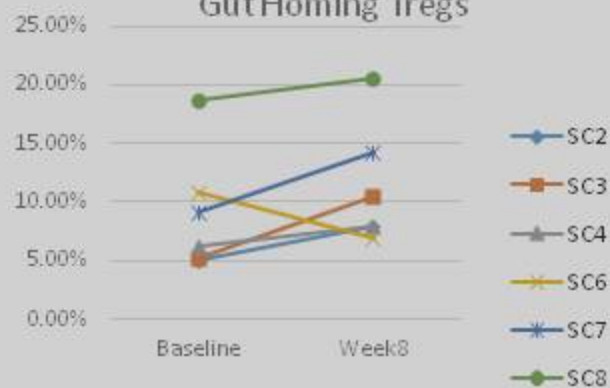
## Central Memory Tregs



## Effector Memory Tregs



## Gut Homing Tregs

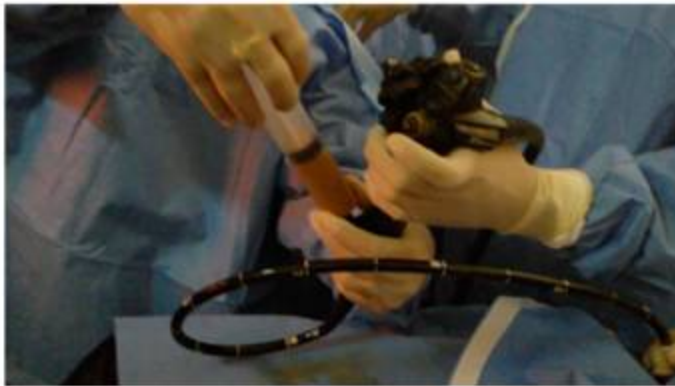


## Faecal Microbiota Transplantation Protocol at New Delhi

Colonoscopic infusion :0,2, 4 weeks  
and every 4 weeks thereafter

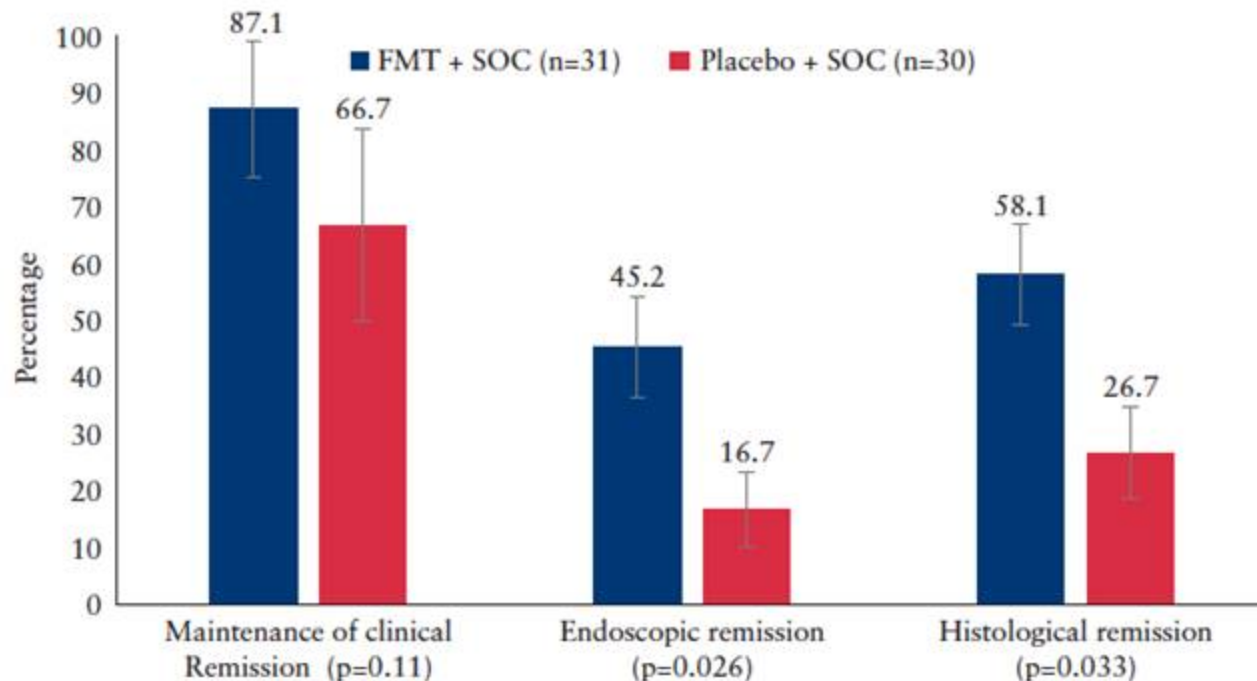
Donors from Rural habitat

No colonoscopic lavage or antibiotics  
prior to FMT



# Role of Faecal Microbiota Transplantation for Maintenance of Remission in Patients With Ulcerative Colitis: A Pilot Study

Ajit Sood,<sup>a</sup> Ramit Mahajan,<sup>a, g</sup> Arshdeep Singh,<sup>a</sup> Vandana Midha,<sup>b</sup>  
Varun Mehta,<sup>a</sup> Vikram Narang,<sup>c</sup> Tarundeep Singh,<sup>d</sup> Anmol Singh Panu<sup>a</sup>



# Pouchitis

- The ileal mucosa after IPAA changes to a colonic phenotype
- The bacterial community of the pouch starts to resemble that of colon
- Pouchitis doesn't develop before ileostomy closure and not in FAP pouches
- Changes in the pouch microbiota with the development of pouchitis
- Colon microbiome predictive

*De Silva et al Gut 1991;32:61-65*

*Kohyama et al 2009*

*Wu H et al. Curr Opin Gastroenterol 2009;25:314-22*

*Reshef L et al Gastroenterology 2015;149:718-727*

*Machiels K et al Gut 2017;66:79-88*



# Pouchitis

13:30 - 14:30

Exhibition Hall N

## FREE PAPERS: PELVIC FLOOR / FUNCTIONAL AND IBD

*Chairs: Tom Øresland (Norway), Peter Christensen (Denmark)*

- **F01** - Can we predict types of fecal incontinence only with pelvic floor investigations? - *Linda Ferrari (UK)*
- **F02** - Transanal irrigation and percutaneous tibial nerve stimulation as treatments for major anterior resection syndrome: a randomised controlled clinical trial - *Ignacio Aguirre-Allende (Spain)*
- **F03** - International Consensus Definition of Low Anterior Resection Syndrome (LARS) - *Celia Keane (New Zealand)*
- **F04** - Colonic motor patterns after distal colorectal resection and relationship to Low Anterior Resection Syndrome - *Celia Keane (New Zealand)*
- **F05** - Long-term function after transanal versus transabdominal ileal pouch-anal anastomosis for ulcerative colitis: a multicenter cohort study - *Pramodh Chandrasinghe (UK)*
- **F06** - Repeated faecal microbiota transplantation is safe and clinically efficient for treatment of chronic pouchitis - *Sabrina Kousgaard (Denmark)*

development of pouchitis

- Colon microbiome predictive

*De Silva et al Gut 1991;32:61-65*

*Kohyama et al 2009*

*Wu H et al. Curr Opin Gastroenterol 2009;25:314-22*

*Reshef L et al Gastroenterology 2015;149:718-727*

*Machiels K et al Gut 2017;66:79-88*

# FMT is not without risk



## FDA In Brief: FDA warns about potential risk of serious infections caused by multi-drug resistant organisms related to the investigational use of Fecal Microbiota for Transplantation

June 13, 2019

Two immunocompromised adults who received investigational FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E.coli*). One of the individuals died.

FMT used in these two individuals were prepared from stool obtained from the same donor.

The donor stool and resulting FMT used in these two individuals were not tested for ESBL-producing gram-negative organisms prior to use. After these adverse events occurred, stored preparations of FMT from this stool donor were tested and found to be positive for ESBL-producing *E. coli* identical to the organisms isolated from the two patients.

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## FDA Suspends Clinical Trials Involving Fecal Transplants

The agency issued a safety warning after two patients contracted antibiotic-resistant infections and one of the patients died.

Jun 14, 2019



BSG / JHI guidelines for donor stool screening

### Box 3 Recommended stool screening for stool donors.

- ▶ *Clostridium difficile* PCR
- ▶ *Campylobacter*, *Salmonella*, and *Shigella* by standard stool culture and/ or PCR
- ▶ Shiga toxin-producing *Escherichia coli* by PCR
- ▶ Multi-drug resistant bacteria, at least CPE and ESBL\*
- ▶ Stool ova, cysts and parasite analysis, including for Microsporidia
- ▶ Faecal antigen for *Cryptosporidium* and *Giardia*
- ▶ Acid fast stain for *Cyclospora* and *Isospora*
- ▶ *Helicobacter pylori* faecal antigen
- ▶ Norovirus, rotavirus PCR.

\*While carbapenemase-producing Enterobacteriaceae (CPE) and extended spectrum beta-lactamases (ESBL) are the only multi-drug resistant bacteria that are recommended to be screened for universally, consider testing for other resistant organisms (including vancomycin resistant Enterococci (VRE) and/or methicillin resistant *Staphylococcus aureus* (MRSA)) based on risk assessment and local prevalence

FMT should not be obtained from unreliable sources.  
Only licensed for Rx of recurrent / refractory CDI  
Patients should be dissuaded from going to unregulated FMT clinics in UK or performing DIY treatments



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# FMT for IBD Ready for prime time?

- No-we need more evidence with regard to:
  - Efficacy
  - How to place it in relation to biologics
- Yes-if you live in India
  - And can't afford biologics



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### The Team

- Tariq Iqbal
- Peter Hawkey
- Vicky McCune
- Sue Manzoor
- Sabida Shabir
- Nabil Quraishi
- Shankar Seetharaman
- Jane Steele
- Stool donors
- Blood bikes

To order FMT for your patient

Call UoBMTC

0121 414 4547

or

email: [bhs-tr.fmt@nhs.net](mailto:bhs-tr.fmt@nhs.net)

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# FMT National Guidelines - 2018



Need for standardisation of FMT preparation and administration in UK

Joint publication in GUT and Journal of Hospital Infection in 2018

- Indications for FMT
- Donor Screening
- FMT preparation and storage
- Patient preparation
- FMT administration
- Requirements for setting up FMT service

Guidelines

The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines

Benjamin H Mullish,<sup>1,2</sup> Mohammed Nabil Quraishi,<sup>3</sup> Jonathan P Segal,<sup>1,4</sup> Victoria L McCune,<sup>5,6</sup> Melissa Baxter,<sup>7</sup> Gemma L Marsden,<sup>8</sup> David J Moore,<sup>9</sup> Alaric Colville,<sup>7</sup> Neeraj Bhala,<sup>3,8,10</sup> Tariq H Iqbal,<sup>3,10</sup> Christopher Settle,<sup>11</sup> Graziella Kontkowsk,<sup>12</sup> Ailsa L Hart,<sup>1,4</sup> Peter M Hawkey,<sup>6</sup> Simon D Goldenberg,<sup>13,14</sup> Horace R T Williams<sup>1,2</sup>



Available online at [www.elsevierdirect.com](http://www.elsevierdirect.com)

Journal of Hospital Infection

Journal homepage: [www.elsevier.com/locate/jhin](http://www.elsevier.com/locate/jhin)



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## The STOP-COLITIS team

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- *Nabil Quraishi*
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- *Nick Loman*
- *Jonathan Mathers*
- *BCTU (Shrushma Loi)*

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- *Clare Blackwell*

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