Meeting update: faecal microbiota transplantation—bench, bedside, courtroom?

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INTRODUCTION
A group of stakeholders met, under the aegis of the British Society of Gastroenterology, to discuss the current landscape of faecal microbiota transplantation (FMT) within the UK and beyond. The meeting covered a wide range of topics, ranging from the practical aspects of establishing an FMT service and regulatory issues relating to its delivery, to research implications and likely future directions.

CLINICAL EVIDENCE TO DATE
Case report and case series data supportive of the efficacy of FMT as treatment for recurrent/refractory Clostridium difficile infection (CDI) have slowly accumulated over many decades, but randomised trial data supporting its use for this indication were lacking until as recently as 2013.1 There are now a growing number of randomised studies/trials that have consistently demonstrated the much greater efficacy of FMT than that of vancomycin in inducing remission from recurrent/refractory CDI; success from a single FMT is quoted at ≥80%, and for two FMTs as ≥90%.1 FMT appears to be similarly as efficacious for this indication regardless of whether the transplant is delivered via the upper gastrointestinal (GI)1 or lower GI tract.2,3 Based on this clinical evidence (along with data supporting the cost effectiveness of FMT in comparison with other treatment strategies), FMT has now been accepted as an appropriate treatment option for recurrent/refractory CDI by the National Institute for Health and Care Excellence,5 Public Health England6 and European guidelines.7

There is increasing recognition that a distinctive pattern of alteration of the structure of the gut microbiota (or ‘dysbiosis’) appears to characterise a number of conditions, including inflammatory bowel disease and metabolic syndrome. Although it remains largely unclear as to whether these microbiota changes are a cause of these conditions, consequence or incidental, there is much interest as to whether manipulation of the gut microbiota might be a successful novel therapeutic strategy; however, clinical studies in this area are largely lacking at present.8 Two recent randomised controlled trials of FMT as a potential treatment for ulcerative colitis9,10 were largely negative, but included microbiota analysis that suggested that only certain stool donors may be effective, and that matching between donor and recipient may be required.

ESTABLISHING A CLINICAL FMT SERVICE
The first session focused on the practical aspects of setting up a clinical FMT service, with Dr Benjamin Mullish sharing his experience of establishing a service at Imperial College Healthcare NHS Trust. Although primarily started to treat patients with recurrent/refractory CDI within the Trust itself, the paucity of similar services within the area means that it has ended up as the primary centre for this service within North London. There are very few exclusion criteria for recipients of FMT within this service; in particular, it was discussed that the currently available clinical evidence for immunosuppressed patients receiving FMT for recurrent CDI has shown a comparable efficacy and limited adverse events.11 Imperial have adopted upper GI administration of FMT of stool that has been previously processed and frozen in

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help explain the efficacy of FMT for CDI, and may
have wider implications as manipulation of the micro-
biota is explored in a range of conditions. Concepts
such as functional redundancy and disability were also
introduced. ‘Functional redundancy’ refers to the pool
of gut microorganisms which may absorb any poten-
tial insults and be replaced by others with little to no
effect on the host, and with no loss of gut microbiota
function. In contrast, ‘functional disability’ describes a
microbial ecosystem with little ability to cope with
any external insult; in humans, this may have been
derived from multiple aetiologies, such as microbiota
depletion as a result of repeated antibiotic use (the
so-called ‘missing microbiota’ hypothesis).

ROLE FOR FMT IN NON-GASTROINTESTINAL
DISORDERS
Professor Max Nieuwdorp, an endocrinologist based at
the Academic Medical Centre in Amsterdam—and
coauthor on the key first randomised trial for FMT in
treating CDI—presented his work on the potential role
of the gut microbiota in metabolic syndrome. Work in
rodents and now in humans has suggested that FMT
from lean donors may increase insulin sensitivity in
those with metabolic syndrome, and that the delivery
of butyrate-producing bacteria may be the key mechani-
sm underlying this. Butyrate-producing strains of bac-
teria may exert metabolic benefits via a number of
routes, including enhancement of mitochondrial activ-
ity, suppression of metabolic endotoxaemia and/or activ-
ination of intestinal gluconeogenesis.

Professor Claudia Mauri (from University College
London) discussed the possible implications of the gut
microbiota to rheumatology. IL-1-receptor antagonist
knockout mice raised in a germ-free (ie, bacteria-free)
environment have no joint disease, but rapidly
develop severe T cell arthritis if raised in conventional
housing, or even after exposure to Lactobacillus
bifidus only. Dysbiosis has been described in patients
with rheumatoid arthritis, with Porphyromonas gingi-
valis detected in higher amounts in oral mucosa. P
gingivalis may have a key mechanistic role in the
onset of rheumatoid arthritis, as it activates enzymes
which may be responsible for protein citrullination;
30% of those positive for anticitrullinated peptide
antibodies will develop rheumatoid arthritis if found
to be positive on screening.

Professor Paul O’Toole—a microbiologist from
University College Cork—discussed the contribution
of the microbiota to human ageing. His research (the
Eldermet project) has shown very distinctive patterns
of microbiota alteration among elderly people in dif-
f erent environments (for instance, between people in
long-term residential care compared with those living
in the community). However, difficulties exist in
designing and interpreting studies in this area—for
instance, is it the person’s living environment that
explains the structure of their microbiota per se, or is
this just a proxy for their diet, medical comorbidities,
etc?

The next topic of discussion was regarding the
brain–gut microbiota axis, a long-standing interest of
Professor John Cryan and his team at University
College Cork. It is increasingly being recognised that
there may be a link between the gut microbiota and a
range of conditions with a neurological component,
including hepatic encephalopathy, multiple sclerosis, affective disorders and even irritable bowel syndrome. In rodents, administration of oral non-absorbable antibiotics or FMT produced consistent changes in behaviour and alterations in the expression of brain-derived neurotropic factor. Similar results have started to emerge for the manipulation of the microbiota in rodent models of neurological and psychiatric disease.

THE FUTURE OF FMT
Despite the efficacy of FMT for recurrent CDI, it evidently has drawbacks, including its unpalatability, the invasive means of administration and concerns regarding transmission of infection. While oral, capsules of FMT has started to emerge, this still represents a considerable pill burden in its current form and remains an essentially untargeted therapy. Of particular interest, a group from Canada has recently demonstrated that a ‘stool substitute’ of 33 pure bacterial strains of commensals isolated from the stool of a healthy person may have similar efficacy in treating CDI as a full FMT. As the mechanisms underlying the efficacy of FMT continue to emerge, future directions may include yet further refinement, perhaps even to a scenario where bacterial derived products (eg, enzymes) or metabolites alone might replace FMT.

REGULATORY AND GOVERNANCE FRAMEWORK FOR FMT
FMT providers have voiced concerns regarding ongoing uncertainties regarding the regulation and ‘quality assurance’ of FMT services in the UK and beyond. Public interest in FMT is high, and already there has started to be the emergence of unregulated private FMT clinics, along with reports of home preparation and administration, with the inherent risks associated with it. Both the British Society of Gastroenterology and Healthcare Infection Society have expressed interest in forming a joint regulatory committee, but none exists at present. Public Health England have sought to engage with FMT providers to define standards of good manufacturing practice/appropriate governance of an FMT service, although these have not been formalised at present. With a move in North America towards FMT increasingly being provided by commercial ‘stool banks’ (such as OpenBiome)—and interest from a number of parties in this developing within the UK—such standards will be of key benefit.

Regulation of FMT within the UK has been explored by the Human Tissue Authority (HTA) and the Medicines and Healthcare products Regulatory Agency (MHRA). The HTA have sought clarification from the European Commission about whether FMT would require regulation under the EU Tissues and Cells Directives; the conclusion was that it would not, and that FMT therefore fell outside of the HTA’s remit. The MHRA are currently having an ongoing dialogue with FMT providers within the UK about whether FMT is defined as a ‘medicinal product’ or not, and whether separate regulation for FMT as treatment for CDI and for use in other conditions/within clinical trials may be more appropriate.

CONCLUSIONS
The huge success of FMT in treatment for CDI has provided a launch pad for interest in the role of the gut microbiota in a range of human diseases, GI and otherwise. Scientifically, the key immediate challenge is to better understand the function of the gut microbiota, and the interaction between the gut microbiota and the host’s physiology. Clinically, once discussions regarding regulation have been resolved, refinement of FMT to a more targeted therapy will be a critical next step.

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Speakers and topics
Clinical experience of setting up a faecal microbiota transplantation (FMT) service—Benjamin Mullish, Imperial College London
FMT for GI disease (Clostridium difficile infection and IBD)—Emma Allen-Vercoe, Univ Guelph, Canada
The potential of FMT for metabolic syndrome—Max Nieuwdorp, Academic Medical Center, Amsterdam
The potential of FMT for rheumatology—Claudia Mauri, University College London
Microbiota of the ageing subject—changes, health associations and modulation prospects—Paul O’Toole, Cork
RePOOPulate: the pros and cons of a synthetic gut microbiota for FMT—Emma Allen-Vercoe, University of Guelph, Canada
FMT and the gut/brain axis—Siobhain O’Mabony, Cork
FMT and the current UK regulatory framework—Victoria McCune and Peter Hawkey, Public Health England Birmingham
REFERENCES


