Gut Microbes, FMT and ME

Simon Carding
Norwich Medical School (University of East Anglia)
&
Gut Microbes and Health Research Programme
The Quadram Institute
Starter Clikapad question

From which end do you peel a banana?

1. Top  1) 88%
2. Bottom  2) 12%
Different perspectives
Question 1

Do you suffer from ME?

1. Yes  
2. No  
3. Maybe

1) 43%  
2) 54%  
3) 4%
Question 2

How long have you suffered from ME?

1. less than 2 years
2. more than 2 years  2) 100%
Causes of ME/CFS?

- ME/CFS
- Immune dysregulation
- Mitochondrial impairment
- Intestinal Dysbiosis
- Viral Infection
- Neuro-endocrine impairment
ME/CFS “Epidemics”: Is it an infectious disease?

1934
Los Angeles, California
Misdiagnosed as polio

1948-49
Akureyi, Iceland
Spread to neighbouring towns

1955
Royal Free Hospital, London
Named ME
Spread to 292 hospital staff

1984
Incline Village and Truckee, Nevada
Named CFS
Sick building syndrome
Flu-like illness (Yuppie flu)

1990
61 other outbreaks up to 1990

1995
CDC “Priority 1” listing – New and Re-emerging Infectious Diseases

2019
Neuropathic virus/bacteria infection (originating in the gut)?

Epstein Barr Virus
Serum anti-virus antibodies, virus antigens

Human Herpes Virus 6/7
Serum anti-virus antibodies

Parvovirus B19
Viral nucleic acid in blood and GI-biopsies

Enterovirus
Viral nucleic acid in muscle and GI biopsies

Cytomegalovirus
Serum antibodies to virus activation antigens
Is there a gut origin for ME/CFS?

- Majority of patients (>80%) have significant GI symptoms
- High prevalence of enterovirus infections in patients
- Leaky gut wall
- Increased sensitivity to food
- Consistent evidence of associated microbiome dysbiosis:
  - Decreased diversity
  - Increase in ‘harmful’ bacteria
  - Decrease in ‘beneficial’ bacteria
- Targeting the microbiome can be an effective treatment
Have you, as an ME patient, ever suffered from gut symptoms (pain, nausea, bloating, IBS etc.)?

1. No never
2. Yes, before onset of ME symptoms
3. Yes, after onset of ME symptoms
4. Yes, both before and after ME symptoms

Question 3

1) 8%
3) 38%
4) 54%
Have you heard the time “microbiome”?

1. Yes
2. No

1) 85%
2) 15%
Question 5

Do you know why the microbiome is important for our health and wellbeing?

1. Yes
2. No
3. Maybe

1) 45%
2) 22%
3) 33%
The Human Microbiome

- 100 trillion microbes comprise human microbiome:
  More microbes than human cells
- >150 more microbiome genes than human genes
- >90% of the microbiome is in the gut
- Individually unique – a microbial fingerprint
- Viruses dominate the gut microbiota
- 1,000s of bacterial species:
  Universal core of ~50 species
- Important for immune function & overall health
- May influence brain health via the Gut-Brain Axis
A Balanced Microbiome = Health

An unbalanced microbiome = disease?

Balanced Gut Microbiota

Microbial Dysbiosis
Our microbiome is shaped by who we are and how we live.
>90% of all human diseases are LINKED to microbiome dysbiosis

- Allergy
- Anxiety
- Alzheimer’s Disease
- Asthma
- Atherosclerosis
- Autism
- Celiac Disease
- Cancers
- Cardiovascular Disease
- Crohn’s Disease
- Depression
- Dental Cavities
- Dermatitis
- Diabetes
- Eczema
- Epilepsy
- Gastric ulcers
- HIV infection
- Irritable Bowel Syndrome
- Obesity
- Parkinson’s Disease
- Rheumatoid Arthritis
- Schizophrenia
- Ulcerative colitis
- ME/CFS

How can we fix a faulty microbiome?
It’s like lawn care!

2018 systematic review of all studies showed that the evidence for the usefulness of probiotics in CFS and FMS patients is limited. (Roman et al., Benef. Microbes 2018)

Which strategy is most effective and ideal for a given individual?

- Probiotics
- Prebiotics
- Bacteriotherapy

Microbiota replacement therapy (FMT)

FMT has proved successful in ME/CFS. (Borody et al., ACNME J. 2012)

FMT is not new!

1941 - German soldiers in North Africa consumed fresh “camel poop soup” for dysentery (B. subtilis - Bactisubtil)

4th century: Ge Hong
First recorded use of human faecal suspension by mouth for diarrhoea and food poisoning “Zhou Hou Bei Ji Fang” (Handy Therapies for Emergencies)

16th century: Li Shizhen
Fermented faeces for abdominal diseases with diarrhoea, abdominal pain, fever, vomiting and constipation: “yellow dragon soup” “Ben Cao Gang Mu” (Compendium of Materia Medica)

1957: Stanley Falkow
Fed surgical patients their own encapsulated faeces post-operatively “Ersatz trial”

1958: Ben Eiseman
Faecal enema used to cure 4 patients with pseudomembranous enterocolitis. Surgery 1958, 44(5):854-9

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1989: Tomas Borody

1990s: Jeff Gordon et al.

2013: Els van Nood et al.

(Adapted from De Groot 2017, Gut Microbes)
FMT and ME/CFS

- 60 mild-severe ME/CFS patients; 52 with IBS
- FMT – mixture 13 enteric anaerobic gut bacteria
- Transcolonic infusion + rectal infusion
- 42 responded – improved sleep deprivation, fatigue & lethargy
- 7/12 (58%) reported being symptom free at 15-20 year follow up
- Resolution of GI-symptoms was seen in 37/42 (88%)
- Promising findings that need to be substantiated in a clinical trial

Can Faecal Microbiota Transplantation (FMT) be used to restore a healthy microbiome in ME patients and improve their physical and mental health?

RESTORE-ME: A Phase IIIB clinical trial
**RESTORE-ME study design**

- Single site, Randomised, Double-Blinded, Placebo Controlled Phase IIb study
- 160 patients (+18y; mild-moderate severity, symptoms) recruited via ECCH
- 80 receive treatment FMT (NJT), 80 receive placebo (autologous FMT) at QI-NHS-NNUH Endoscopy Unit
- Donors from QI Stool Bank (used to treat C. difficile infection by NHS-NNUH)

**Distinct Features of the trial**

- The **first** (Phase IIb) clinical trial to assess efficacy of FMT in ME
- The **first** trial in ME to use objective outcome measures; physical activity & cognitive function assessments
## Study Team & Design

### Study Team includes:
- Primary Care Specialists (ECCH)
- Consultant Clinical Microbiologist (NNUH)
- Physical Activity Specialist (UEA)
- Gastroenterologist (NNUH)
- FMT Specialists (QIB)
- Clinical Trials Specialists (UEA-CTU)
- Bioinformaticians (QIB)
- Ageing and dementia research (UEA)
- Human research governance (QIB)
- Statisticians and data analysis (QIB)

### Data collection

<table>
<thead>
<tr>
<th>Data collection</th>
<th>Time point</th>
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<tbody>
<tr>
<td>Written consent</td>
<td>+</td>
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<tr>
<td>Modified DePaul Questionnaire (DSQ2)</td>
<td>+</td>
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<tr>
<td>Cognitive function (ACE-III, CCI, PHQ-9)</td>
<td>+</td>
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<tr>
<td>Hospital Anxiety Depression Scale</td>
<td>+</td>
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<tr>
<td>Actimeter (wrist/thigh worn)</td>
<td>+</td>
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<tr>
<td>Quality of life (SF-36)</td>
<td>+</td>
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<tr>
<td>Patient reported adverse event Q</td>
<td>+(L)</td>
</tr>
<tr>
<td>Antibiotics, food supplements Q</td>
<td>+</td>
</tr>
<tr>
<td>Microbiome Questionnaire (Long, Short)</td>
<td>+(S)</td>
</tr>
<tr>
<td>Stool sample</td>
<td>+</td>
</tr>
<tr>
<td>Blood sample</td>
<td>+</td>
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<tr>
<td><strong>FMT</strong></td>
<td>+</td>
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- **-1w**: 1 week before intervention
- **0**: Baseline
- **+1m**: 1 month
- **+3m**: 3 months
- **+6m**: 6 months
Outcome Measures

- The intervention will be considered a success if there is an improvement in at least one of the following outcome measures:

**Primary:**
- Overall physical activity
- Change in cognitive function (cognition, episodic memory, executive function)

**Secondary:**
- Safety
- Acceptability
- Improvement in any pre-intervention symptoms of GI disorders (e.g. IBS) at any of the follow ups
- Number of Participants with Adverse Events as a Measure of Safety and Tolerability
The UK Medicine and Healthcare Products Regulatory Agency (MHRA) classifies FMT as a medicinal product. All medicinal products should be produced according to the principles of GMP under MHRA licence.

The QI Faecal FMT Facility

GMP Compliant QI-FMT Facility

MHRA approved
Fit Out

MHRA Insp

MHRA License

Licenses/Approvals

IRAS/HRA

MHRA

Recruitment

Dec. 2019-Feb. 2020
Mar. 2020
Apr.-May 2020
Apr. – Aug. 2020
Sept 2020 (Trial starts)

Funding Applications

More Fundraising

Medicines & Healthcare Products Regulatory Agency (June 2015),
Faecal microbiota transplantation

Dr Ngozi Elumogo, MBBS, FRCPath
Consultant Microbiologist (NNUH)
Senior Research Fellow in Translational Medicine (Quadram Institute)
Aims

• Why FMT at NNUH/Quadram Institute?
• How we set up our FMT service
• Safety of FMT
Brief history of FMT

- Bacteriotherapy, faecal transfusion, faecal transplant, stool transplant, faecal enema, human probiotic infusion
- 4th century China (yellow soup, golden syrup)
- Some baby animals eat their mothers' faeces to get good bacteria (coprophagia) – rabbits, elephants, hippos calves, koalas etc.
Faecal microbiota transplant for recurrent Clostridium difficile infection
Issued: March 2014
NICE interventional procedure guidance 485
guidance.nice.org.uk/ipg485
FMT approved by NICE

• Current evidence on the **efficacy** and **safety** of faecal microbiota transplant for recurrent *Clostridium difficile* infection is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit.

• Clinicians should ensure that a confidential record is kept of the donor and recipient of each faecal microbiota transplant.

• NICE encourages further research into faecal microbiota transplant for *C. difficile* infection, specifically to investigate optimal dosage, mode of administration and choice of donor.
Objectives on FMT

- Replace with healthy flora
- Right composition
- Restore Microbial diversity
Stages of FMT

- Pre-screened donor register
- Identify eligible patient
- Notify donor and FMT lab
- Administer donor questionnaire
- Book endoscopy, prep patient
- Prepare donor material
- Infuse FMT
- Store aliquots (donor and recipient)
- Follow up
### Donor exclusion criteria for fecal microbiota transplant

<table>
<thead>
<tr>
<th>Absolute</th>
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<tbody>
<tr>
<td><strong>Risk of infectious agent</strong></td>
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<tr>
<td>Known HIV, hepatitis B or C infections</td>
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<tr>
<td>Known exposure to HIV or viral hepatitis (within the previous 12 months)</td>
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<tr>
<td>High-risk sexual behaviors</td>
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<tr>
<td>Use of illicit drugs</td>
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<tr>
<td>Tattoo or body piercing within six months</td>
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<tr>
<td>Incarceration or history of incarceration</td>
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<tr>
<td>Known current communicable disease (eg, upper respiratory tract infection)</td>
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<tr>
<td>Risk factors for variant Creutzfeldt-Jakob disease</td>
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<tr>
<td>Travel (within the last six months) to areas of the world where diarrheal illnesses are endemic or risk of traveler’s diarrhea is high</td>
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<tr>
<td><strong>Gastrointestinal comorbidities</strong></td>
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<tr>
<td>History of inflammatory bowel disease</td>
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<tr>
<td>History of IBS, idiopathic chronic constipation, or chronic diarrhea</td>
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<tr>
<td>History of gastrointestinal malignancy or known polyposis</td>
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<tr>
<td><strong>Factors that can or do affect the composition of the intestinal microbiota</strong></td>
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<tr>
<td>Antibiotics within the preceding three months</td>
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<tr>
<td>Major immunosuppressive medications (eg, calcineurin inhibitors, exogenous glucocorticoids, biological agents, etc)</td>
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<tr>
<td>Systemic antineoplastic agents</td>
<td></td>
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<tr>
<td><strong>Additional recipient-specific considerations</strong></td>
<td></td>
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<tr>
<td>Recent ingestion of a potential allergen (eg, nuts) where recipient has a known allergy to this (these) agent(s)</td>
<td></td>
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<tr>
<td><strong>Relative exclusion criteria that might be appropriate to consider</strong></td>
<td></td>
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<tr>
<td>History of major gastrointestinal surgery (eg, gastric bypass)</td>
<td></td>
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<tr>
<td>Metabolic syndrome</td>
<td></td>
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<tr>
<td>Systemic autoimmunity (eg, multiple sclerosis, connective tissue disease)</td>
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<tr>
<td>Atopic diseases including asthma and eczema, eosinophilic disorders of the gastrointestinal tract</td>
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<tr>
<td>Chronic pain syndromes (eg, chronic fatigue syndrome, fibromyalgia)</td>
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HIV: human immunodeficiency virus; IBS: irritable bowel syndrome.
General/metabolic donor screening:

- Full blood count with differential
- Creatinine and electrolytes to measure kidney function
- Liver function test
- C reactive protein to measure inflammation
NNUH/QI donor screening - More stringent than UK and European guidelines

Blood screening:
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis E
- HIV-1 and HIV-2 antibodies
- HTLV-1 and HTLV-2 antibodies
- Treponema pallidum (Syphilis)
- Epstein-Barr virus
- Cytomegalovirus
- Strongyloides stercoralis
- Entamoeba histolytica serology

Stool screening:
- Ova, cysts and parasites
- Cryptosporidium and Giardia PCR
- Acid fast stain for Cyclospora and Isospora
- Salmonella, Shigella, Campylobacter, by PCR/culture
- Shiga toxin-producing *Escherichia coli* by PCR
- *Clostridioides difficile* PCR and Toxin assay
- Helicobacter pylori faecal antigen
- Norovirus & rotavirus PCR
- Extended spectrum beta lactamase producing organisms (ESBLs)
- Vancomycin resistant enterococci (VRE)
- Meticillin resistant Staphylococcus aureus (MRSA)
- Carbapenemase producing Enterobacteriaceae (CPE)

Unrelated healthy donors, motivated, well informed
Administration via naso-jejunal tube

FMT delivery
Possible side effects

• Belching, abdominal cramps, tummy pain
• Diarrhoea, constipation
• Risks from insertion of tube e.g. bowel perforation
• Possibility of infection- hence NICE governance recommendation and screening guidelines
• Aspiration
• Sepsis
Conclusion

- 90% efficacy (95% if two FMTs) in C. diff
- Natural product
- No supply problems
- Affordable
- No under or over dose
- No drug reaction
- No drug interaction
- No absolute contraindication
- Generally well tolerated
Acknowledgement

- FMT collaborators- (Quadram Institute /NNUH)
- Donors
- NNUH Microbiology lab staff
- Endoscopy unit

- THANK YOU!
- Any questions?
Physical activity measurement in the RESTORE-ME study

Andy Atkin
Lecturer in Behavioural Epidemiology
UEA School of Health Sciences
Outline

- Who am I and what do I do?
- What is physical activity and how do we measure it?
- Physical activity measurement in the RESTORE-ME study
- Some questions for you
- Questions for me
Who am I and what do I do?

- Behavioural Epidemiology
  - Physical activity
  - Sedentary behaviour

- Patterns, Distribution, Determinants
What is physical activity and how do we measure it?

**Physical activity**: Any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal (resting) level.

- Everyday activities (walking, climbing stairs)
- Household chores
- Occupational tasks
- Active hobbies
- Sport and exercise
What is physical activity and how do we measure it?

Multi-dimensional construct:

- Frequency
- Duration
- Intensity
- Type
- Timing
- Context
Physical activity measurement in the RESTORE-ME study

GENEActiv (Activinsights, Kimbolton, Cambs)

- Tri-axial accelerometer
- Waterproof up to 10m
- Designed for 24h wear
- Can be worn on various parts of the body
- Widely used in clinical/non-clinical populations
Physical activity measurement in the RESTORE-ME study?

Physical activity measurement in the RESTORE-ME study?

What can we do with this data:

- Overall activity level
- Time in particular intensities
- Patterns of activity – time of day, day of the week

What the data does not tell us:

- Where you are or who you are with
- The specific activity you are doing
Question 6

How would you feel about wearing an activity monitor for 7 days or more?

1. Fine, no problem
2. Not sure, maybe
3. No, not for me

1) 100%
Question 7

Where would you prefer to wear the activity monitor?

1. On my wrist
2. On my hip
3. On my thigh
4. No preference

1) 92%
4) 8%
Question 8

Which aspects of physical activity are most interesting to you?

1. My overall activity level
2. How long I spend sitting, sleeping or moving
3. Times of day/week I am most/least active

1) 69%
2) 23%
3) 8%
Norfolk and Suffolk ME/CFS Service: East Coast Community Healthcare

Jo Wiggins
ECCH
Norfolk and Suffolk ME/CFS Service
East Coast Community Healthcare

Overview

◆ Outpatient services to both adults and children - appointments, email, home visits

◆ GPs with specialist interest (GPwSI) and knowledge of ME/CFS and specialist therapists including Occupational Therapists & Physiotherapists

◆ Commissioned by all CCGs in Norfolk and Suffolk

◆ Outpatient clinics at Lowestoft, Reydon, Stowmarket, Great Yarmouth, Aylsham, Norwich, Kings Lynn

◆ Variety of input: pacing and activity management, rest and relaxation, analysing activity and energy conservation, goal planning, sleep strategies, illness and other people and managing set-backs
Question 9
How many new referrals do you think ECCH received for the ME/CFS service last year?

1. Less than 350
2. 350 - 750
3. 750 – 1,000
Question 10

How may active patients do you think ECCH have in the ME/CFS service?

1. Less than 600
2. 600 – 1,200
3. 1,200 – 1,800

1) 12%
2) 21%
3) 67%
RESTORE-ME: Research Pathway

- Aim to recruit 160 patients
- Can include both current patients of the service and previously seen patients with a diagnosis of ME/CFS
- Previously discharged patients do not need to be re-referred to service to access research. Interested participants will be able to contact service via telephone to express their interest and assessment will then be organised
- Patients will be (telephone) assessed by a senior member of the team to ensure they meet recruitment criteria
- Current patients will be asked about their interest as part of their normal appointment process
- To register interest in the trial patients can call East Coast Community Healthcare ME/CFS Team on 01493 809977
**RESTORE-ME: Proposed Inclusion and Exclusion Criteria**

**Inclusion**

- Minimum of 18 years of age
- Mild-severe ME/CFS that fulfil the Canadian and the 2015 Institute of Medicine criteria - to be reviewed and finalized by the European ME Clinicians Group, Feb 2020
- Symptom duration for 2-15 years
- Disease coincident with a clinically diagnosed gastrointestinal disorder and/or IBS

**Exclusion**

- Kidney failure
- Congestive heart failure
- Immunocompromised or use of immunosuppressive drugs
- Other disease that may explain ME/CFS symptoms discovered during work up
- Use of antibiotics the last three months
- Pregnancy or breastfeeding
- Serious endogenous depression
- Chronic infectious disease (HIV, hepatitis B or C etc.)
- Introduction of new food supplements, change in diet or introduction of new medications the last three months
Wrap up

Simon Carding
Final question

Based upon what you have learned today about the microbiome, its importance for our health and FMT, do you feel you would be willing to participate in the RESTORE-ME clinical trial?

1. Yes
2. No
3. Maybe

1) 92%
3) 8%