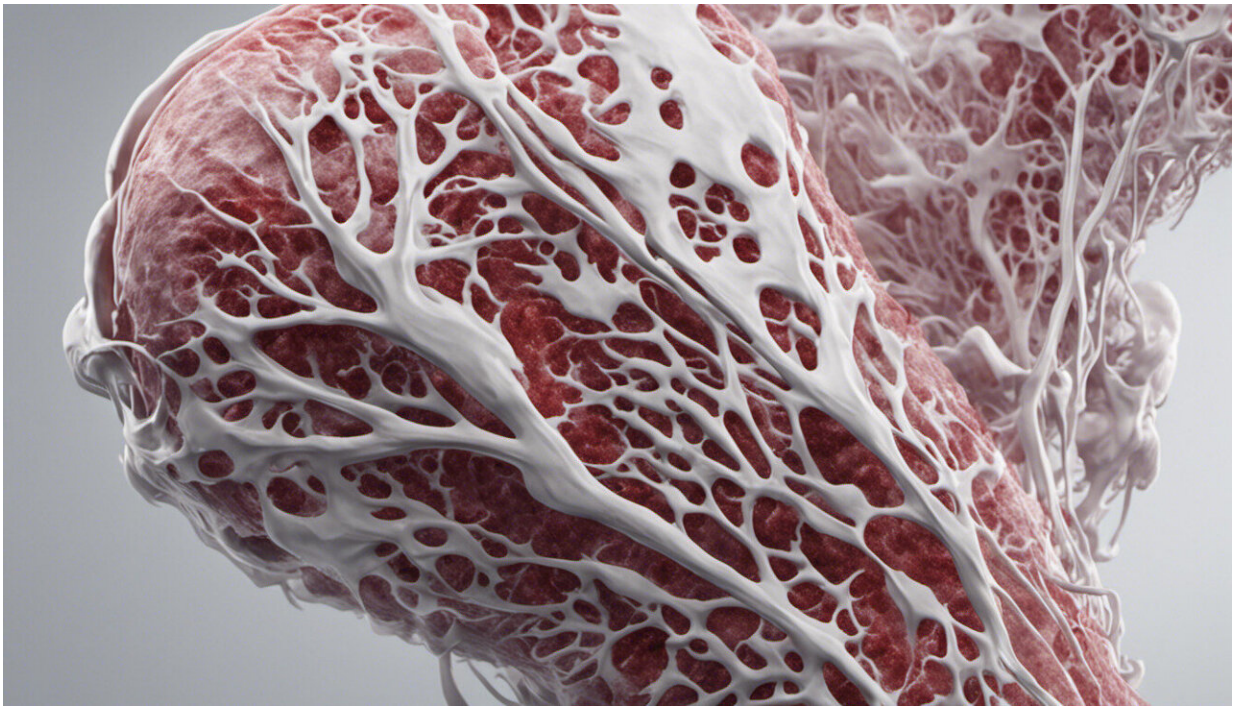
# Faecal transplants, 'robotic guts' and the fight against deadly gut bugs

December 13 2018, by Ryan O'hare



Credit: AI-generated image (disclaimer)

A simple compound found in our gut could help to stop dangerous bacteria behind severe, and sometimes fatal, hospital infections.

Dr. Ben Mullish understands more than most about the seriousness of gut bugs. Although many people will appear to have no more than an upset

stomach for a couple of days, infections of the gut and intestines can prove deadly to vulnerable patients, such as the elderly or those undergoing cancer therapy.

"A typical story is someone is admitted to hospital with a stubborn chest or bladder infection and so have needed a prolonged course of antibiotics. But this treatment then also kills off their normal 'healthy' gut bacteria, leaving them much more vulnerable to infection from harmful bugs," explains Dr. Mullish, a clinical research fellow at the Department of Surgery and Cancer.

One of the most common culprits is Clostridium difficile, or C. diff. The bacterium is a common cause of serious illness, particularly among hospital patients.

The bug causes nasty infections in the bowel, but for the most vulnerable groups, severe and repeated C. diff infections can kill – with more than 1,600 deaths in England and Wales in 2012 alone involving C. diff.

While antibiotics and even giving patients a liquid solution of another person's 'friendly' gut bacteria – harvested from their faeces – can boost recovery from these infections, the intensive treatment and the delivery methods can take their toll on patients and may be less than appealing.

But researchers at Imperial may have uncovered a key to the problem in the form of naturally occurring molecules, called fatty acids, found in our guts – including one that can keep the growth of these harmful bacteria in check.

The hope is that we may one day be able to give these kinds of molecules to vulnerable patients in the form of a pill or supplement – to prevent them from developing a stomach bug in the first place.


By bringing together findings from patients, animal models and even a 'robotic gut' in the lab, the scientists' work is revealing more than ever before about what happens in the guts of patients who repeatedly

succumb to C. diff infections

If their research can be transferred to the clinic, it has the potential to help the most vulnerable patients avoid future infections and complications linked to treatments, tipping the balance in the fight against a dangerous microbial threat.

## Balancing act

On the frontlines of healthcare, C. diff presents a huge problem for infection control. The bacterium can live harmlessly in the guts of some people, but once it takes hold can spread from person to person through poor hygiene. If cases are not isolated and treated, it can lead to outbreaks.

Infections are often very unpleasant, causing gastrointestinal problems for patients like nausea, cramps, pain, diarrhoea and inevitable dehydration and weakness.

However, figures from NHS England estimate that as many as one in every 12 patients (8%) with a C. diff infection may die. The elderly or those with weakened immune systems tend to be most at risk, including patients who have had extended stays in the hospital and treatment with antibiotics, or who have undergone chemotherapy.

"There are about 14,000 cases of C. diff infection in the UK each year, and those with the worst infections often require lengthy stays in the hospital and prolonged rehabilitation," says Dr. Mullish, who treats patients at St Mary's Hospital.

When patients are struck by a bacterial infection, one of the first responses from clinicians is to attack the bacterial invaders with antibiotics to wipe them out. However, this approach is not without risk.

Using broad-spectrum antibiotics for an extended period can make patients more vulnerable to C. diff. infections by wiping out healthy gut bacteria which may have a protective effect.


The chemostat or 'robogut' mimics the environment of the human gastrointestinal tract. Credit: Julie McDonald

The gut is home to trillions of bacteria, fungi, viruses and other microbes, with the average person carrying around up to two kilograms of microbes – collectively called the microbiota. But upsetting this balance can clear the path of competition for other, more harmful bacteria to gain a foothold and colonise the gut – like evicting good tenants from a housing block, leaving a vacant building for rowdy C.diff squatters to move in.

Clinicians are also increasingly coming across stubborn forms of C. diff and other bacteria that can survive these clinical counterattacks, with the harmful bugs developing resistance to antibiotics and recolonising the gut.

## Out with the bad (and the good…)

One approach turned to for some of the hardest to treat patients is faecal microbial transplant (FMT), which aims to give patients' beleaguered gut bugs a boost by introducing bacteria from a healthy donor.

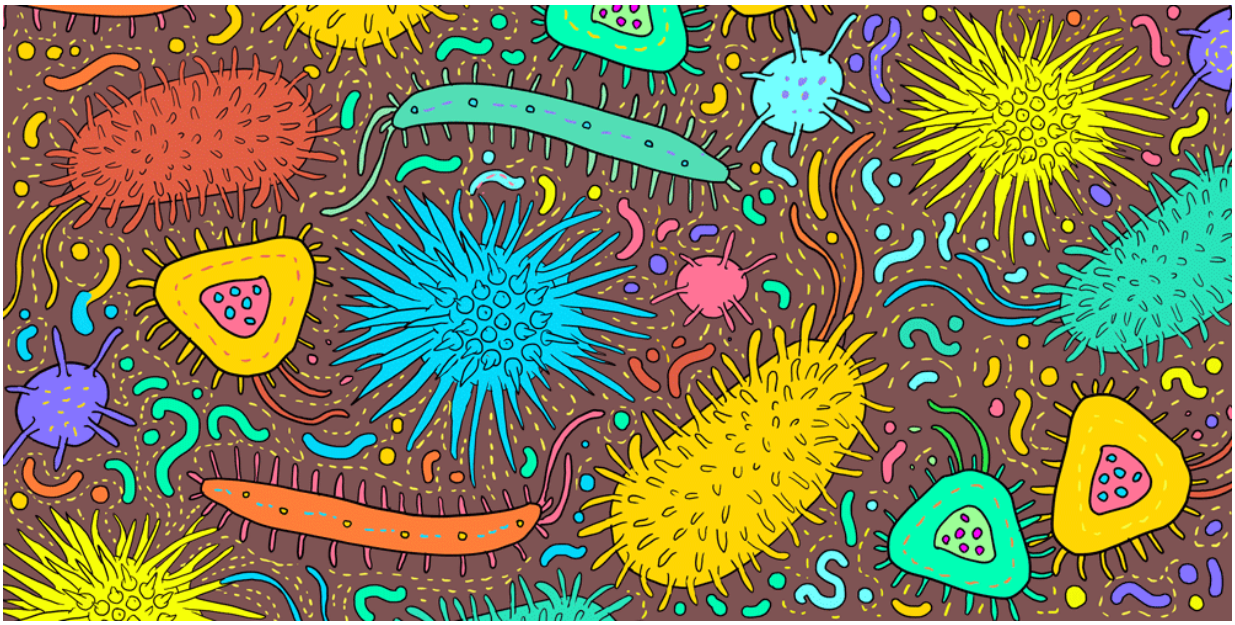
FMT involves taking a sample of a donor's faeces – their poo – and processing it until eventually what's left is a watery fluid packed with microbes. Donors need to be regularly screened for anything that might be harmful, including bacteria like C. diff, viruses like HIV and hepatitis, and any other microbes.

Sick patients can then be given the resulting bacterial suspension via a tube through the mouth and into the stomach, via a colonoscopy, or swallowing multiple capsules, which helps to rebalance their microbiome, often with rapid improvements to health.

"It can work surprisingly well," explains Dr. Mullish. "Some people may

have been in hospital for months, receiving antibiotics. Then you give them this odd treatment and they start to get quite a lot better within a few days."

Dr. Mullish is part of the FMT programme at St Mary's Hospital, one of only a handful of NHS centres in the UK that regularly carries out the procedure.



Credit: Li-Anne Dias

Then there are the 'known unknowns', with concern that introducing other bacteria to patients who are already unwell has the potential, however small, to lead to other diseases in the longer-term.

But evidence is emerging that indirectly targeting a patient's own ailing gut ecosystem could help to supplement, or even supersede approaches

such like FMT, and reduce the potential collateral damage from clinical treatments for C. diff and other bacterial infections.

## Missing ingredient

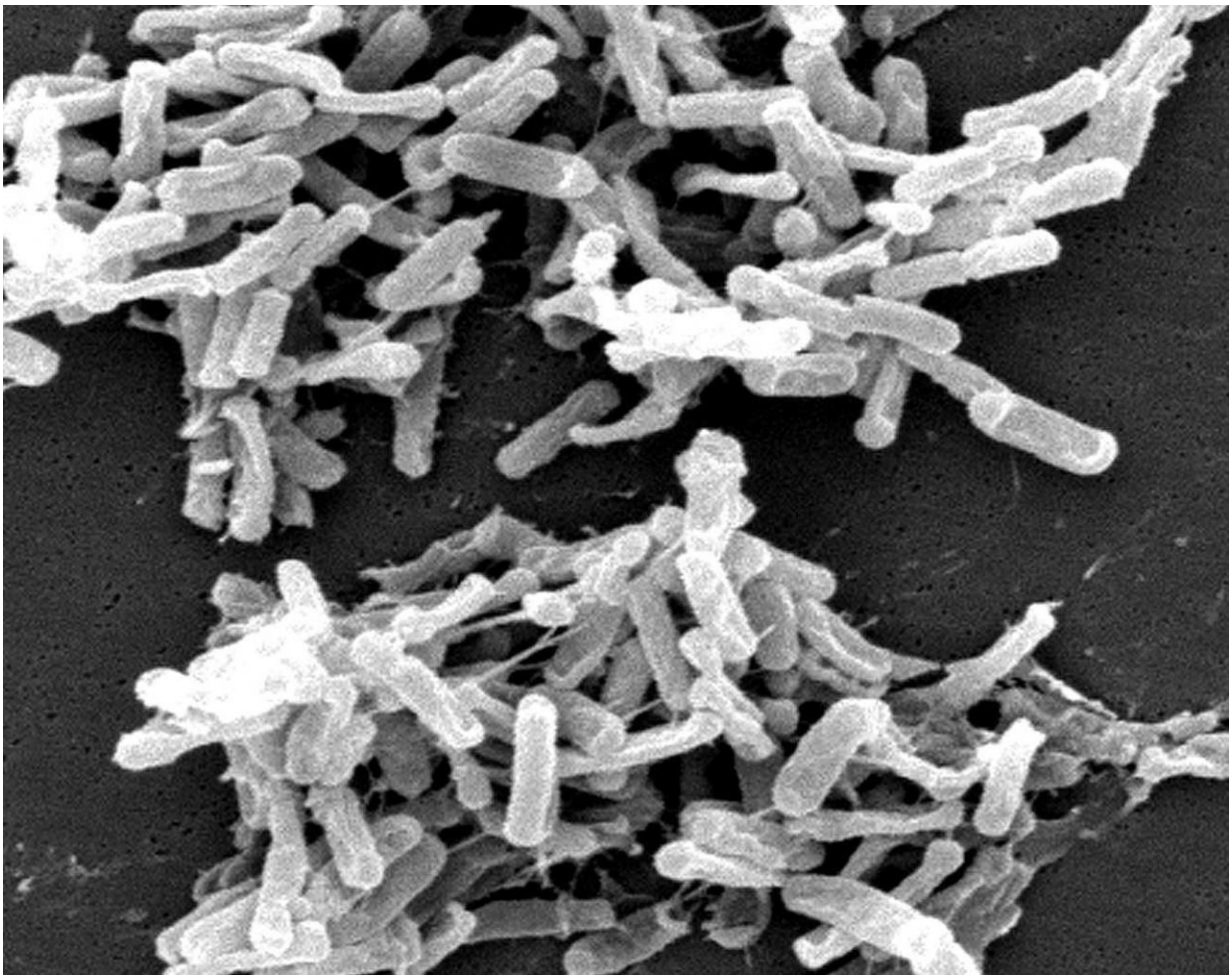
The team at Imperial is zeroing in on the effects on the microbiome before and after infection, to see how the balance shifts and how it might be redressed.

In a recent study, faecal microbes were grown in a chemostat, a sort of 'robotic gut' set up to mimic the environment of the human gastrointestinal tract, which enables scientists to get a snapshot of the patient's gut microbiome.

"It's a cleaner system, so we don't have to worry about confounding factors," explains Dr. Julie McDonald, from the Department of Surgery & Cancer, who is leading the microbial analysis.

Once the microbial cultures were grown, they were hit with a dose of the antibiotic clindamycin to mimic the effects of treatment in hospital. The researchers found that after an initial wave of bacterial death, the microbial populations partially recovered, but the diversity of bugs – the number of different species present – dropped off considerably compared to pre-treatment levels.

However, after faecal transplant, this bacterial biodiversity increased again, with the treatment restoring a far healthier mix of bugs and a richer overall gut environment.



The researchers hope is that dietary supplements – just like a cod liver oil tablet – could shift the environment of the gut to one less favourable to C. diff. Credit: Wikicommons / CDC Public Health Image Library

A closer look revealed that antibiotic treatment also affected the levels of metabolites – substances used and produced by the gut bugs – and revealed one key molecule that particularly stood out, a fatty acid called valerate. In the laboratory, changing the availability of metabolites can either promote or prevent the growth of bugs, giving some bacteria an edge under particular conditions. The same, it may seem, is true in our gut.

"We found valerate decreased after exposure to antibiotics, when C. diff was growing very well, and increased after FMT, where C. diff growth was inhibited," says Dr. McDonald.

The findings, published recently in the journal *Gastroenterology*, suggest that antibiotics may be dampening down certain metabolic pathways found in healthy gut environments and that this change in balance in patients may even promote the growth of C. diff.

Beyond unpicking the mechanism by which harmful bugs gain a firm foothold for infection, the research offers the tantalising prospect of being able to prevent infections just by supplementing someone's diet with molecules like valerate.

They then went on to show that C. diff infected mice given valerate had significantly less C. diff in their faeces compared to mice that did not receive valerate, showing promise for the use of valerate as a treatment. The team stress that more work is needed before this molecule is tested in human trials to see if it could help patients.

The hope is that dietary supplements – just like a cod liver oil tablet – could nudge certain metabolic pathways in the gut, shifting the environment to one less favourable to C. diff, but without the collateral damage of treatments like antibiotics and faecal transplant.

"This could be a potential new way to treat these patients," explains Dr. McDonald. "It could prove safer than existing treatments, especially for vulnerable patients, and it could help to avoid transferring bacteria that could later result in disease."

Dr. Mullish added: "If you could give these patients a simple chemical that exists in all of our guts, instead of or in addition to antibiotics, that would be a much neater process.

"These findings are a great 'bench to bedside' story, highlighting the successful collaboration of clinicians and scientists. We set up the clinical service, sourced samples, used cutting edge techniques at Imperial including microbiome analysis, metabolomics and chemostat modelling."

**More information:** Julie A.K. McDonald et al. Inhibiting Growth of Clostridioides difficile by Restoring Valerate, Produced by the Intestinal Microbiota, *Gastroenterology* (2018). DOI: 10.1053/j.gastro.2018.07.014

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