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Harnessing the gut microbiome to combat antimicrobial resistance: Current strategies and future perspectives

Microbiome therapies are a promising avenue of research for tackling antimicrobial resistance.

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In this article, Blair Merrick explains how therapies involving the gut microbiome, including faecal microbiota transplant, dietary interventions and phages, can be used to suppress the expansion of antimicrobial-resistant pathogens.

Introduction

Antimicrobial resistance (AMR) is one of the most pressing public health threats of the 21st century. If current trends continue, AMR could surpass cancer as a leading cause of death by 2050, with the projected global economic impact exceeding $100 trillion annually.[1] Multidrug-resistant organisms (MDROs) – including the WHO-labelled priority pathogens of extended-spectrum β-lactamase-producing *Enterobacterales* (ESBL-E), carbapenemase-producing *Enterobacterales* (CPE), and vancomycin-resistant *Enterococcus* (VRE) – frequently colonise the gastrointestinal tract before causing infection.[2–4] In doing so, they act as reservoirs for antimicrobial resistance genes (ARGs) and facilitate onward transmission.

Conventional antimicrobial strategies, such as selective digestive decontamination, are insufficient to eradicate these colonisers and may even exacerbate resistance pressures.[5] This has prompted the search for innovative solutions that address the ecological dynamics of resistance.

The gut microbiome is a diverse ecosystem of trillions of microorganisms[6] that plays a pivotal role in health and disease, including colonisation resistance[7] – the ability of native microbiota to suppress pathogen expansion.[8] Perturbation, particularly through antibiotic exposure, creates ecological niches for MDROs. Restoring or enhancing microbiome-mediated colonisation resistance is, therefore, emerging as a strategy to combat AMR.

Therapeutic approaches under investigation include faecal microbiota transplant (FMT), dietary interventions, pre- and probiotics, bacterial consortia and bacteriophages.[9] Each offers a unique pathway to reducing colonisation and infection risk, while highlighting broader questions around scalability, regulation and global accessibility. Addressing these challenges will be essential if microbiome-based interventions are to shift from experimental therapies to mainstream tools in the fight against AMR.

The gut microbiome and colonisation resistance

Human gastrointestinal microbiota are essential for numerous physiological functions, including nutrient metabolism,[10] immune system modulation[11] and maintenance of gut barrier integrity.[12] They also serve as a major reservoir of ARGs, collectively termed the resistome.[13] Antibiotic exposure disrupts microbiota diversity and composition, facilitating expansion and dominance of MDROs.[14]

Colonisation resistance relies on direct competition for nutrients and niches, secretion of antimicrobial metabolites, modulation of bile acid metabolism and immune system priming.[8] When this balance is disrupted, niches are created for MDRO colonisation and persistence, increasing infection risk and onward transmission. Interventions aimed at restoring or enhancing colonisation resistance seek to decrease MDRO burden within the gut, limiting infection and spread.

FMT

FMT involves transferring screened, minimally processed stool from healthy donors into recipients to restore microbial diversity and function. It is an established treatment for recurrent and refractory *Clostridioides difficile* infection (rCDI)[15] and is increasingly being explored for other indications, including MDRO decolonisation.

Uncontrolled studies have reported reductions in MDRO carriage following FMT,[16–21] but results from randomised controlled trials have been mixed, with some showing non-significant trends or feasibility outcomes rather than definitive efficacy.[22–24] Notably, FMT may exert benefit not solely

through donor microbiota engraftment but also via increased dissimilarity between donor and recipient communities and conspecific strain replacement[23,24] – mechanisms that warrant further study.

Despite its promise, FMT faces practical and regulatory hurdles. Donor screening is essential to exclude pathogens, yet this – as well as processing methods, delivery routes and dosing protocols – varies between centres, limiting reproducibility. Capsule FMT offers advantages in safety and acceptability, but some evidence suggests rectal administration may be more effective for decolonising MDROs.[23] Manufacturing capacity remains a major barrier, with demand exceeding supply[25] and regulatory frameworks fragmented internationally.[26] Although licensed stool-based products now exist in North America for rCDI, their cost may restrict widespread use elsewhere, including the UK.[27,28]

Future progress will depend on standardising protocols, clarifying regulatory classification – likely assisted by new European legislation coming into effect in 2027[29] – and expanding supply chains, while also refining clinical endpoints. Importantly, prevention of infection, as demonstrated in renal transplant recipients[23] and in other cohorts,[16] may prove a more relevant goal than MDRO eradication.

Alternative and complementary microbiome modulation strategies

FMT is just one of numerous approaches to modulating the gastrointestinal microbiome. Its limitations underscore the importance of considering alternative and/or complementary strategies.

Dietary interventions are a fundamental lever: fibre-rich and fermented foods promote commensal growth and microbial diversity,[30] potentially reducing ARG carriage and MDRO colonisation.[31] Conversely, diets high in processed foods and saturated fats may disrupt microbiota balance and facilitate MDRO expansion.[32] Observational studies link animal product consumption with specific resistance patterns,[33] with some evidence that targeted restrictions – e.g. avoiding lactose – may reduce VRE carriage in vulnerable populations.[34] Clinical trials are ongoing to validate dietary interventions as adjunctive therapies, but these studies are themselves challenging to run and fund, owing to a lack of commercial interest.

Prebiotics and probiotics offer accessible, scalable tools. Prebiotics may enhance colonisation resistance indirectly by supporting commensal growth, strengthening gut barrier function and modulating immunity,[35] although clinical evidence for MDRO eradication is lacking. Meta-analyses of probiotics suggest they can reduce pathogen persistence, though efficacy appears limited for *Enterobacterales* and VRE, and effects may be strain-specific.[36] Defining which strains or combinations are effective against MDROs is a key research frontier.

Defined consortia of bacterial strains aim to restore colonisation resistance by ecological competition and direct inhibition. Multi-strain consortia have been shown to reduce colonisation by *Klebsiella pneumoniae* and *Escherichia coli* in murine models,[37] and be capable of suppressing antibiotic-resistant Enterobacterales through nutrient competition.[38] Competition is likely to be most efficient when highly related species are used, e.g. *K. oxytoca* and *pneumoniae*,[39] aligning with the conspecific strain competition data in FMT.[23,24] Live biotherapeutic products may offer a safer, standardised alternative.

Phage therapy utilises viruses that infect and lyse specific bacterial hosts, allowing precise targeting of MDROs while sparing commensals. Case reports show success against carbapenemase-producing *K. pneumoniae* and ESBL-producing *Klebsiella* in complex clinical scenarios.[40] Phage therapy faces hurdles, including regulatory oversight, development of phage resistance and manufacturing scalability. Larger clinical trials are needed to define efficacy and safety profiles.

Together, the above strategies illustrate a growing toolkit to be deployed in combination, tailored to context and/or integrated with antimicrobial stewardship. The challenge is moving from proof-of-concept studies towards scalable, regulated interventions with demonstrable benefit.

Conclusion

As traditional antimicrobials face diminishing returns against MDROs, harnessing the gut microbiome emerges as a promising frontier. FMT has laid foundational evidence; early data suggests these interventions may not only reduce colonisation but also translate into meaningful clinical outcomes such as fewer infections – a more relevant endpoint than eradication alone. However, its variability, regulatory uncertainty and limited scalability underscore a pressing need for more standardised and mechanistically defined approaches. Dietary modification, prebiotics, probiotics, targeted bacterial consortia and phage therapy offer complementary avenues.

Emerging technologies, including engineered microbes,[41] CRISPR-based antimicrobials[42] and microbiome-derived metabolites,[43] may further expand the therapeutic landscape, though their safety, delivery and regulatory frameworks remain to be fully defined. Accessibility must also remain a central concern: AMR disproportionately affects low- and middle-income countries.[44] Future strategies must be scalable and affordable globally if they are to mitigate the projected worldwide burden.

Medical microbiologists are uniquely positioned to lead this paradigm shift. Key efforts include integrating microbiome science with antimicrobial stewardship, designing trials that prioritise clinically meaningful outcomes and collaborating internationally to ensure equitable access. By combining mechanistic insight with pragmatic implementation, microbiome-based interventions could become a powerful tool in the global fight against AMR.

References available on our website.

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