Review

Should probiotics be co-prescribed alongside antibiotics to mitigate gut microbiome disturbances?

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Abbreviations

AAD - Antibiotic-associated diarrhoea
NHS - National Health Service

It is well known by now the altering effects certain antibiotics can have on our gut microbiome, with studies postulating long-term disruption being associated with diabetes, asthma and even obesity.[1] Any change in the microbiota, from a healthy pattern to one associated with disease is termed dysbiosis and has a wide range of studied causes, not just antibiotics. One of the first signs of early dysbiosis from antibiotic use is antibiotic-associated diarrhoea (AAD).[2] Despite this association, the current treatments include firstly stopping the antibiotics course early, possibly followed by more, secondary, antibiotics.[3] However, such an approach has increased antibiotic resistance radically, with the latter also being costly for the National Health Service (NHS).[4] With these pressing concerns in mind, along with the NHS' renewed interest in reducing antibiotic use, as seen in the NHS Long Term Plan, probiotics could be the future.[5] Probiotics, literally meaning 'positive bacteria' (for the gastrointestinal tract) are, on the surface, a simple idea of replacing the bacterial diversity lost due to antibiotics.[11] This article will explore evidence-based findings and the possible complications of these tablets to evaluate their future in prescriptions alongside antibiotics.

The gut microbiome

The terms 'gut microbiota', 'microflora' or 'microbial phyla' all describe the community of microorganisms (majorly bacteria) that inhabit the human gastrointestinal tract (gut), while the gut microbiome refers to this community and all their collective genomes.[6] With an approximated 100 trillion microbes in one gut microbiota, it is now considered to be the latest human organ under active research.[7] For the most part, the gut bacteria and their host work in a commensal manner, with these bacteria being vital for digestion, nutrient supply, barrier strength promotion and immune system regulation.[8] In return, they get a protective host environment. While this topic is still elusive in some areas, much research has been done into the effects of the disruption of this reservoir of life, particularly when caused by antibiotics.

The gut microbiome and antibiotics

A systematic review of 31 articles confirmed the disturbances of antibiotics on our gut microbiome. The evidence shows that antibiotics (specifically those commonly prescribed in primary care in the UK) cause rapidly diminishing levels of bacterial diversity and changes in the abundance of certain bacteria.[9] These changes prevent the microbiome from carrying out its vital role, as well as allowing for 'bad' bacteria to increase in numbers. All the studies chosen had a low or unclear risk of bias, although it should be mentioned there was a concern about small sample sizes; however, this was not believed to have skewed the evidence or conclusion. The length of time taken for gut bacteria to recover to pre-antibiotic levels differed between studies, with most stating within a few weeks, but some suggesting longer term issues ongoing for two to six months after antibiotic cessation. This establishes the link between antibiotics and gut dysbiosis and brings to light the prolonged recovery of the gut

even after the antibiotics are stopped.

This proven dysbiosis secondary to antibiotics then goes on to cause AAD in a large majority of patients.[2] This is most common in response to antibiotics that act on anaerobes, namely aminopenicillins and cephalosporins. Between 5 and 30% of patients who take antibiotics will experience AAD either at the beginning or as late as two months after the end of treatment. This is thought to be due to a few reasons, including the new gut bacterial imbalances causing decreased short chain fatty acids absorption which subsequently results in osmotic diarrhoea.[3]

Currently, the control of mild cases of AAD is carried out by halting antibiotic use. This, however, raises questions of antibiotic resistance associated with the early stopping of the course without the patient having fully recovered.[3,4] Severe AAD events are further treated with antibiotics. Oral metronidazole is usually the first given, followed by oral vancomycin if the symptoms persist.[3] However, with the growing threat of antibiotic resistance and growing number of diseases resulting from dysbiosis, the World Health Organization has said that the world "urgently needs to change the way it prescribes and uses antibiotics".[10] Therefore, this author raises the question of whether the preventative pill of probiotics could be the answer.

Probiotics

Probiotics are bacteria that positively influence the gastrointestinal microbiome. These can be found in certain foods or can be consumed in tablet form, the latter of which this article is focussing on. Probiotics are made from bacteria and/or yeast that naturally live inside of us, but are not to be confused with prebiotics, which are compounds that promote the growth of these beneficial microbes.[11,12] As a type of immunomodulating bacteria, probiotics can stimulate or suppress the immune system and may help the body combat cancer, infection or other diseases.[13] They have a much lower virulence compared to their more pathogenic gut microbiome counterparts. Many probiotics are presumed to have the ability to protect gut bacterial balance, thereby preventing the incidence of dysbiosis-related disease from antibiotics and its side effects. The history of probiotics is long, going back nearly 10,000 years, but only recently has it gained traction through new evidence-based medicine.[13]

Firstly, evidence has highlighted that probiotics act beneficially on our gut microbiome, specifically when taken in conjunction with antibiotics. A 2020 study was carried out into the efficacy of Bacillus *subtilis* and *Bacillus coagulans* probiotic, which exhibits characteristics of the *Bacillus* and *Lactobacillus genera*, on gut dysbiosis.[14] This was executed via an in vitro gut model, a mucosal simulator of the human intestinal microbial ecosystem. This study found that, in conditions of antibiotic-induced dysbiosis, probiotics could significantly reduce gut membrane barrier damage compared to when no probiotic was present. It is important to mention the study's limitations, such as the use of the model gut and a single healthy donor's gut microbiome, neither of which are representative to the general population. Therefore, more research should be done into this topic to look at the effects of probiotics in different microbiome environments.

Probiotics are thought to protect the gut during antibiotic intake, it is possible to see this by reviewing probiotics effectiveness in preventing AAD. The biggest limitation of these studies was the difference in probiotic strains used between them, and a review found that this impacts on whether a definitive conclusion can be drawn.[15] To understand the importance of probiotic type, a systematic review and meta-analysis reviewed all the standard medical databases up until 2018.[16] It specifically investigated the evidence-based efficacy of probiotics on a strain and disease individual probiotic level. It specifically investigated the evidence-based efficacy of probiotics on strains of bacteria and disease at an individual level across 249 trials and 22 different types of probiotics. Several of these had strong evidence for the prevention of AAD (*Saccharomyces boulardii*, a mixture of *Lactobacillus strains* and *Lactobacillus casei*) with others showing positive evidence for additional diseases such as irritable bowel disease. Thus, highlighting that further research is needed to assess the impact of different probiotics on AAD and antibiotic-associated dysbiosis.

A systematic review and meta-analysis in 2020 looked into probiotic specificity further.[17] It evaluated existing evidence from 42 studies with 11,305 participants and found that the co-administration of probiotics with antibiotics reduces the risk of AAD in adults by 37%, with a relative risk of 0.63 (95% CI from 0.54 to 0.73, $p<0.00001$). This review investigated the best probiotic species used, finding that only a certain group seemed to be effective, namely *Lactobacillus* and *Bifidobacteria genera*. This addresses conflicting evidence and proves that selection of the probiotic strain is vital in its efficacy in reducing incidence of ADD. Therefore, these differences show that more research needs to be done into strains of probiotics, proving this topic is not as simple as 'any probiotic will do'.

Antibiotic resistance from probiotics

This debate is complicated further by the possible link between probiotics and antibiotic-resistant genes. Probiotics, being live microbes, are not exempt from the naturally occurring antibiotic resistance.[18] Consequently, it could be possible for the horizontal transfer of these resistant genes. This can be shown with the genus *Lactobacillus* (a popular probiotic strain) belonging to the lactic acid group which is known for its possible vancomycin-resistant phenotype.[19]

With all evidence-based applications, there is an element of a risk-benefit analysis. For cases of severe ADD, oral metronidazole or vancomycin is prescribed, which further increases the risk of resistance. Therefore, although there is a chance of resistant gene transfer, the use of probiotics in addition to antibiotics is thought to reduce antibiotic resistance indirectly by preventing the need for secondary antibiotics to treat any side effects. Furthermore, the screening of gut microbes for antibiotic resistant genes before using them as probiotics is possible and should perhaps become strongly advised, if not enforced.[18] This implies that reducing the risk of antibiotic resistant bacteria with probiotics could be feasible, while achieving this with antibiotics is more challenging.

Despite the improvement in AAD in patients, it is important to consider the cost impacts that prescribing probiotics alongside antibiotics would have on our health service. As of May 2022, the prescribing of over-the-counter medicines by the NHS has changed, with prescriptions generally no longer being written for probiotics to reduce costs to the NHS.[20] Bringing back probiotic prescriptions would add this cost back onto the health service. However, this article raises the question of whether the benefits outweigh the costs. Probiotics could be the future in preventing antibiotic dysbiosis, thus reducing the frequency of secondary antibiotics required, as well as meaning patients are more likely to finish their antibiotic course. Therefore, probiotics should perhaps start being prescribed alongside all, or certain, antibiotics. By making them a prescribed drug, it could not only increase their popularity in the population, but also make them more readily available to those in lower socioeconomic areas. While it may raise costs for the NHS in the short term, it could save in the future due to fewer secondary antibiotics needed, as well as less antibiotic waste, and fewer ADD hospital admissions, perhaps also making this an economical choice.

Conclusion

This article has briefly looked at the dysbiosis-causing effects antibiotics can have on the human gut microbiome, and subsequently the associated diarrhoea a large proportion of individuals suffer as the first sign of this dysbiosis. Although for most, these changes in bacteria are likely to return to pre-medication levels, for others this is not the case. With probiotics thought to lessen the impact of antibiotics on the healthy gut, future research should investigate the potential of

probiotics as a potential prescription alongside antibiotics. Moreover, their ability to reduce the unwanted side effects of AAD will mean more individuals will not be stopping their antibiotic course early, whether out of choice or following the instructions of a healthcare professional. This may help in the current war against antibiotic resistance, as well as increasing patient satisfaction. Furthermore, less frequent, or less severe AAD will mean fewer antibiotics for secondary infections will be required, again reducing the chances of resistance, as well as saving the NHS' valuable but limited resources. Despite this, probiotics are not ready for prescriptions just yet. This article raises the question of whether naturally sourced probiotics via food and drink could solve the above issues, while still providing the population with antibiotic protection. It is clear a lot more research needs to be invested into probiotics and the best strains of probiotics for each of our unique gut microbiomes. This may mean a more personalised approach to probiotic prescriptions, but in the new age of personalised medicine, all healthcare is moving in this direction anyway, so why not strive for an individualised wall of protection against antibiotics and other dysbiosis-causing events.[21]

References

1. Patangia DV, Anthony RC, Dempsey E, Paul RR, Stanton C. Impact of antibiotics on the human microbiome and consequences for host health. Microbiologyopen. 2022; 11:e1260.
2. Barbut F, Meynard JL. Managing antibiotic associated diarrhoea. BMJ. 2002; 324:1345–1346.
3. Ayyagari A, Agarwal J, Garg A. Antibiotic associated diarrhoea: infectious causes. Indian J Med Microbiol. 2003; 21:6–11.
4. Laxminarayan R. The overlooked pandemic of antimicrobial resistance. Lancet. 2022; 399:606-607.
5. National Health Service (NHS). Prevention: NHS long term plan. https://www.longtermplan.nhs.uk/areas-of-work/prevention/ Accessed: 10 February 2023
6. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018; 361:k2179.
7. Baquero F, Nombela C. The microbiome as a human organ. Clin Microbiol Infect. 2012; 18:2–4.
8. Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, Li HB. Impacts of gut bacteria on human health and diseases. Int J Mol Sci. 2015; 16:7493–7519.
9. Elvers KT, Wilson VJ, Hammond A, Duncan L, Huntley AL, Hay AD, et al. Antibiotic-induced changes in the human gut microbiota for the most commonly prescribed antibiotics in primary care in the UK: a systematic review. BMJ Open. 2020; 10:e035677.
10. World Health Organization. Antibiotic resistance: World Health Organization. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance Accessed: 10 February 2023
11. Berger A. Science commentary: probiotics. BMJ. 2002; 324:1364.
12. Noonan S, Zaveri M, Macaninch E, Martyn K. Food & mood: a review of supplementary prebiotic and probiotic interventions in the treatment of anxiety and depression in adults. BMJ Nutr Prev Health. 2020; 3:bmjnph-2019-000053.
13. Ozen M, Dinleyici EC. The history of probiotics: the untold story. Benef Microbes. 2015; 6:159–165.
14. Marzorati M, Van den AP, Bubeck SS, Bayne T, Krishnan K, Young A, et al. Bacillus subtilis HU58 and *Bacillus* coagulans SC208 probiotics reduced the effects of antibiotic-induced gut microbiome dysbiosis in an M-SHIME® model. Microorganisms. 2020; 8:1028.
15. Issa I, Moucari R. Probiotics for antibiotic-associated diarrhea: do we have a verdict? World J Gastroenterol. 2014; 20:17788–17795.
16. Sniffen JC, McFarland LV, Evans CT, Goldstein EJC. Choosing an appropriate probiotic product for your patient: an evidence-based practical guide. PLoS One. 2018; 13:e0209205
17. Goodman C, Keating G, Georgousopoulou E, Hespe C, Levett K. Probiotics for the prevention of antibiotic-associated diarrhoea: a systematic review and meta-analysis. BMJ Open. 2021; 11:e043054.
18. Imperial ICVJ, Ibana JA. Addressing the antibiotic resistance problem with probiotics: reducing the risk of its double-edged sword effect. Front Microbiol. 2016; 7:1983.
19. Gueimonde M, Sánchez B, G de Los Reyes-Gavilán C, Margolles A. Antibiotic resistance in probiotic bacteria. Front Microbiol. 2013; 4:202.
20. Coventry University Medical Centre. Prescribing of over-the-counter medicines is changing. https://www.covunigp.co.uk/2022/05/27/prescribing-of-over-the-counter-medicines-is-changing/ Accessed: 11 February 2023
21. Funanage VL. Impact of genetic testing on human health: the current landscape and future for personalized medicine. Del J Public Health. 2021; 7:10–11.

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Hi, I am Sophie, a third-year medical student at Peninsula. As well as submitting an article for the Inspire journal, I am also one of this year's journal editors. I initially got involved with INSPIRE through the research program, which eventually led me to do a summer project with the same lab. My current research interests include cancer endocrinology and the role of APP in the pathogenesis of Alzheimer's, breast and prostate cancer, as well as, of course, the gut microbiome. Outside of medical school, I love running and anything else outdoors, including walking my three cockapoos :)).