MILESTONE 15

Antibiotics alter the gut microbiome and host health

Antibiotics not only act on bacteria that cause infections but also affect the resident microbiota. Although this side effect has long been appreciated, advances in sequencing technologies enabled detailed study of how antibiotics alter the gut microbiome.

Although the composition of the gut microbiota varies between individuals, the community in each individual is relatively stable over time (MILESTONE 7). In 2008, Relman and colleagues studied three healthy individuals and showed that treatment with ciprofloxacin influenced the abundance of about one third of bacterial taxa in faecal samples. These changes decreased the taxonomic richness, diversity and evenness of the community. Although most bacterial groups recovered after treatment, several taxa did not (even after six months) and the level of reconstitution varied between the individuals. A follow-up study showed that a second course of ciprofloxacin had similar effects. There was no correlation between the magnitude of the microbiome shift in the first and second treatments within any individual; each treatment was another 'roll of the dice'.

Owing to the close links between the resident microbiota and the host, such disturbance of the microbiota by antibiotics can be expected to affect host physiology and potentially host health. Indeed, one study found that administration of antibiotics to young mice increased adiposity and levels of metabolic hormones in the blood, and faecal transplantation from antibiotic-treated mice to germ-free mice transferred the metabolic phenotype. Besides effects on metabolism, the gut microbiota also closely interacts with and influences the host immune system, and thus microbiome disturbances have the potential to affect the development of several autoimmune, inflammatory and allergic diseases.

Antibiotic treatment of mice from birth also alters the expression of genes and the number of cells that regulate immune responses. Pulsed antibiotic treatment increased the incidence of type-1 diabetes in susceptible mice, and the relative levels of anti-inflammatory T cells were lower in these mice (prior to the onset of disease) than in untreated mice. Neonatal treatment with antibiotics increased the susceptibility of adult mice to imiquimod-induced psoriasis.

Credit: yulia Petrova / Alamy Stock Photo

> "Treatment with ciprofloxacin influenced the abundance of about one third of bacterial taxa [and] decreased the taxonomic richness, diversity and evenness of the community"

Similar observations have been made for asthma. Children who are exposed to antibiotics in their first year of life had a slightly increased risk of developing asthma, and the risk increased with the number of antibiotic courses. Regression analysis from children with asthma identified that early exposure to antibiotics is a risk factor. The abundance of the genera *Faecalibacterium*, *Lachnospira*, *Veillonella* and *Rothia* (FLVR) were decreased in children at three months of age who had been treated with antibiotics and later developed asthma. In faecal transfer experiments from one of these children, the addition of FLVR decreased disease severity in an asthma mouse model. The changes in community composition were accompanied by changes in metabolites such as acetate, a short chain fatty acid that is known to influence host metabolism and immune function. In another study, early life exposure to the antibiotic vancomycin indeed increased immunoglobulin E and decreased regulatory T cell levels in mice.

A study looking at antibiotic perturbation of the gut microbiota and the risk of developing inflammatory bowel disease, also showed that transfer of the disturbed gut microbiota from mouse mothers to their newborn pups, promoted and accelerated the development of gut inflammation in the offspring.

Certain interventions could help restore the gut microbial community to its original state if antibiotics are needed. For example, Elinav and colleagues recently found that the administration of certain probiotics hindered, and autologous faecal transplantation helped restore, the microbiome.

The observation that the gut microbiome can be permanently perturbed even by short-term or low-dose antibiotic treatment, and that this change can have long-term effects on health, cautions against widespread and potentially unnecessary use of antibiotics, particularly in young children and pregnant women, and illustrates that antibiotics should not be considered harmless. However, it also raises hopes for microbiome modulation as a therapeutic treatment for immune conditions.

Megan Cully,
Nature Reviews Drug Discovery

ORIGINAL ARTICLES Dethlefsen, L. et al. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol.* **6**, e280 (2008) | Dethlefsen, L, & Relman, D. A. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc. Natl Acad. Sci. USA* **108**, 4554–4561 (2011) | Cho, I. et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature* **488**, 621–626 (2012) | Cox, L. M. et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* **158**, 705–721 (2014) | Zanvit, P. N. et al. Antibiotics in neonatal life increase murine susceptibility to experimental psoriasis. *Nat. Commun.* **6**, 8424 (2015) | Marra, F. et al. Antibiotic use in children is associated with increased risk of asthma. *Pediatrics* **123**, 1003–1010 (2009) | Arrieta, M. C. et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci. Transl. Med.* **7**, 307ra152 (2015) | Russell, S. L. et al. Perinatal antibiotic treatment affects murine microbiota, immune responses and allergic asthma. *Gut Microbes* **4**, 158–164 (2013) | Livanos, A. E. et al. Antibiotic-mediated gut microbiome perturbation accelerates development of type 1 diabetes in mice. *Nat. Microbiol.* **1**, 16140 (2016) | Schulfer, A.F. et al. Intergenerational transfer of antibiotic-perturbed microbiota enhances colitis in susceptible mice. *Nat. Microbiol.* **3**, 234–242 (2018) | Suez, J. et al. Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. *Cell* **174**, 1406–1423 (2018)

FURTHER READING Willing, C. P. et al. Shifting the balance: antibiotic effects on host-microbiota mutualism. *Nat. Rev. Microbiol.* **9**, 233–243 (2011)