GENOME WATCH

Antibiotics, gut bugs and the young

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Two recent studies have investigated the effects of antibiotic use on the intestinal microbiota of preterm infants and young children.

Treating bacterial infections with antibiotics can cause long-term changes to the commensal microbiota, which is at its most vulnerable and malleable in preterm infants and young children. Using sequence-based approaches combined with *in vitro* phenotyping, two recent studies have investigated the effects of treating infants with antibiotics by characterizing changes to microbial community composition and the acquisition of antibiotic resistance genes in the gut microbiota.

Korpela *et al.*[1] leveraged the comprehensive health records maintained in Finland to understand how the use of specific antibiotics can affect the intestinal microbiota in different ways. The authors undertook 16S rRNA amplicon gene sequencing of the bacterial community obtained from the faecal samples of 142 children 2–7 years of age in Finland, sampling the majority of children 7 months apart. The sequencing data showed that the biggest changes to microbial community composition were associated with the use of antibiotics belonging to the macrolide class, which account for nearly 25% of all antibiotics purchased in Finland. These differences included an overall reduction in species richness, together with changes in the abundance of specific genera. For example, in the Actinobacteria phylum, the abundance of the *Eggerthella* genus, which contains known pathogenic and commensal species, was increased, whereas the abundance of the commensal *Bifidobacterium* and *Collinsella* genera were reduced. Even when the data were adjusted for the natural changes that occur in the gut microbiota as children mature, differences in microbial community composition associated with the use of macrolides were still observed two years after treatment ceased. This was longer than the average time interval between courses of antibiotic, which suggests that the microbiota may not recover its normal composition between courses.

The intestinal microbiota of children that were recently exposed to macrolides also had high levels of resistance to this antibiotic, as shown by metagenomic sequencing of a subset of the same samples followed by the annotation of antibiotic resistance genes and validation using culture-based methods. Furthermore, children who had been treated with macrolides in the first two years of life were more likely to have developed asthma and to be overweight than children who had not been treated with antibiotics, which might be caused by disruption to microbial homeostasis during this critical developmental window.

Moving from the young to the very young, Gibson *et al.*[2] used longitudinal metagenomic sequencing of 401 faecal samples to examine the effects of antibiotic use on 84 preterm infants, who usually receive antibiotics shortly after birth. Similarly to Korpela *et al.*[1], this study also observed a reduction in species richness following the use of antibiotics. The authors created metagenomic libraries of the extracted microbial DNA in *Escherichia coli* and then functionally selected for antibiotic resistance genes by picking colonies that were growing on agar supplemented with one of 16 different antibiotics. Sequencing of the library fragments that conferred resistance identified 794 antibiotic resistance genes. Demonstrating the value of this approach, the majority of these sequences had not been previously annotated as associated with antibiotic resistance, which suggests that our knowledge of antibiotic resistance genes and resistance mechanisms is quite incomplete.

Opportunistic pathogens, such as *E. coli*, *Enterobacter cloacae* and *Klebsiella pneumoniae*, were prevalent across all preterm infants that were sampled in the study and were associated with a higher number of antibiotic resistance genes than other species, whereas treatment with specific antibiotics resulted in an enrichment of different sets of antibiotic resistance genes that, for each antibiotic tested, were associated with a single species. For example, treatment with ticarcillin–clavulanate was associated with an increase in the abundance of *K. pneumoniae*.

Both studies build on results from mouse models of paediatric antibiotic use[3] to provide further evidence that antibiotics can perturb the intestinal microbiota of the young, which may have long-term effects on host physiology. The results from these experiments may help guide treatment strategies, such as selecting antibiotics that are less likely to have long-term effects on the commensal microbiota and trying to allow recovery of the microbiota between courses of antibiotic treatment.

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Competing interests statement
The author declares no competing interests.