TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

MEDICAL GRAND ROUNDS

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Our missing microbes: Short-term antibiotic courses have long-term consequences

RECENT YEARS have seen dramatic increases in the prevalences of chronic diseases such as type 1 diabetes,[1] gastroesophageal reflux disease,[2] asthma,[3] inflammatory bowel disease,[4] and, notably, obesity.[5] I propose the hypothesis that much of this increase may be due to loss of diversity in the bacteria that make our guts their home.[6] While multiple causes contribute, much of the blame may be attributed to the use—and overuse—of antibiotics.

Hypothesis: Much of the rise in chronic diseases is due to loss of microbial diversity

FAT AND GETTING FATTER

Today, nearly 40% of US adults are obese, and nearly three-fourths are either obese or overweight.[7] More alarming, the prevalence of obesity is also high and getting higher in children and adolescents,[8] having increased from 10.0% in 1988–1994 to 17.8% in 2013–2016.

And not just in the United States. Trends in weight have been going up around the world, with a lag of about 30 years between developing countries and industrialized countries.[5]

OUR BACTERIA, OURSELVES

I believe that the bacteria we carry are not random, but rather have coevolved along with us, passed down from generation to generation in a state of dynamic equilibrium between microbes and host. Evidence supporting this comes from a study by Ochman et al,[9] who analyzed the DNA from fecal samples from different hominid species (including *Homo sapiens*) and found that the phylogenic relationships among the bacteria mirrored those among the apes.

Interacting with each other and with us in complex ways, our bacteria are a diverse community to which we can apply the term *microbiome*. They are acquired in a standard, choreographed process,[10] and their composition comes to resemble that of adults by the age of 3.[11]

Before modern times, microbes were transferred from mother to child during vaginal birth, from the mother's breast during nursing, through skin-to-skin contact, and from the mother's mouth by kissing. Now, widespread cesarean delivery, bottle-feeding, extensive bathing (especially with antibacterial soaps), and especially the use of antibiotics have changed the human ecology and altered transmission and maintenance of ancestral microbes, which affects the composition of the microbiota. The microbes, both good and bad, that are usually acquired early in life are especially important, since they affect a developmentally critical stage.[12]

Loss of microbial diversity in the mother appears to be cumulative over succeeding generations.[13] For example, in a study in Japanese families, Urita et al[14] found a decline in the prevalence of *Helicobacter pylori* colonization from 68.7% in the first generation to 43.4% in the second generation and 12.5% in the third. Clemente et al[15] studied the intestinal microbiota in a previously uncontacted group of Yanomami people in the Amazon jungle and found they had the highest diversity of bacteria ever reported in a human group. By comparison, the research team calculated that we in the United States have already lost 50% of our microbial diversity, and 2 other groups, the Guahibo (another Amerindian group) and rural Malawians, were in between. More recent studies are confirming these observations.[16,17]

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USE AND OVERUSE OF ANTIBIOTICS

More than 73 billion antibiotic doses are prescribed worldwide yearly,[18] or about 10 doses for every man, woman, and child on Earth, and the numbers are rising. In the United States 262 million courses were prescribed in 2011, or 842 per 1,000 population.[19] Children receive a mean of 2.7 courses by age 2, and 10.9 by age 10. More than 50% of women receive antibiotics during pregnancy or perinatally. This is in addition to an unknown level of exposure from agricultural use of antibiotics.

Repeated antibiotic exposure is common in early life, varies widely by country, and is often not medically justified.[20] In the United States, antibiotic use varies by region, with the heaviest use in the South.[19,21] It also varies widely among prescribers.[22] Jones et al[23] examined antibiotic prescribing for acute respiratory infections in US veterans and found that the top 10% of physicians gave an antibiotic more than 90% of the time. Physicians in Sweden prescribe about 60% fewer antibiotics than we do in the United States.[21,24]

Observational data indicate that people who receive antibiotics have a higher risk of chronic diseases later in life, eg:

- Type 2 diabetes (odds ratio 1.21, 95% confidence interval 1.19–1.23 with 2 to 4 courses, and odds ratio 1.53 (1.50–1.55) with 5 or more courses, up to 15 years after[25]
- Obesity: US states with the highest prevalence of antibiotic use also have the highest prevalence of obesity[26]
- Kidney stones: prior antibiotic exposure in a large UK study was associated with increased kidney stone risk, for exposures up to 5 years earlier.[27]

The meat industry has exploited the weight effect for decades, adding subtherapeutic doses of antibiotics to animals' feed to make them gain weight.[28]

FINDINGS FROM STUDIES IN MICE

Laboratory studies of the relationship between antibiotic exposure and disease phenotypes in mice have yielded interesting findings.

Mice exposed to antibiotics had more body fat at 10 weeks (32.0%) than control mice (22.9%).[29]

Low-dose penicillin, started at birth, induces long-lasting effects on the expression of genes involved in immunity and enhances the effect of a high-fat diet in terms of weight gain.[30] If the antibiotic exposure is limited to early life, the effect on the microbiota is transient, but the mice still gain weight. If the microbiota from the mice who received penicillin is transferred to germ-free mice, the recipients also become fat, indicating that the bacteria, not the antibiotics per se, cause the weight gain.

In other experiments,[31] a series of short, therapeutic doses of antibiotics early in life modeled after those given to children to treat their acute infections caused long-term changes in the composition of the microbiome and in metabolism.

A single course of a macrolide antibiotic also had long-term effects on the microbial population and on the host's ileal gene expression, T-cell populations, and secretory immunoglobulin A expression.[32] These effects were seen only in mice that had a microbiome to begin with, not in germ-free mice, indicating that the antibiotics had their effect through the changes in the microbiome, not directly. But when germ-free mice received a fecal transplant of an impaired microbiome, it was sufficient to affect immunity.

In nonobese diabetic mice, treatment with antibiotics early in life altered the gut microbiome and its metabolic capacities, intestinal gene expression, and T-cell populations, accelerating the onset of type 1 diabetes.[33]

In a study in Danish children,[34] the likelihood of inflammatory bowel disease increased with early-life antibiotic exposure: the more courses the child received, the greater the likelihood of disease. This observation led researchers to wonder if an antibiotic-altered microbiome affects the outcome of inflammatory bowel disease in the next generation.[35] Germ-free female mice who received microbiota from mice who had received antibiotics passed the altered microbiome to their pups. Mice lacking the gene for interleukin 10 are genetically susceptible to colitis, and when this experiment was done in mice lacking this gene, the offspring developed markedly more colitis. This indicated the mothers could pass down their altered microbiome to the next generation and that it would affect their risk of disease.

For decades, the meat industry has added antibiotics to animals' feed to make them gain weight

WHAT CAN WE DO?

All physicians must adhere to the principles of antibiotic stewardship,[36] not only to prevent the development of resistant strains of pathogens and the overgrowth of potentially dangerous species such as *Clostridium difficile*, but also, possibly, to prevent the loss of diversity in the human microbiome and thus discourage the development of chronic diseases.

In the future, as we discover more about the microbiome and the optimal mix of bacteria to carry, this information may find practical application in medicine. A pediatrician, for example, may want to analyze a child's microbiome and, if it is abnormal, administer specific organisms to reshape it.

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