A closer look—
The current analysis of the human microbiome is providing a more comprehensive understanding of the diverse types of bacteria that not only exist in various anatomical locations (e.g., skin, oral cavity, nasopharynx, groin, axilla), but whose presence is essential to health. Caroline McDaniel, RN, BSN, MSN, provided an overview of the microbiome in the fall 2013 Prevention Strategist article titled, “The Human Microbiome Project: What’s in it for IPs?” Foremost among these is the intestinal tract, where the normal flora, often called the microbiota, are the most dense and diverse than any other location. Recent studies have estimated that over 40,000 bacterial species, primarily anaerobes, are part of the natural biodiversity of the gut ecosystem. In fact, the variety and complexity of the gut microbiota is now described as a “virtual organ” or emerging body system. In addition, bacterial diversity changes along the gastrointestinal tract; high levels are reported in the oral cavity and intestines but are low in the stomach.

Research conducted during the past 10 years consistently reports that homeostasis within the intestinal microbiota is essential for health. Disruptions may occur from diet, surgery, alcohol abuse, and medications—especially antibiotics. No matter what the trigger, impaired bacterial function, referred to as dysbiosis, has been associated with inflammatory bowel conditions, insulin resistance, diabetes, and obesity. In many cases it remains unclear if
the changes in intestinal microbiome are a symptom of the disease or a contributing factor. Due to the wide variation in microbiota among individuals, no single bacterial species can serve as a marker of disease.

Other factors are thought to contribute to bacterial homeostasis in the gut. Environmental, immunological, hormonal, and genetic variables have been investigated. While much remains unknown, it is clear that maintenance of the microbiota is a far more complex process that previously believed.

The emerging science of metagenomics or environmental gene sequencing holds great promise for a deeper understanding of gut ecology. The intestinal microbiota has been almost impossible to analyze using traditional laboratory approaches such as culture and strain typing, as less than 1 percent of intestinal bacteria have been successfully cultured. PCR-based approaches eliminate the need for culture, but they can only detect previously identified genes when compared to the metagenome that now lists more than 5 million non-redundant genes. The field of metagenomics uses this vast pool of information to produce a more complete description of all types of human microbiota, as well as reduce the previous risk of underreporting the size and nature of microbial communities.

THE ENVIRONMENTAL RESISTOME
The first step in understanding antibiotic resistance is recognition of the environment as a natural reservoir. A growing number of studies suggest that human health may not only be determined by individual genetics, but also by the genes of the trillions of microorganisms that exist on and within the human body.

Antibiotic resistance is now viewed as an ancient process. New technologies have revealed the presence of antibiotic resistance in the environment, suggesting a co-evolution between antibiotic and antibiotic resistance that occurs as a natural event. The environmental microbiota, even in antibiotic-free conditions, possesses a large and diverse number of antibiotic resistant genes—some of which resemble the genes of pathogenic microbes. This global environmental combination of susceptible and resistant bacteria comprises a worldwide resistome. The contemporary resistome is under increasing selective pressure from human activities—especially agriculture—that may accelerate resistance and gene transfer. Changes in the environment then impact the clinical resistome. For example, evidence now suggests links between aminoglycoside and vancomycin resistance enzymes and the environment.

Today’s commercial production and widespread use of both natural and synthetic antibiotics intensifies the pressure on both environmental and clinical resistomes. For this reason, scientists have used the beta lactamases for modeling as they represent the most widespread mechanism of resistance among pathogenic bacteria worldwide. Early testing has been promising. For example, in one of the first metagenomic studies on antibiotic resistance in the human intestinal microbiome, researchers identified 10 novel beta lactamase families that reflected only 35–61 percent of known genes.

ANTIBIOTIC RESISTANCE AND NEW RESEARCH
Antibiotic resistance is a serious and growing threat to the prevention and containment of communicable diseases worldwide. According to the most recent data, antibiotic resistance in the United States causes an estimated $20 billion a year in excess healthcare costs, $35 million in other societal costs, and more than 8 million additional acute care inpatient days. In the United States, a growing list of resistant pathogens includes not only the long-recognized MRSA and vancomycin-resistant Enterococci, but also cases of H1N1 influenza, carbapenem-resistant Enterobacteriaceae, Klebsiella pneumoniae, TB, and gonorrhea.

Antibiotic resistance develops in one of two basic ways. A bacterium can undergo spontaneous genetic mutation. It can also receive genetically coded resistance via plasmids or transposons from other bacteria that already contain this genetic information. However, bacteria can also receive resistance genes from viruses, as well as via direct exposure to DNA in the environment. These processes can occur at varying times, increasing the number and types of antibiotics that they can resist.

Once resistance is acquired, it may be transferred vertically, through bacterial replication, or horizontally, via contact between bacteria without any type of reproduction. The density of intestinal bacteria, especially during disease progression, increases the risk of
horizontal transfers of antibiotic resistant genes within the microbiota. Due to the probability of genetic exchange during disease, the intestinal microbiota may represent the largest reservoir for resistance. Previous antibiotic susceptibility studies, attempting to analyze this lateral transfer mechanism, have relied on *Escherichia coli*. However the use of metagenomic sequencing has, as in the study of beta lactamasases, now identified resistant genes previously unknown and not recognized using *E. coli* cultures.

New research is also examining the role of bacteriophages (also known as phages). Phages are viruses that attack bacteria. The community of phages is referred to as a *phageome*. The rapid increase in antibiotic resistance since the 1990s has focused renewed attention on phage-based research. Recent research in animal models has attempted to analyze the role of phages in the spread of antibiotic resistance. In one study, phages were studied as a potential reservoir for bacterial adaptation. In this study, antibiotic treatment led to enrichment of phage-encoded genes. This research demonstrated that phages from treated laboratory mice lead to increased resistance in aerobically cultured naïve microbiota. More research is needed to fully understand the role of the phageome in antibiotic resistance.

Another area of investigation focuses on biochemical alteration of the intestinal epithelium. Disruption of normal epithelial permeability and mucous integrity can impact the microbiota. For example, one project has examined carbohydrate metabolism. Laboratory analysis has shown that antibiotic impact on intestinal microbiota changed mucosal carbohydrate availability in ways that supported the growth of *S. typhimurium* and *Clostridium difficile*. Other studies have looked for relationships between medication use, especially antibiotics and proton pump inhibitors, and *Clostridium difficile*. Research in these areas is ongoing.

**MICROBIOTA AND OBESITY**

Obesity is rarely a consequence of only nutritional imbalance. It is a complex problem linked to both metabolic and immunologic functions. The intestinal microbiota are increasingly recognized as part of the connection between genes, environmental factors, and the immune system. Specifically, emerging research shows a link not only between gut microbiota and obesity, but also with insulin resistance and type 2 diabetes. Although a causal relationship is not yet absolutely described in the literature, experts are increasingly looking at the association of gut microbes, a high fat/high sugar diet, and excessive weight gain. While studies are ongoing, the number of potentially confounding variables—including factors such as antibiotic use, previous dietary habits, meal frequency, and physical activity—makes conclusive investigation challenging.

**MANIPULATING THE MICROBIOTA**

As more is learned about the intestinal microbiome and its impact on overall health, various strategies have been proposed to restore or maintain gut homeostasis. Foremost among these future strategies is the judicious use of antibiotics. In addition, the future may yield new pharmacological treatments, immunomodulatory vaccines, and nutritionally based therapies. Targeted modification of microbial communities may be accomplished through deployment of antibiotics (to remove or suppress undesirable segments of the microbiota), and/or administration of pre- and probiotics. A better understanding of the development of gut microbiota early in life may yield new opportunities to prevent or manage adult disease. More information about nutritional components is needed to understand and manage endotoxinemic and inflammatory responses in the gut, especially related to lipid and fructose intake. However, all proposed methods of manipulation are based on varying approaches to human host-microbiota co-regulation of intestinal homeostasis.

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**References**


