

# Therapies Aimed at the Gut Microbiota and Inflammation: Antibiotics, Prebiotics, Probiotics, Synbiotics, Anti-inflammatory Therapies

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## KEYWORDS

- Gut microbiota • Antibiotics • Prebiotics • Synbiotics
- Anti-inflammatories

Several recent observations have raised the possibility that disturbances in the gut microbiota and/or a low-grade inflammatory state may contribute to symptomatology and even, perhaps, the etiology of irritable bowel syndrome (IBS), if not in all sufferers, possibly in some subpopulations. Consequent on these hypotheses and also as a result of blind trial and error by the patient and the physician, several quite unexpected therapeutic categories have found their way into the armamentarium of those who care for IBS sufferers. Before these new (to IBS) agents (eg, probiotics, prebiotics, antibiotics, and anti-inflammatory agents) are discussed, one should first consider the context in which such therapeutic strategies are being considered. The logical place to begin is the microbiota.

## THE NORMAL MICROBIOTA: AN ESSENTIAL FACTOR IN HEALTH

The human gastrointestinal (GI) microflora (now more usually referred to as the microbiota) is a complex ecosystem of approximately 300 to 500 bacterial species comprising nearly 2 million genes (the microbiome). Indeed, the number of bacteria within the gut is about 10 times that of all of the cells in the human body. At birth, the entire intestinal tract is sterile; bacteria enter the gut with the first feed.<sup>1</sup> Following infancy, the composition of the intestinal microbiota remains relatively constant

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thereafter. When disturbed, the microbiota has a remarkable capacity to restore itself and to return to exactly the same state as it was in before.<sup>2</sup>

Because of the normal motility of the intestine (peristalsis) and the antimicrobial effects of gastric acid, the stomach and proximal small intestine contain relatively small numbers of bacteria in healthy subjects; jejunal cultures may not detect any bacteria in as many as 33% of subjects. The microbiology of the terminal ileum represents a transition zone between the jejunum containing predominantly facultative anaerobes and the dense population of anaerobes found in the colon. Bacterial colony counts may be as high as  $10^9$  colony-forming units (CFU)/mL in the terminal ileum immediately proximal to the ileocecal valve, with a predominance of Gram-negative organisms and anaerobes. On crossing into the colon, the bacterial concentration and variety of the enteric microbiota change dramatically. Concentrations as high as  $10^{12}$  CFU/mL may be found, comprised mainly of anaerobes such as *Bacteroides*, *Porphyromonas*, *Bifidobacterium*, *Lactobacillus*, and *Clostridium*, with anaerobic bacteria outnumbering aerobic bacteria by a factor of 100 to 1000 to 1.<sup>3</sup> The predominance of anaerobes in the colon reflects the fact that oxygen concentrations in the colon are very low; the microbiota has simply adapted to survive in this hostile environment.

It must be emphasized, however, that the true size and diversity of the human microbiota are largely unknown. The application of modern technologies—genomics, metagenomics, and metabolomics—to the study of the colonic microbiota has the potential to expose the true diversity and metabolic profile of the microbiota and the real extent of changes in disease.<sup>4</sup> Techniques based on 16S rDNA sequences have revealed that the diversity of the human microbiota is much greater than previously thought and that most bacterial sequences correspond to unculturable sequences and novel bacteria.<sup>5</sup> At any given level of the gut, the composition of the microbiota also demonstrates variation along its diameter, with certain bacteria tending to be adherent to the mucosal surface while others predominate in the lumen; studies that rely on the analysis of the fecal microbiota alone may miss the impact of an important population of organisms, those closely adherent to the mucosa.<sup>5</sup> In people, the composition of the microbiota is also influenced by age, diet, socioeconomic conditions and, above all, the use of antibiotics. Studies purporting to identify variations in the microbiota in disease states must, accordingly, be interpreted with great care and some degree of skepticism.

The normal enteric bacterial microbiota influences various intestinal functions and plays a key role in nutrition, maintaining the integrity of the epithelial barrier, and the development of mucosal immunity.<sup>6</sup> The relationship between the host's immune system and nonpathogenic constituents of the microbiota is important in protecting the host from colonization by pathogenic species. In this regard, intestinal bacteria produce various substances, ranging from relatively nonspecific fatty acids and peroxides to highly specific bacteriocins, which can inhibit or kill other, potentially pathogenic, bacteria.<sup>7</sup>

## THE GUT MICROBIOTA IN DISEASE

The key role of the microbiota in health is only beginning to be understood and it has only been in very recent years that the true extent of the consequences of disturbances in the microbiota, or in the interaction between the microbiota and the host, to health has been recognized.<sup>6,8</sup> Some of these are relatively obvious; for example, when many components of the normal microbiota are eliminated or suppressed by a course of broad-spectrum antibiotics, the stage is set for other organisms that may be

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