For 70 years, antimicrobial agents, known as antibiotics, have been successfully fighting infectious diseases, dramatically reducing rates of illness and death worldwide. However, their widespread use has led to adaptations in the infectious organisms that they are designed to kill, reducing the drugs' effectiveness.

In the US, antibiotic-resistant bacteria cause at least 2 million cases of disease and 23,000 fatalities annually. As a result, the Centers for Disease Control and Prevention (CDC) have outlined the top 18 drug-resistant threats to the US and categorized them based on level of concern: urgent, serious or concerning. Health professionals have been encouraged to limit the use of antibiotics.

Those in the "urgent" category are currently:

- *Clostridium difficile (C. difficile),* which causes life-threatening diarrhea
- Carbapenem-resistant Enterobacteriaceae (CRE), mostly occurring in medical facilities, where it causes bloodstream infections that prove fatal in almost 50% of cases
- *Neisseria gonorrhoeae* that cause gonorrhea, a sexually transmitted disease, affecting 820,000 people a year.

The current study, led by Egija Zaura, PhD, an associate professor in oral microbial ecology at the Academic Centre for Dentistry in Amsterdam, the Netherlands, looked at 66 healthy adults from the UK and Sweden who were prescribed different antibiotics. Participants were randomly assigned to receive a full course of one of four antibiotics: ciprofloxacin, clindamycin, amoxicillin or minocycline, or a placebo. The researchers collected fecal and saliva samples from participants at the start of the study, immediately after taking the antibiotics, and 1, 2, 4 and 12 months after finishing the course.

Single antibiotic course has long-term impact

A laboratory technique called 16S rRNA gene amplicon sequencing identified the presence of bacteria on 389 fecal and 391 saliva samples. Another lab technique, metagenomic shotgun sequencing, highlighted the largest differences before and after antibiotic usage, which enabled researchers to study the emergence of antibiotic resistance.

The drugs were found to enrich genes associated with antibiotic resistance and to severely affect microbial diversity in the gut for months after exposure. By contrast, microorganisms in the saliva showed signs of recovery in as little as a few weeks.

The microorganisms in participants' feces were severely affected by most antibiotics for months. In particular, researchers saw a decline in the abundance of health-associated species that produce butyrate, a substance that inhibits inflammation, cancer formation and stress in the gut.

Microbiome diversity in feces was significantly reduced for up to 4 months in participants taking clindamycin and up to 12 months in those taking ciprofloxacin. In contrast, diversity in the oral cavity microbiome was only altered for up to a week after drug exposure.

Amoxicillin had no significant effect on microbiome diversity in either the gut or oral cavity, but it was associated with the greatest number of antibiotic-resistant genes.

'Antibiotics should only be used when really necessary'

Researchers are not sure why the oral cavity returns to normal sooner than the gut, but it could be because the gut is exposed to a longer period of antibiotics. Alternatively, the oral cavity may be intrinsically more resilient toward stress because it is exposed to different stressors every day.

UK participants started the study with more antibiotic resistance than those from Sweden, possibly due to different attitudes toward antibiotics. Sweden has seen a significant decline in antibiotic use over the last 2 decades.

Zaura says:

"Antibiotics should only be used when really, really necessary. Even a single antibiotic treatment in healthy individuals contributes to the risk of resistance development and leads to long-lasting detrimental shifts in the gut microbiome. Certainly we cannot live or survive without antibiotics; that's out of the question. But there are situations when we should not use them, like when there are no evidence-based reasons."

Medical News Today recently reported that hospital treatments in the US are severely hampered by antibiotic resistance.

Brazier, Yvette. "One course of antibiotics disrupts gut microbiome for a year." Medical News Today. MediLexicon, Intl., 10 Nov. 2015. <http://www.medicalnewstoday.com/articles/302179.php>

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For enquiries, comments, suggestions or article contribution, please write to:

The Editor (The Probiotics News)
MD Pharmaceuticals Pte Ltd
896 Dunearn Road #02-01A
Sime Darby Centre Singapore 589472

Tel: (65) 6465 4321
Fax: (65) 6469 8979

Website: www.mdpharm.com
Email: frederick.sim@mdpharm.com or waisin.leong@mdpharm.com

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Message from the Editor

16th Edition

We are glad to be able to bring to you a very special article on the history and evolution of probiotics. I'm sure many of you will find it interesting and beneficial. Also, in this issue we highlight the effect of a single course of antibiotics on the gut microbiome.

For our Chinese readers, we would like to take this opportunity to wish you and your families a very blessed Lunar New Year and a joyous and healthy 2016.

God Bless !

Melvin Wong
Editor-in-chief

Probiotics: History and Evolution

Vijaya K Gogineni, M.D.
Pulmonary and Critical Care Fellow, Creighton University Medical Center, Division of Pulmonary, Critical Care and Sleep Medicine, USA

Lee E Morrow, M.D.
Associate Professor of Medicine and Pharmacy Practice, Nebraska and Western Iowa Veteran's Affairs Hospital, Creighton University Medical Center, Division of Pulmonary, Critical Care and Sleep Medicine, USA

Philip J Gregory, PharmD
Associate Professor of Pharmacy Practice, Center for Drug Information & Evidence-Based Practice, Creighton University School of Pharmacy and Health Professions, USA

Mark A Malesker, PharmD
Professor of Pharmacy Practice and Medicine, Creighton University School of Pharmacy and Health Professions, USA

Introduction: Probiotics and Fermentation

Probiotics are viable microbial species, which are ingested for the purpose of altering the gastrointestinal flora in a manner, which confers health benefits. Currently available probiotic products include a wide array of bacterial and fungal species which are consumed in a variety of preparations. The use of microbials originated (unintentionally) centuries ago when people first noted the beneficial health effects of eating fermented foods. Modern probiotic-containing foods and products are the direct derivatives of these early fermented foods. The use of fermented milk and yogurt are the part of human history and their role has been with humanity, to date, between legends and historical data [1]. The present review outlines the origins of probiotic-containing foods and our subsequent refinement of these biologic agents.

Fermentation is the metabolic process by which an organism converts a carbohydrate, typically starch or a sugar, into an alcohol or an acid. These metabolic byproducts lower pH and have a host of other effects that prevent spoilage of fermented foodstuffs. The term fermentation is derived from *fermentum*, the Latin word for boiling. The name came from the observation that mixtures of crushed grapes kept in large vessels produced bubbles, as though they were boiling. While no one knows precisely when man began to use the fermentation process it is agreed that it is an ancient tool for preserving foods. Many believe the only older method of food preservation is dehydration. There is strong evidence to suggest that the art of fermentation originated in the great Indus Valley civilization. Several artifacts suggest that fermentation was known from the ancient times in Egypt and the Middle East [2]. The earliest recordings of fermentation date back as far as 6,000 B.C. in the Fertile Crescent region of lower Mesopotamia between the Tigris and Euphrates rivers [3]. Traditional Egyptian fermented milk products, Laban Rayeb and Laban Khad, were consumed as early as 7000 BC [4].

While serendipity probably played a major role in the genesis of fermentation, the process became popular not only because it preserved food, but also because it provided a variety of tastes and may have improved digestion or had other perceived beneficial effects. It was propagated through subsequent generations in the form of oral communication. By the middle ages, people were consuming a wide variety of fermented foods and drinks depending on raw materials, environmental conditions, and local taste preferences (Table 1).

Fermented Milk

Man began domesticating animals in Asia and/or northeast Africa somewhere between 8,000 and 5,000 B.C. The Vedic hymns of India, written before 2,000 B.C., indicate that Hindu people used fermented milk products in their diet since prehistoric times [5]. Between 2,000 and 3,000 B.C. a multitude of other civilizations (the Egyptians, Greeks and Romans) left many records to indicate that milk, cheese, and butter were commonly used [6]. As an example, Sumerians crossed expanses of deserts with milk carried in bags made from the stomachs of sheep. The enzymes present in the stomach wall fermented the milk into curd which improved the taste and shelf-life. The Bible, dated to the thirteenth century B.C, reports that "Abraham offered to God, showed in an oak wood, fermented milk" (Genesis 18, 1-8). During this time almost every civilization regularly ingested fermented milk products for its taste and health benefits. Geographic separation and cultural differences resulted in a variety of names used to describe these similar compounds (Table 2). Credited with saying "All disease begins in the gut" the Greek physician Hippocrates considered fermented milk both a food product and a medicine with the potential to cure intestinal disorders. Plinius, the Roman historian, stated that fermented milk products could be used for treating gastroenteritis [7].

Fermented Vegetables

Nearly every civilization has developed food fermentation of some type. The peoples of Japan, China and Korea have relied heavily on fermentation as a pickling agent for cabbage, turnip, eggplant, cucumber, onion, squash and carrots over the centuries. Records in China document that cabbage has been fermented for over 6,000 years. Fermented vegetables were regularly provided to Chinese workers during the construction of the Great Wall of China (around 300 B.C.) to promote their health and well-being [8]. Several Roman texts document consumption of sauerkraut - a lacto-fermented cabbage - describing both its "delicious taste" and its medicinal properties. The Roman Emperor Tiberius regularly carried sauerkraut on his long voyages to prevent intestinal disorders. Nearly 2,000 years later, Captain James Cook and his crew similarly consumed sauerkraut on their long voyages to prevent illness (scurvy) [9].

Commonly Used Fermented Foods
Bread
Milk and Cheese
Vegetables
Beer and Wine
Sausage
Chocolate
Soy sauce

Table 1: Different fermented food used in various civilizations.

Fermented Milk Product	Country
Kumiss	Mongolia
Kefir	Balkan
Taettemjolk	Scandinavia
Zabadi	Egypt
Doogh	Iran
Dahi	India
Koumiss	Russia
Cieddu	Italy

Table 2: Different names given to fermented milk in various parts of the world.

Bread

The first records of bread-making are contained in ancient Egyptian hieroglyphs [3]. Egyptians discovered that if dough was left untreated for several hours prior to baking, the resulting bread became airy and lighter. They attributed this phenomenon to a divine process rather than fermentation [3]. As Egyptians conquered more lands and expanded their empire this practice spread to other cultures. The Romans are known to have used yeasts collected from wines to make bread from fermented dough. Similarly, leaven - referred to repeatedly in the Bible - was a soft, fermented dough-like medium.

Beer and Wine

Between 9,000 and 7,000 B.C. the nomadic life of the hunter-gatherer societies evolved into the more settled life of farmers. Many historians believe that brewing beer and wine originated during this period as a result of the first domestic cereal crops [2]. The earliest evidence that beer was produced and consumed comes from China more than 7,000 years ago. The archaeological record shows that as early as 4,000 B.C, yeast was used both as a leavening agent and for brewing ale in Egypt [2]. Centuries later, the Greeks and Romans are known to have used starter cultures to inoculate fresh fruit juice for fermentation [3].

Defining Probiotics

The connection between fermented foods, bacteria, and health originated with the foundation of the discipline of microbiology. In 1680, van Leeuwenhoeck, used his newly built microscope to observe yeast cells in fermenting beer [10]. Because he never made an association between the presence of these yeast cells and the process of fermentation his observations were forgotten. In the late 1700's Lavoisier, a founder of modern chemistry, delineated the process of transformation of sugars to alcohol and carbon dioxide. He described this phenomenon of alcoholic fermentation as "one of the most extraordinary in chemistry". However, he erroneously wrote that yeast played a physical rather than a chemical role in this process. In the 1840's, Theodor Schwann and Charles Cagniard-Latour suggested a possible association between the growth of yeast and the process of alcoholic fermentation. It was the great French chemist Louis Pasteur who definitively concluded that lactic acid fermentation was initiated by microorganisms based on his investigations. Pasteur originally defined fermentation as 'respiration without air' and stated, *"I am of the opinion that alcoholic fermentation never occurs without simultaneous organization, development, and multiplication of cells. If asked in what consists the chemical act whereby the sugar is decomposed, I am completely ignorant of it"*. Pasteur published his seminal results in a preliminary paper in 1857 and in a final version in 1860, which was titled "Mémoire sur la fermentation alcoolique" [11].

In 1899 Henry Tissier isolated Bifidobacteria from the stools of breast-fed infants. He found that they were a predominant component of the intestinal flora in healthy humans and later recommended the administration of *Bifidobacteria* to infants with diarrhea [12]. Ilya Ilyich Metchnikoff, a Russian scientist, in the beginning of early 20th century linked the health and longevity of Bulgarian peasants with their heavy ingestion of yoghurt which contained large quantities of *Lactobacillus* species. In 1895, Metchnikoff became the director of the Pasteur Institute after Louis Pasteur's death. In 1908 he received the Nobel Prize in Medicine for his contributions to immunology - much of which stemmed from his investigations regarding ingestion of living organism. In 1907, Metchnikoff wrote his famous text, "The Prolongation of Life" based on his findings. This book is the first scientific description of the potential to improve human health through eating substances, which favorably alter the gastrointestinal microflora - a concept now widely accepted as the probiotic principle.

In 1907, a German chemist named Eduard Buchner received the Nobel Prize for proving that enzymes in yeast cells cause fermentation. Arthur Harden and Hans Euler-Chelpin received the Noble Prize in 1929 for elucidating how such enzymes cause fermentation. Probiotic therapy took a major step towards reality in 1930 when the Japanese microbiologist Minoru Shirota first discovered bacterial flora that survived passage through the gut after ingestion. Shirota was subsequently able to isolate and cultivate what is now known as *Lactobacillus casei* strain *shirota*. These efforts led to the first fermented bacteria-containing drink, which was commercially marketed as Yakult in 1935 - a product that continues to be manufactured and sold worldwide today.

The term *probiotic* is derived from Latin (pro) and Greek (bios) meaning literally "for life" [13]. It was first used by Kollath in 1953 to generically describe various organic and inorganic supplements that were believed to have the ability to restore the health of malnourished patients [14]. In 1954, the German researcher Ferdinand Vergin proposed the term *probiotika* to describe "active substances that are essential for a healthy development of life". Lily and Stillwell published an article in Science in 1962 wherein they expanded the definition of probiotics to include "the anaerobic bacteria that are able to produce lactic acid and stimulate the growth of other organisms [15]. Parker in 1974 proposed that the term probiotic should include not only microbial organisms but also other substances that contributed to intestinal microbial balance [16].

Our current usage of the term probiotic was proposed by Roy

Fuller who deleted "other substances" from the definition and defined probiotics as "live microbial feed supplements which beneficially affects the host animal by improving its intestinal microbial balance [17]. Our current definition of probiotics was formulated in 2001 by FAO/WHO as 'live microorganisms which, when administered in adequate amount, confer health benefit to the host'. In 2002 FAO/WHO subsequently drafted guidelines regarding the evaluation of probiotics in various food products. Prebiotics are indigestible food ingredients that selectively promote the growth or activity of beneficial bacteria, thereby benefiting the host [18]. Synbiotics are combinations of probiotics and prebiotics designed to improve the survival of ingested microorganisms and their colonization of the intestinal tract [18].

Commercialization of Probiotics

In 1906, "Le Fermente" a French Society began marketing a fermented milk product (Lactobacilline) containing *Streptococcus thermophilus* and *Lactobacillus delbrueckii*. In 1919, Isaac Carasso similarly began commercial production of yogurt in Spain. It is unclear that these products contained living organisms and, if so, whether these organisms were able to survive transit through the upper gastrointestinal tract. Accordingly, Yakult (described above) fermented milk is commonly cited as the first commercially available probiotic.

In the earlier part of last century, focus was on the use of fermented milk with probiotics to take care of intestinal infections. Gradually focus has shifted to survival of these bacteria in the gastrointestinal tract and the carrier food to have their beneficial effect on the host [19,20]. From the late 1930's onward, interest in probiotics gradually decreased as a result of the pressures of the Great Depression, World War II, and the discovery and proliferation of various antibiotics. However, global trends from the 1980's to the present have included increasing antimicrobial resistance, limited pharmaceutical research and development in infectious diseases, skyrocketing costs for new antibiotics, and discrepancies in availability and/or utilization of routine infection prevention measures. Accordingly, interest in probiotics has again increased as it is widely viewed as a non-antibiotic strategy to prevent and potentially treat a variety of infections. In 1994, passage of the Dietary Supplement Health and Education Act (DSHEA, see below) led to dramatic growth in the sales of products marketed as probiotics. This legislation allowed these agents to be marketed as dietary supplements without the rigorous requirements necessary to approve prescription drugs. Since this time, marketing and sales of probiotic products in the United States has grown exponentially. The global market of probiotic ingredients, supplements and food was $14.9 billion in 2007 and is expected to reach $19.6 billion in 2013. This represents a compound annual growth rate of 4.3 % [21].

United States (U.S.) Regulation of Probiotics

Probiotics can be marketed in several different ways in the U.S. depending on their intended usage. They can be marketed as foods, medical foods, dietary supplements or drugs. Each of these categories has unique requirements in terms of formulation, scientific documentation, and/or FDA approval. In most cases, probiotics are marketed as either a dietary supplement (e.g., products in pill form) or as a food substance (e.g., yogurt). Several of probiotic organisms including *Lactobacillus acidophilus, Streptococcus thermophilus,* and *Bifidobacterium lactis* have "generally recognized as safe" (GRAS) status, meaning that they are permissible additives in food substances. Similarly, these species and many others are contained in products marketed as dietary supplements, which are regulated via the aforementioned DSHEA. This legislation allows these products on the market without any premarketing approval. However, manufacturers are responsible for collecting data about adverse events that are reported. Manufacturers marketing probiotic-dietary supplements are also not permitted to make therapeutic claims. Those that do make medical claims are considered to be drugs in the eyes of FDA regulators. Current FDA guidelines state that if any agent (including probiotics) is ingested for the purpose of curing, mitigating, treating, diagnosing or preventing disease, it is classified as a "drug" and must undergo the regulatory process similar to any new pharmaceutical [22].

While such regulatory oversight is intended to ensure patient safety, it may not be entirely aligned with public desires. A recent qualitative study of U.S. consumers' perceptions of therapeutic probiotic agents confirms that patients expect rigorous federal regulations regarding accurate labeling and the evaluation of efficacy and safety endpoints [23]. However, study respondents also called for limited involvement by pharmaceutical companies, wide-spread access, and low costs. These observations suggest that from probiotics' origins as homebrewed fermented milk products to our present-day commercially manufactured supplements, our understanding and acceptance of these agents has evolved to where we want our (probiotic) cake and to eat it too.

Current role of Probiotics in Various Diseases

Probiotics seems to have a promising role in either shortening the duration or prevention of infections. Several laboratory studies and clinical trials are being conducted to evaluate the safety and efficacy of probiotics in several diseases. One of the biggest challenges we encounter now in probiotics is extrapolating the immunomodulatory effects found on laboratory studies with the outcomes in human trials. Multiple factors like genetics, microbial diversity etc play a role in the discrepancies between the laboratory studies and clinical trials. With meta-analysis of strain-specific clinical trials, the role of probiotics has been evolving.

Antibiotic-associated Diarrhea (AAD)

Antibiotics have shown to alter the intestinal microbiota of the host leading to decrease in amylolytic activity, [24] decreased short chain fatty acid production and increased proteolytic activity [25]. Several probiotic organisms have been studied in various clinical trials in children and adults to prevent or decrease the AAD. With increasing number of strain-specific clinical trials, a strain-specific meta-analysis of randomized clinical trials testing the efficacy of *S. boulardii* in preventing AAD, showed *S. boulardii* was significantly protective for AAD [26]. The number needed to prevent one case of AAD was 10.2.*Lactobacillus rhamnosus* GG (LGG) has showed benefit over the placebo or no treatment in several randomized control trials [27-30] in preventing antibiotic-associated diarrhea in children and adults.

Clostridium difficile (C. difficile) infection (CDI)

Probiotics have been studied in prevention, and treatment of *Clostridium difficile* infections (CDI) and recurrent CDI. In *in vitro* studies, *Saccharomyces boulardii (S. boulardii),* a probiotic yeast has shown to degrade *C. difficile* toxin A and B [31] and increase in anti-toxin secretory IgA levels [32]. *Lactobacillus rhamnosus* GG (LGG) has shown to increase the expression of mucins [33] and decrease the bacterial adherence [34]. With CDI or *C. difficile* toxin acquisition as primary or secondary outcome, several randomized controlled trials have been done [35-42]. None of them except one trial [42] has shown a statistically significant decrease in CDI or *C. difficile* toxin acquisition. In a randomized controlled trial on patients with recurrent CDI, high dose vancomycin (2g/d) with probiotics *(S. boulardii)* has shown a statistically significant reduction in recurrence rate compared with low dose vancomycin or metronidazole with probiotics [43].

Necrotizing Enterocolitis (NEC)

Bacterial colonization patterns are important in the pathogenesis of NEC since preterm infants of mothers receiving broad-spectrum antibiotics prenatally or preterm infants receiving antibiotics directly postnatally have been found to have higher risk for Necrotizing Enterocolitis sec to a change in the intestinal microbiota [44,45]. Several meta-analysis [46-49] have shown to reduce the relative risk of NEC and death when *Bifidusbacterium spp.* and *Lactobacillus acidophilus* are used prophylactically in neonates with birth weight <1500 gms. Among neonates with birth weights <750 gms, there was an increase in the risk of sepsis with the use of probiotics [50].

Inflammatory Bowel Disease (IBD)

Lactobacillus paracasei demonstrated immunomodulatory effects by reducing proinflammatory cytokines in the plasma of patients with Ulcerative Colitis (UC) [51]. VSL#3 induces IL-10 and down regulates IL-12p40 production by lamina propria in patients with UC [52]. But none of the clinical trials [53-56] have been able to demonstrate any significant improvement in IBD symptoms in comparison with placebo. We need several large randomized controlled trials and metaanalysis to demonstrate the superiority of probiotics over placebo or anti-inflammatory agents like steroids. At this moment, there is no role of probiotics in the management of inflammatory bowel diseases either in induction or maintenance phase of remission.

Irritable Bowel Syndrome (IBS)*

IBS is one of the most common intestinal disorders in the industrialized and developing nations and incurs significant health care costs. Irritable Bowel Syndrome is defined by symptom criteria of chronic recurring episodes of abdominal pain or discomfort with altered bowel habits in the absence of organic disease [57]. In addition, sensations of bloating with and without visible abdominal distension, increased anxiety and several extraintestinal symptoms commonly occur [58]. Although several animal and human studies suggests alteration in gut microbiota in patients with IBS, it needs to be determined if it is a consequence or the cause [59]. Increased incidence of irritable bowel syndrome following gastroenteritis, [60] abnormal lactulose breath testing sec to small bowel bacterial overgrowth and intestinal inflammation suggests alteration in the intestinal microbiota [61] In a systematic review of several randomized controlled trials, *Bifidobacterium infantis* 35624 was the only probiotic to provide significant improvement in IBS symptoms [62].

*Update from the editor: Please see Note.

Acute Pancreatitis

Infectious complications are the most frequent and severe complications of acute necrotizing pancreatitis (AP) with a mortality rate up to 80% [63]. Bacterial translocation has been proven to be an important mechanism for the infectious complications in patients with acute severe necrotizing pancreatitis [64]. Several randomized controlled trials [65-70] have shown that probiotics with or without prebiotics have shown to reduce the infectious complications in patients with acute severe pancreatitis. Besselink et al. (PROPATRIA trial) conducted a multicenter, double blind, placebo-controlled clinical trial [71] that randomized 296 acute pancreatitis patients to receive 28 days of enteral probiotic therapy (multi-species probiotics preparation) or placebo. This study found no differences in infectious complication rates between the probiotic group and their placebo controls (30% vs. 28%). Nine patients developed bowel ischemia (8 died) in the probiotics group, whereas none developed this complication in the placebo group. Surprisingly, the mortality rate was significantly higher in probiotic treated patients than in those given placebo (16% vs. 6%). This study has been criticized for the design and execution of the study like inappropriate blinding, insufficient reporting of serious adverse events, increase in the sample size after the study was initiated, changing the study population from 'severe pancreatitis' to 'predicted severe pancreatitis' and incorrect execution of the intention-to-treat analysis [72]. The patients in the Besselink group also received a higher number and more strains of probiotic organisms (six strains of probiotics vs. 1-4 strains of probiotics in other studies) and some of the patients were receiving pressors. Randomized controlled trials and meta-analysis have not demonstrated significant benefits of prophylactic antibiotics on patients with necrotizing acute pancreatitis.

Ventilator Associated Pneumonia (VAP)

Ventilator-associated pneumonia (VAP) is a leading hospital-acquired infection in the US [73]. It not only prolongs the duration of mechanical ventilation, length of stay in the intensive care unit (ICU) and possible recovery of the lung function [74] but also increases the risk of death by 2-10 fold [75, 76]. The pathogenesis of VAP is complex but typically involves colonization of the aero digestive tract with pathogenic bacteria, formation of biofilms, and microaspiration of contaminated secretions [77,78]. Several randomized control trials have studied the use of probiotics in prevention of VAP, ICU mortality, ICU stay, and in hospital mortality as primary or secondary end point. A meta-analysis [79] of 12 randomized controlled trials found significant reductions in the rate of ventilator-associated pneumonia, ICU length of stay, and colonization of the respiratory tract with Pseudomonas aeruginosa but no significant reduction in ICU mortality, hospital mortality or hospital length of stay.

Obesity and Insulin Resistance

The composition of the microbiota not only varies from person to person but also varies along the length of the gastrointestinal tract [80]. Genotype, confirmed on studies involving monozygotic twins, also plays an important role on the composition of the intestinal microbiota [81]. The most abundant phyla are Bacteroidetes, and Firmicutes, together representing 90% of the total microbiota [80]. Despite wide variability in species composition of the intestinal microbiota, functional gene profiles (microbiomes) are similar across healthy individuals [82,83]. Diet probably plays a pivotal role in influencing the composition of the intestinal microbiota. Bacteroides enterotype was associated with high dietary consumption of saturated fats and protein and Prevotella enterotype was associated with low protein and fat intake along with high ingestion of carbohydrates [84]. The change in the dietary calorie load was rapidly (within 3 days) associated with changes in the bacterial composition of the gut microbiota [85]. Significant decrease in fecal Enterobacteriaceae and sulfate reducing bacteria were noted in obese adolescents who experienced weight loss with low calorie diet and exercise program [86]. Surprisingly, roux-en-Y gastric bypass surgery for weight loss has been associated with increase in pathogenic gut bacteria and loss of beneficial species [87]. There is no consensus on the specific patterns of bacteria that are implicated in obesity and insulin resistance. Obesity is a state of chronic and low-grade inflammation with metabolic complications [88]. High fat diet has shown to increase gut permeability and increase in plasma lipopolysaccharide (a major component of the outer membrane of Gram-negative bacteria) levels suggestive of low-grade endotoxemia (metabolic endotoxemia) [89,90] along with an increase in the amount of total bacteremia, Gram-negative bacteria, and E. coli DNA in the ileal mucosa, blood and mesenteric adipose tissue (metabolic bacteremia) [91]. Metabolic endotoxemia correlates positively with fasting insulin levels, insulin resistance, and cholesterol and triglyceride levels in type 2 diabetic patients [92]. Effect of the innate immune receptor, the pattern recognition receptor Tlr5, on the structural microbial composition and development of insulin resistance has been revealed. In this study, [93]. Tlr5-/- mice exhibited hyperphagia, obesity and insulin resistance. Even lean Tlr5-/- mice had insulin resistance. Food restriction has prevented obesity but not insulin resistance. Transplantation of the gut microbiota from Tlr5-/- mice to a germ free wild type mice resulted in hyperphagia, obesity and insulin resistance [93]. Antibiotic treatment of Tlr5-/- mice ameliorated insulin resistance, obesity and hyperphagia [93]. This suggests a good relationship between intestinal microbiota, innate immune system and insulin resistance.

In a study on school children, [94] *Bifidiobacterium spp.* number in fecal samples during infancy was higher in children who were normal weight at 7 years than in children becoming overweight. This study suggests the aberrant gut microbiota composition precedes overweight. *Bifidiobacterium spp.* is also present in higher numbers in normal weight vs. overweight women and also in women with lower weight gain during pregnancy. The number of *Bifidiobacterium spp.* has been shown to increase in the presence of inulin-type fructans with prebiotic properties [95]. Effect was seen within a few days and disappears in a week after the discontinuation. In a double-blind, randomized, placebo-controlled trial, [96] consuming 200 g/day of fermented milk with *Lactobacillus gasseri* SBT2055 (LG2055) for 12 weeks was associated with significant decrease in abdominal visceral and subcutaneous fat area, body weight and waist circumference as compared to fermented milk alone.

Gut microbiota seems to be a potential nutritional and pharmacological target for the management of obesity and insulin resistance. This is an exciting and rich area of investigation involving many fields like gastroenterology, immunology, endocrinology and microbiology.

Summary

Probiotics are now being studied in various gastrointestinal and non-gastrointestinal disorders and its role has been slowly emerging over the last 2-3 decades. We need large randomized placebo-controlled single strain trials with standard dosing, formulation and duration of treatment in various diseases to get the consistent results. At this moment it is difficult to recommend any particular probiotic for a particular disease as the preparation and dosing may not be available commercially. The interaction of the gut microbiota with its host and mutual regulation has become one of the important topics of biomedical research. Their relevance in human diseases require much more research.

Gogineni VK, Morrow LE, Gregory PJ, Malesker MA (2013) Probiotics: History and Evolution. J Anc Dis Prev Rem 1:107. doi:10.4172/2329-8731.1000107

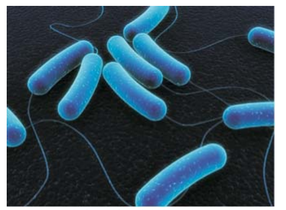
Note from the editor: Later studies have shown other probiotics strains (e.g. Lactobacillus plantarum 299v) significantly improve symptoms of IBS#

#Ducrotte P et al. Clinical trial: Lactobacillus plantarum 299v (DSM 9843) improves symptoms of irritable bowel syndrome. World J Gastroentol 2012;18(30):4012-4018.

One course of antibiotics disrupts gut microbiome for a year

by Yvette Brazier

A single course of antibiotics is strong enough to disrupt the normal makeup of microorganisms in the gut for up to a year, potentially leading to antibiotic resistance, says research published in *mBio*.



Antibiotics are increasingly unable to fight bacteria as resistance develops.