PROBIOTICS: AN EXAMINATION OF THEIR EFFICACY IN THE PREVENTION
AND CONTROL OF ANTIBIOTIC ASSOCIATED DIARRHEA
PRACTICE IMPLICATIONS FOR PRIMARY CARE PROVIDERS

by

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ABSTRACT

Antibiotic associated diarrhea (AAD) can be a significant problem for patients needing antibiotic therapy. It can affect patient compliance resulting in incomplete duration of therapy and development of microbial resistance. Severe complications can develop secondarily including electrolyte imbalances, dehydration, pseudomembranous colitis, toxic megacolon or even death. If there was a simple, safe, inexpensive and effective method to prevent or shorten the duration of AAD, this would provide a significant benefit to the health of affected patients. Health claims have long been attributed to probiotics with research into their efficacy dating back to the 1970s. However, there are still no evidenced-based and generally accepted practice guidelines for their use in AAD. The purpose of this report is to examine the medical potential of probiotics in both reducing and preventing the occurrence of AAD and to develop clinical practice guidelines for primary care providers for use in recommending probiotics to their patients.
CHAPTER 1 PURPOSE AND SIGNIFICANCE

Introduction

In 1893, John Finney and Sir William Osler described the first case of pseudomembranous colitis in a patient who died, shortly after gastric surgery, of a severe case of diarrhea, which they called “diphteric colitis” (Finney, 1893). Though this incident occurred before the advent of antibiotics and the widespread preoperative use of antibiotics in the mid-1900s, it could be considered the first case of a severe type of what is now part of a spectrum of antibiotic-associated diarrheal illnesses known as antibiotic associated diarrhea (AAD) which have become a common medical problem in the twentieth century (Pimentel, 2003). While most AAD is a benign, self-limiting condition, Clostridium difficile caused AAD (CDAD) is associated with significant morbidity and increased healthcare costs. Since the mid 1970s, researchers have been investigating the efficacy of probiotics in the prevention and treatment of AAD. While some of the early research was poorly designed without stringent double blind, randomized controlled trials, there is a preponderance of convincing data supporting the use of probiotics for the treatment of ADD (Marteau, De Vrese, Cellier, & Schrezemeir, 2001).

Humans have a long history of attributing health claims to food which contains living organisms. In a Persian version of the Old Testament, Genesis 18:8 states: "Abraham owed his longevity to the consumption of sour milk" (Schrezenmeir & de Vrese, 2001, p. 1). Likewise, the Roman historian Plinius in 76 BC advised fermented milk products in the treatment of gastroenteritis (Schrezenmeir & de Vrese). As early as 1900, Elie Metchnikoff (the father of immunology) developed a theory attributing the
longevity of Bulgarian peasants to the fact that they ate yogurt (Metchnikoff, 1905). He proposed that the responsible ingredient in the yogurt was "Bulgarian bacillus". This strain is now called *Lactobacillus bulgaricus* and is used in the preparation of yogurt.

AAD occurs in 5-30% of adults and 11-40% of children taking antibiotics (Kotowska, Albrecht, & Szajewska, 2005). Incidence is affected both by the antibiotic used and individual patient characteristics. Wistrom *et al.* (2001), examining the frequency of ADD and CDAD occurrence in 2462 hospitalized patients, determined two or more comorbidities and duration of treatment greater than three days was the greatest risk. Levy *et al.* (2000), in a retrospective cohort study did not find a significant difference in duration of treatment and development of CDAD unless type of antibiotic was considered. In those patients taking Amoxicillin, CDAD developed within nine days versus greater than 30 days in patients taking tetracycline. Damrongmanee and Ukarapol (2007) in a pediatric study, found a moderate inverse relationship between duration of treatment and onset of AAD (5.9 ± 2.2 days); however, most patients stopped their antibiotic with the onset of AAD.

Development of AAD and its unpleasant and potentially harmful side effects frequently cause patients to stop taking their antibiotics prematurely. Not finishing the complete course of treatment further contributes to the development of antibiotic resistant bacteria and infections that are incompletely cured. Although most AAD is self limiting and not serious, severe complications can develop secondarily including electrolyte imbalances, dehydration, pseudomembranous colitis, toxic megacolon or death (Correa, Peret-Filho, Penna, Lima, & Nicoli, 2005). The increased morbidity leads to additional
outpatient office visits, emergency department visits, hospitalizations, need for additional medications, and productivity losses attributed to missed work or school days; all contribute to increased healthcare costs. If there were simple, safe, inexpensive and effective methods to prevent or shorten the duration of AAD, this would provide a significant benefit to the health of affected patients as well as lower healthcare costs.

Purpose of Project

Since antibiotics disturb the natural balance of "good" and "bad" bacteria in the intestinal tract, the administration of live microorganisms in appropriate amounts could potentially confer a significant health benefit in a number of cases, either alone or in conjunction with more conventional treatments. Such dietary supplements are termed probiotics (FAO/WHO, 2001). The purpose of this report is to examine the medical potential of probiotics in both reducing and preventing the occurrence of antibiotic associated diarrhea and to develop clinical practice guidelines for primary care providers for use in recommending probiotics to their patients.

Background and Significance of Problem

Antibiotic use has been steadily rising both in the United States and abroad since its accidental discovery in 1928 by Alexander Fleming, and initial use during World War II. This discovery has allowed mankind to control and treat bacterial caused illnesses that previously were devastating. However, inappropriate prescribing and overuse of these agents have produced several new problems. Results of a survey conducted by Goossens, Ferech, Vander-Stichele and Elseviers (2005) determined that antibiotic use varies by country and that those with the highest consumption have the highest rates of antibiotic
resistance. Antibiotic use also carries with it the risk of further medical complications. Some possible side effects are AAD, pseudomembranous colitis, allergic reactions, fever, nausea, Candida, and adverse drug interactions. AAD can be particularly disruptive as it causes people to stop taking their prescriptions too early.

A serious form of AAD is caused by the bacteria *Clostridium difficile* (*C. difficile*). Pathogenic organisms are responsible for 20-25% of AAD and of these approximately 20% of them are caused by *C. difficile* (Hawrelak, Whitten, & Myers, 2005). Infection by *C. difficile* is a major nosocomial infection that lengthens hospital stays, significantly adds to morbidity and mortality, and considerably increases healthcare costs. Incidences of *C. difficile* associated diarrhea (CDAD) have been steadily rising in hospitals throughout North America (Dendukuri, Costa, McGregor, & Brophy, 2005). An estimate of cost savings obtained by supplementing with probiotics for the prevention of CDAD found that the administration of probiotics resulted in a 50% reduction in treatment costs (£20,000 expenditure to treat a placebo-group positive patient versus £10,000 to treat a probiotic-group patient) (Plummer, Weaver, Harris, Dee, & Hunter, 2004). For suggestions regarding the diagnosis of AAD and CDAD see Table 1.1.

Children have unique risk factors for AAD. Turck *et al.* (2003) examined the particular epidemiology of AAD in children. They determined that the two greatest risk factors were the child’s age and the type of antibiotic prescribed. In a sample of 650 children, 11% developed AAD. Of those, children younger than two years of age were particularly at risk of AAD (18%) compared to children older than two (3%). Amoxicillin/clavulanate caused AAD most frequently (23%) although prescribed only
9% of the time. Diarrhea in children is especially difficult because of their greater risk for dehydration, parental anxiety, prohibitions from attending school, and economic loss to parents due to missed work.

Definitions

*Probiotics*

Probiotics derived from the Greek, literally means "for life" (Michail, Sylvester, Fuchs, Issenman, 2006, p. 550). In 1965 Lilly and Stillwell (1965) first created the term probiotics, defining them as “nonpathogenic growth promoting factors produced by living microorganisms” (p. 747). Fuller (1989) defined them as: “live microbial feed supplements which beneficially affects the host animal by improving its intestinal microbial balance” (Schrezenmeir & de Vrese, 2001, p. 1). According to the World Health Organization (WHO), probiotics are: “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (FAO/WHO, 2002, p. 8). Today, probiotics are understood to be dietary supplements or functional foods which contain potentially beneficial bacteria or yeast which can colonize the intestines and are beneficial to health. There are several different genus and species of probiotics. One of the most studied genera is *Lactobacillus* of which there are several species: *L. acidophilus, L. brevis, L. bulgaricus, L. casei, L. delbrueckii, L. fermentum, L. helveticus, L. plantarum, L. rhamnosus, L. rhamnosus GG (LGG), L. reuteri, and L. sanfranciscensis.*
Antibiotics

Antibiotics are chemical compounds which destroy, inhibit, or prevent the growth of microorganisms, such as bacteria, fungi, or parasites. They are classified by their chemical structure, microbial origins, mode of action, or effective range. Examples of different classes are: beta-lactams, macrolides, tetracyclines, floroquinolones, penicillins, cephalosporins, and polymixins.

Antibiotic Associated Diarrhea (AAD)

The World Health Organization (WHO) defines AAD as three or more abnormally loose stools per 24 hours (WHO, 2008). AAD is defined as an otherwise unexplained, benign, self-limiting diarrhea that occurs following the use of antimicrobials. It can occur either during treatment or up to eight weeks after treatment finishes. The strongest predictor for development of AAD is type of antibiotic used; with ampicillin/amoxicillin, cephalosporins, and clindamycin having the highest reported frequency of AAD (25-50%) (McFarland, 1998). There is also an age correlation, with increased frequency occurring in children under six and adults over 60 (McFarland, 1998). In its most typical form, there are no pathogens identified and the diarrhea is due instead to an imbalance and consequential disruption in the composition and function of the intestinal microflora. AAD is also defined as an acute inflammation of the intestinal mucosa caused by antibiotics (Kotowska et al., 2004). Patients present with frequent, loose, watery stools, minimal signs of colitis, and no constitutional symptoms (Pimentel, 2003). Most patients respond to stopping their antibiotics and engaging in supportive measures.
**Clostridium Difficile Associated Diarrhea (CDAD)**

CDAD is a serious form of diarrhea caused by the toxins produced by the *C. difficile* bacteria, including severe colitis with or without the presence of pseudomembranes. It is the most common identifiable and treatable pathogen (Bartlett, 2002). Presentation is often accompanied by nausea, vomiting, dehydration, fever, leukocytosis, cramping, tenesmus, and profuse, mucous, foul-smelling diarrhea (Pimentel, 2003). Characteristic colonic changes which are visible on computed tomography or with endoscopy are colonic distention, thickening, pericolonic inflammation, or free air. CDAD is far more common in hospitalized patients than in the out-patient setting. Risk factors include gender, advanced age, a compromised immune system, previous abdominal surgery, comorbidity, type and prolonged use of antibiotics (especially broad-spectrum cephalosporins and fluoroquinolones), multiple antibiotics, and length of hospitalization (Bartlett, 2006; Pimentel, 2003). Age greater than 70 and length of hospitalization are the greatest risk factors in hospitalized patients (Asha, Tompkins, Wilcox, 2006). Multiple antibiotic use and comorbidities are the greatest risk factors in the outpatient setting (McFarland, 1998). CDAD accounts for 15-20% of all AAD cases (Pimentel). In the past five years, *C. difficile* has become more frequent, severe, refractory to standard therapy, and more likely to relapse (Bartlett, 2006). Several synonyms for CDAD exist: antibiotic-associated colitis, *C. difficile* colitis, and pseudomembranous colitis (PMC).
Summary

The increasing use of antibiotics corresponds with a corresponding increase in AAD and its associated problems and complications. Its frequent occurrence, significant morbidity, and associated health care costs, make prevention or treatment of AAD a high priority. Currently there is no treatment offered to assist patients in preventing or controlling the incidence of AAD. With no help available, patients may stop taking their antibiotics and prevent complete treatment of their infections. Practitioners are left searching for ways to increase patient compliance and prevent development of antibiotic resistant superbugs. The use of probiotics provides a low cost, minimally adverse solution to the problem of AAD. A review of the current evidenced-based literature is a first step in the development and dissemination of practice guidelines for use by primary care providers.
CHAPTER 2 PHILOSOPHY OF HEALING AND LITERATURE REVIEW

Introduction

This chapter will discuss the theoretical underpinnings behind the use of probiotics as well as a comprehensive review of current literature to inform the development of practice guidelines. A thirty year history investigating the beneficial effects of probiotics and its relationship to AAD has generated a large volume of literature. In developing this report, over seventy research articles were reviewed. Refining the search, a selection of the most informative, evidence-based studies is included. Many of the review articles and meta-analyses identified the same original sources and, therefore, drew similar conclusions.

Philosophy of Healing

Holism is a state of harmony among body, mind, emotions and spirit within an ever-changing environment. Bohm in Koitham (1997, p. 261) describes a state “wherein no particle is separate and the whole is enfolded into each part”. This assumption reflects a world view which is based on an understanding of the equality and interdependence of all living beings. Life is a process of growth, change and transformation. It is a function of becoming, creating our own destiny, health and self-awareness. How we live our lives, our health and our personhood reflects this continual state of flux. Because health is a lived experience, it is not just a state of being but a matter of mental, physical, and spiritual evolvement.

Naturopathic and Oriental medicine view human beings as interconnected parts of the universe, without separation, and directly linked to their environment physically,
emotionally, and spiritually. According to this philosophy, health is a natural state of being in which mind, body and spirit are functioning in balance and harmony. By living harmoniously, all living things have an innate ability to heal themselves through the actions of a vital force. This force directs the body in a process of self-cleansing, self-repair, and self-healing to achieve and maintain a state of balance or homeostasis. Mosby defines homeostasis as “a relative constancy in the internal environment of the body, naturally maintained by adaptive responses that promote healthy survival” (Henderson, 2005, ¶2). Taber defines homeostasis as “the state of dynamic equilibrium of the internal environment of the body that is maintained by the ever-changing processes of feedback and regulation in response to external or internal changes” (Thomas, 1997, p. 909).

The nursing perspective which best reflects this worldview is the unitary-transformative (UT) way of understanding. It has a holistic point of view which conveys the notion of the inseparability of mind, body, and spirit, as well as the idea of oneness with the universe. It describes the universal order as one which is a “dynamic web of relations that emphasize change, process and transformation” (Grof in Koithan, 1997, p. 261).

This author conceptualizes health as an expression of balance and disease as the physical expression of imbalance within the body. Healing is the process of honoring the inherent wisdom and integrity of the whole person and working to bring the individual back into their state of balance. With support, nourishment and the ability to function freely without suppression, the immune, hormonal, nervous, detoxification/elimination, and organ systems can restore equilibrium. When this occurs health follows.
Overview of Intestinal Health

The gastrointestinal tract is populated by up to 100 trillion microorganisms of which there are more than 400 bacterial species; greater than any other location in the human body. These commensal bacteria have a fundamental role in maintaining health and preventing disease. The intestinal tract starts out sterile at birth but within a few hours becomes colonized with *Escherichia coli*, *Clostridium welchii*, and *Streptococcus* (McCance & Huether, 2002). Assuming normal delivery, within one week after birth Bifidobacteria, a gram-positive prokaryote, colonizes the neonatal intestinal tract where it remains for life (Correa et al., 2005). Three to four weeks after birth normal flora is established. The composition of this flora is affected by the manner in which children are born (vaginally or caesarean) and by whether children are breast or formula fed and changes with age (Fanaro, Chierici, Guerrini, Vigi, 2003; Torun et al., 2002). Maternal vaginal and fecal (intestinal) flora is the source of bacteria for the neonate via amniotic fluid in-utero, and through passage down the birth canal. In babies born by caesarean section, environmental factors are the main influence in their intestinal colonization because they do not come in contact with maternal vaginal and fecal flora. The establishment of a stable flora characterized by low incidence of *Bacteroides* spp. and high concentrations of *Bifidobacterium* spp. and lactobacillus is delayed (Fanaro et al.).

Breast milk stimulates the development of flora rich in *Bifidobacterium* spp., with smaller amounts of lactobacilli, *Clostridium* spp. and *Bacteroides* spp and relatively few enterobacteria and enterococci (Fanaro et al., 2003). Formula fed babies are colonized more heavily with enterobacteria, and the development of bifidus flora is very slow. The
obligate anaerobes *Clostridium spp.* and *Bacteroides spp.* are common. Numbers of *Bifidobacterium spp.* are one-tenth of that in breastfed infants (Fanaro *et al.*). Furthermore, in breast fed infants the particular species of *Bifidobacterium* which are present more closely resemble those found in the adult intestinal tract. In very low birthweight infants in intensive care units, the gut is colonized by smaller numbers of bacterial species and lactobacillus and *Bifidobacteria spp* are rarely present (Fanaro *et al.*).

The digestive organs are densely populated with several different species of commensal bacteria collectively known as bacterial flora (Saladin, 2001). The majority of these complex populations of bacteria inhabit the small and large intestine. The stomach, due to the secretion of acid, is a relatively sterile environment. Bacterial growth is also largely suppressed in the duodenum because of bile acid, intestinal motility, and antibody production. The duodenum and jejunum are mostly inhabited by aerobes, primarily streptococci, lactobacilli, staphylococci, enterobacteria and bacteroides (McCance & Huether, 2002). The colon or large intestine is where the majority of bacterial flora reside. Anaerobes constitute about 95% of the flora in the colon and comprise one third of the bulk of feces. From the ileum to the cecum the most common microorganisms are bacteroides, clostridia, anaerobic lactobacilli, and coliforms (McCance & Huether).

Intestinal bacteria have a multitude of functions: assisting with digestion, absorption, metabolism, protection, and maintenance of the balance and health of the colon. Some of their functions are fermentation of cellulose and other undigested carbohydrates, synthesis of vitamins B and K, metabolism of bile salts, metabolism of
hormones and lipids, protection against exogenous infection and final reduction of food to feces. The anaerobic component of the fecal microbiota is responsible for providing a protective barrier which resists colonization and proliferation of intestinal pathogens (Correra *et al.*, 2005). Any interruption or disturbance in the complex bacterial-host interactions can lead to infection by opportunistic pathogens, imbalance and disease.

**Antibiotics and Intestinal Health**

All categories of antibiotics affect the normal bacterial flora by inducing changes in their composition and function; primarily, they disturb the intestinal microbial balance. They can also affect the enteric nervous system which controls intestinal transit time and physiology. Certain classes have a more detrimental effect, particularly those with broad spectrum coverage and poor intestinal absorption or high biliary excretion. Beta-lactam antibiotics have been found to have the highest incidence of AAD because of their impact on the anaerobic component of the fecal microbiota (Correa *et al.*, 2005). The degree of alteration is influenced by the ability of the normal flora to resist colonization and the type of antibiotic used (Pimentel, 2003). The most common culprits are cephalosporins, extended coverage penicillins, and clindamycin (Wistrom *et al.*, 2001). For example: erythromycin accelerates the rate of gastric emptying; and, clavulanate stimulates small bowel motility (Bartlett, 2002). Some drugs have multiple effects on the gastrointestinal tract. Ampicillin, clindamycin, erythromycin and lincomycin can all depress muscle tone and neuroeffector transmission to the intestinal muscularis mucosa (McFarland, 1998).

The normal composition of the anaerobic flora is altered causing detrimental changes in metabolism and microbiology. The concentration of fecal anaerobes may be
substantially reduced. This can result in an overgrowth of opportunistic pathogens. The most common implicated pathogen is *C. difficile*. Both *C. difficile* exotoxins A and B exhibit potent enterotoxin and cytotoxic effects that are responsible for the clinical manifestations of CDAD. The toxins bind to intestinal receptors leading to disruption of the cellular skeleton and the intracellular junctions, inhibiting protein synthesis and cell division. Important inflammatory mediators attract neutrophils and monocytes, increasing capillary permeability, tissue necrosis, hemorrhage, and edema (Pimentel, 2003).

Decreases and disruption in anaerobic flora also interfere with carbohydrate and bile acid metabolism, resulting in malabsorption, decreased colonic production of short-chain fatty acids, and an increase in nonabsorbable carbohydrates that may lead to the onset of osmotic or secretory diarrhea (Hawrelak *et al.*, 2005). Because short-chain fatty acids are potent stimulators of water and electrolyte absorption, their decrease may result in diarrhea caused by a lack of water absorption (McFarland, 1998).

Other enteric pathogens that have been implicated in connection with AAD are *Staphylococcus aureus* (*S. aureus*), *candida albicans*, *C. perfringens* type A, and salmonella (Bartlett, 2002). *S. aureus* was thought to be the chief cause of antibiotic associated pseudomembranous enterocolitis in the 1950s and 1960s. In 1978 the development of a tissue culture assay and cytotoxin assay test identified *C. difficile* as the causative agent (Bartlett, 2006). This is important because metronidazole, the primary treatment for CDAD, is not effective against *S. aureus*. Comment: Why has this thinking changed? New test development
Mechanisms of Action

There are many different species of probiotics with a wide variety of mechanisms of action. The most commonly studied for use in the treatment of diarrhea are: *Lactobacillus*, *Bifidobacterium* and *Saccharomyces boulardii*. Other less studied, but possibly effective, agents are *L. rhamnosus*, *L. casei*, *L. plantarum* 299v, *Enterococcus faecium*, *S. thermophilus*, and *S. cerevisiae* (see Appendix D). Research suggests probiotics act through several different mechanisms: protecting the intestinal epithelial cell and barrier function, preventing enterotoxin binding, immunomodulation (enhance cellular and humoral immune response), producing protective factors, improving the microbial balance of the intestinal tract, and regulating intestinal function (Yan & Polk, 2006). They compete for nutrients which are necessary for pathogen survival (Michail et al., 2006). Probiotics produce substances which inhibit or kill destructive pathogens as well as modulate toxin production (Vandenbergh in Correa et al. 2005). They are thought to promote the secretion of antimicrobial substances, produce acetic acid, lactic acid, and hydrogen peroxide. By restoring equilibrium to the altered gastrointestinal flora, probiotics can protect against colonization by pathogens such as *C. difficile*. Probiotics are instrumental in aiding in reestablishing or modifying intestinal microflora which has been damaged and disturbed.

*L. acidophilus* and *S. thermophilus* prevent disruption of the intestinal epithelial barrier function and modulate intestinal permeability (Resta-Lenert & Barrett, 2003). *L. acidophilus* and *Bacteroides thetaiotaomicron* prevent cytokine-induced increases in permeability in intestinal epithelial cells through regulating signaling pathways (Resta-
Lenert & Barrett). “LGG prevents cytokine-induced intestinal epithelial injury by preventing apoptosis and promoting cell growth” (Yan & Polk, 2006, p. 719). Probiotics compete with pathogens for adhesion sites and nutritional resources as well as inhibit the production or action of bacterial toxins (Correa et al., 2005).

Antibiotics cause qualitative and quantitative changes in the intestinal bacterial flora that probiotics are able to modulate. In two different studies, *L. acidophilus* and *Bifidobacterium bifidum* prevented antibiotic induced increases in facultative anaerobic bacteria and decreased antibiotic resistant enterococci (Madden et al., 2005 and Plummer et al., 2005). Gorbach (2000) found administration of *LGG* resulted in an increase in IgA and other immunoglobulin secreting cells which produced an enhanced immune response to *C. difficile* toxins.

*S. boulardii* is a live, nonpathogenic yeast. Its method of operation is to displace *C. difficile* toxin A by binding to its glycoprotein receptor sites at the intestinal brush border (Pimentel, 2003). In animal and in vitro studies, *S. boulardii* produces a protease that inactivates toxin A receptors, increases levels of secretory IgA and IgA antitoxin A, competes for attachment sites, and blocks the in vitro adherence of *C. difficile* to cells (Qamar et al., 2001; Tasteyre, Barc, Karjalainen, Bourlioux, & Collignon, 2002).

**Probiotic Use in Children**

Several studies have examined the effects of probiotics on AAD in children. Correa *et al.* (2005) found a significant difference in the incidence of AAD in children six to 36 months of age taking a probiotic formula consisting of *Bifidobacterium lactis* and *Streptococcus thermophillus* compared to placebo (16% versus 31%). The total efficacy of
the probiotic formula in preventing AAD was 47.7%. Probiotics did not significantly shorten the duration of diarrhea in the two groups although those patients taking the control formula had increased episodes of AAD compared to those on the probiotic formula. The predominant antibiotics used in their study were Beta-lactams (88%), known to have the highest frequency of AAD.

An earlier study by Vanderhoof et al. (1999) explored the role of *LGG* in reducing the incidence of ADD in 202 children between the ages of six months and ten years. In this study, an antibiotic was coadministered with either *LGG* or placebo. Again, results were significant with 8% of the children in the probiotic group having an occurrence of diarrhea compared to 26% in the placebo group. The probiotic group also had a slightly shorter duration of their diarrheal episodes than the placebo group (4.7 versus 5.9 days). The authors concluded that coadministration of *LGG* with an antibiotic reduced the incidence and duration of diarrhea, reduced stool frequency, and increased stool consistency in children.

Kotowska et al. (2005) wanted to ascertain whether *S. boulardii*, which has been shown to successfully lower the risk of AAD in adults, would also prove effective in children. They conducted a randomized, double-blind, placebo-controlled trial evaluating the efficacy, safety and tolerability of *S. boulardii* in preventing AAD in children. In this study, the researchers provided outcome measures and definitions for diarrhea and AAD. Diarrhea was defined as ≥3 loose or watery stools per day for a minimum of 48 hours and AAD was diagnosed if the diarrhea was caused by *C. difficile*. Their results demonstrated that *S. boulardii* dosed at 250mg twice daily significantly reduced the risk
of diarrhea compared to placebo (7.5% versus 23%) and reduced the risk of AAD to 3.4% versus 17.3%. They also determined that *S. boulardii* was well tolerated with no adverse reactions. However, the researchers did not investigate the role of *S. boulardii* in the treatment of AAD.

Most recently, Johnston, Supina, Ospina, and Vohra (2007) conducted a meta-analysis to assess the efficacy and adverse effects of probiotics in the prevention of AAD in children. Ten studies met the inclusion criteria which was limited to prospective, randomized, controlled trials with a placebo, active or no treatment control arm. There were a total of 1015 treated patients versus 971 controls who ranged in age from one month to 15 years. Four of the studies were in primary care practices, two were outpatients in a teaching hospital, two involved hospitalized patients, and two did not disclose the setting. The studies ranged in length from 15 days to three months. The probiotics studied were *Lactobacillus spp.*, *Bifidobacterium spp.*, *Streptococcus spp.*, and *S. boulardii*. There was a statistically significant reduction in the incidence of AAD from 37.5% to 8.9%. The best results were obtained with *LGG*, *L. sporogenes*, and *S. boulardii* at 5 to 40 billion colony forming units (cfu)/day. There were no reported adverse events. The research did not make a determination regarding the effects of age or antibiotic duration (5 versus 10 days) on the development of AAD. There was also insufficient data available to correlate the effects to the particular antibiotics used.

**Probiotic Use in Adults**

While there have been several meta-analyses examining the effects of probiotics on AAD in children, there are none that review the results of the many randomized,
controlled trials conducted solely on adults. There are several meta-analyses which combine both adult and children studies together and these will be discussed in the following section.

Although there is still disagreement among researchers and clinicians as to the proven efficacy of probiotics on the prevention and treatment of AAD in adults, there are several clinical studies demonstrating their effectiveness. Hickson et al. (2007) conducted a randomized double blind placebo controlled study to determine the efficacy of a probiotic yogurt drink containing *L. casei*, *L. bulgaricus*, and *S. thermophilus* in preventing AAD in 125 patients, 50 years or older in three London hospitals. Participants drank 97ml twice a day during antibiotic therapy and for a week afterwards. In the probiotic group only 12% (7/57) developed diarrhea versus 34% (19/56) in the placebo group. A secondary outcome was the discovery that no probiotic patients developed CDAD and 17% (9/53) of placebo patients were positive for *C. difficile* in their diarrhea.

**Clinical Outcomes of Probiotics and AAD**

There are inconsistent findings regarding the efficacy of probiotics in adults compared to children. *LGG* has clearly demonstrated effectiveness in reducing both the incidence and duration of AAD in several randomized controlled trials involving children which were reviewed in the previous section. However, in a large randomized, double-blind, placebo-controlled trial of 302 hospitalized adults, the administration of *LGG* failed to prevent diarrhea in the intervention group (Thomas et al., 2001). Overall, 39 out of 133 patients receiving *LGG* developed diarrhea and 40 out of 134 patients receiving a placebo. Possible explanations for these differences between children and adult
populations are insufficient doses in adults, differences in antibiotics, and age related
differences in the pathogenesis of AAD (Kotowska, Albrecht and Szajewska, 2005).

A meta-analysis by Cremonini et al. (2003) suggested “a strong benefit” of
probiotics on AAD, yet the authors determined the evidence was still not conclusive.
Their selection criteria included only randomized placebo-controlled studies culled from
a search of MedLine and Cochrane, which were submitted to the Mantel-Haenszel test for
homogenity. Based on the additional criteria of a minimum of two weeks follow-up and
administration of a single probiotic species, seven studies (881 patients) were included:
five with adults and two with children. The researchers determined current evidence is
“flawed by the lack of a placebo design and by peculiar population features” (p.146). The
probiotics studied in their meta-analysis were: LGG, and S. boulardii. In the seven studies
reviewed, they concluded probiotic supplementation was beneficial in reducing the
incidence of AAD by approximately 60%.

A systemic review of six clinical trials (four with adults and 2 with children) by
Hawrelak, Whitten and Myers (2005) examined the efficacy of LGG in the prevention of
AAD. Inclusion criteria were use of only LGG as the probiotic being examined, placebo
control, and diarrhea as the primary end-point. The Mantel-Haenszel test for homogenity
was performed to assess for level of comparability. Total subjects included were 692. In
four of the studies, LGG significantly reduced the incidence of AAD; in one study it
reduced the duration of diarrhea, and in one study there was no difference between LGG
and a placebo. Differences in results could be attributable to the range of dosages used:
1x10^{10} to 4x10^{10}. The two studies reviewed with children were the same ones included in
the Cremonini et al. (2003) meta-analysis. The authors concluded that additional research is needed to further clarify LGG’s effectiveness.

Szajewska and Mrukowicz (2005) reviewed the effectiveness of S. boulardii in preventing AAD in adults and children. Selection criteria included randomized-controlled trials which used only S. boulardii. In their analysis of five double blind, randomized, placebo controlled trials (four in adults, one in children), consisting of 1076 subjects, they found that co-administration of S. boulardii with antibiotics reduced the risk of AAD compared to placebo from 17.2% to 6.7%. The probiotic was effective, well tolerated and had no adverse reactions. The research reviewed, however, made no conclusions regarding S. boulardii’s efficacy in regards to any particular class of antibiotic. There were also wide variations in follow-up, ranging from two to seven weeks, ranges in dosing from 200mg to 1 gram, and types of antibiotics used.

The largest meta-analysis to-date was conducted by McFarland (2006). She evaluated 25 randomized controlled trials involving 2810 subjects (16 in adults and nine in children) for efficacy of probiotics in preventing AAD. The probiotics evaluated were S. boulardii, LGG, Bacillus clausii, Bifidobacterium longum, Clostridium butyricum miyairir, L. acidophilus, Enterococcus faecium SF68 in either single strain or mixed strain combinations. Doses ranged from $1 \times 10^7$ to $1 \times 10^{11}$ with high doses of $\geq 10^{10}$ per day demonstrating highest efficacy. Seven (44%) of the adult trials and six (67%) of the children trials showed a significant reduction in AAD in the probiotic group compared to the placebo group. Overall, of the 25 studies reviewed, 13 (52%) reported a significant reduction in AAD. The two strains which showed the highest efficacy were S. boulardii
and *LGG*. The researcher postulated that the trials that did not show significant efficacy could be due to differences in populations (children versus adults), type of probiotics, sub-therapeutic doses, or duration of treatment. There were no serious adverse events reported in any of the trials reviewed.

Clinical Outcomes of Probiotics and CDAD

In a double-blind, placebo controlled study, Plummer, Weaver, Harris, Dee, and Hunter (2004) examined the role of *L. acidophilus* and *B. bifidum* in the prevention of CDAD in 150 hospitalized elderly patients receiving antibiotics. Neither ages of patients nor a definition of "elderly" was disclosed. Patients were included in the study based on their requiring antibiotics during hospital admission. Fecal samples were taken upon admission and again in the event of diarrhea developing. Patients received one capsule with a strength of $2 \times 10^{10}$ cfu beginning with 36 hours of antibiotic therapy and continuing for 20 days. The authors found that 46% of probiotic patients were toxin positive with 2.9% developing diarrhea, and 78% of placebo patients were toxin positive with 7.25% developing diarrhea. Patients were contacted after discharge with 14 reporting diarrhea developing at home (9 placebo and 5 probiotic).

A systematic review of eight randomized placebo-controlled studies by Dendukuri, Costa, McGregor, and Brophy (2005) examined the effectiveness of probiotics in the prevention and treatment of CDAD. They determined that probiotics appeared most beneficial in patients with severe disease and that further study is still needed before routine probiotic use should be recommended. The researchers were further limited in their analysis due to small sample sizes (which were not disclosed) and
follow up of less than six weeks which may be too short a period of time for CDAD to develop. Only two out of the eight studies they reviewed demonstrated benefit in preventing CDAD. One possible problem suggested by Dendukuri et al. was insufficient dosage. In several studies reporting no benefit, the adults were given the same doses as pediatric patients who did demonstrate positive results. Another issue is the viability and quality of the probiotic preparations. More high quality large trials need to be conducted to definitively prove the efficacy of probiotics in treating CDAD.

McFarland (2006) in her meta-analysis, examined the efficacy of probiotics in treating existing CDAD and preventing additional recurrences. Six randomized controlled trials, involving 354 patients, met inclusion criteria. In five of the six studies examined the patients had established CDAD. Of the six trials evaluated, only two reported a significant reduction of CDAD recurrences. The probiotics assessed were *S. boulardii*, *LGG*, *L. plantarum* 299v, and a combination of *L. acidophilus* and *B. bifidum*. Dosages ranged from $2 \times 10^{10}$ to $6 \times 10^{11}$ cfu and duration of treatment varied from three to five weeks. Of the probiotics included, only *S. boulardii* showed a significant clinical effect. The researcher postulated that the contradictory results could be due to differences in type of probiotics used, sub-therapeutic doses, or duration of treatment. There were no serious adverse events reported in any of the trials reviewed. Sample sizes were small ranging from 15-138. Larger trials need to be conducted. There were no serious adverse events reported in any of the trials reviewed.
Risks

Probiotics are not entirely without risk. There have been approximately 30 reports of *S. boulardii* fungaemia (also known as invasive candidiasis) in the literature (Kotowska, Albrecht, Szajewska, 2004). There have also been rare reports of complications such as endocarditis and liver abscess connected with *L. rhamnosus* (Sipsas, Zonios, Kordossis, 2002). Kunz, Noel, and Fairchok (2004) present two cases of *LGG* bacteremia. Both patients were very ill newborns who received the probiotics for the treatment of short gut syndrome. It was surmised that the probiotics transmigrated across their already fragile and inflamed intestinal mucosa causing bacteremia. Land *et al.* (2005) reported on two additional cases of bacteremia and sepsis in children who received *LGG* through gastrostomy tubes following the development of AAD after long courses of antibiotics. Both children were immunocompromised; one after extensive cardiac surgery and the other suffering with cerebral palsy, microcephaly, mental retardation, and a seizure disorder.

Probiotic use is becoming widespread without sufficient studies examining its safety. To address these concerns Finnish researchers explored whether increased use of *LGG* led to an increase in *L. bacteremia* (Salminen *et al.*, 2002). They found that even though *LGG* is widely consumed in Finland, after its introduction into dairy products in 1990, there has been no increase in the incidence of *L. bacteremia*.

Most patients who suffer from complications after probiotic use are immunocompromised and/or suffering from life-threatening illnesses hospitalized in intensive care units (Kotowska *et al.*, 2004). Caution should be exercised with patients
receiving their nutrition or antibiotics through an open port such as a catheter or nasogastric tube. However, this is not usually an issue in the outpatient setting.

Recommendations for Future Study

There is a growing body of evidence supporting the use of probiotics in the treatment of AAD. However, there is still a need for large, well-designed randomized placebo-controlled clinical trials to demonstrate unequivocally the effectiveness of probiotics in preventing and treating AAD. Particularly with children, several studies examined the effectiveness of probiotics in preventing AAD but did not examine its role in treatment. Studies need to be designed that randomize patients within different categories of antibiotic regimens to clarify whether effectiveness varies according to type of antibiotic. Duration of microbial treatment is another variable which needs to be controlled for in future studies. Current research does not allow for an analysis of its impact on development of AAD. Also because AAD can occur up to eight weeks after treatment stops, trials with longer follow up times after antibiotic use are indicated. New and continuing challenges exist to further identify mechanisms of action, minimum effective doses, concentrations, viability of products, and possible useful combinations of different species. Probiotic preparations are fragile and frequently commercial preparations have been shown to have either less than the numbers of stated organisms or no live organisms. Therefore, careful handling and quality control is necessary to ensure product viability and reliability. It is also critical to ascertain the correct combination and concentration of probiotics that should be recommended for clinical practice. Given the
low cost and relative easy availability of probiotics, a cost-benefit analysis should be a part of future investigations.

There is a continuing need for more research examining probiotics in the treatment and prevention of CDAD. An important consideration is the effect on carriers versus actively diseased patients and initial versus recurrent cases.

Summary

Although research addressing health benefits of probiotics has been conducted over the past 50 years, a shortage of high quality, randomized controlled studies with large sample sizes have been identified. It follows that most of the meta-analyses and systematic reviews include many of the same studies.

The beneficial effects of probiotics may be probiotic specific. Different probiotics work on different conditions. However, because not all probiotics have the same mechanisms of action or exert a similar effect, conclusions from one strain may not apply to another. The bioavailability of products remains an important consideration. Due to the lack of FDA oversight for supplements, there is no guarantee as to bioavailability, content, and quality of individual products. Furthermore, there is still a lack of standardization of products and confusion as to appropriate dose and formulations. It is still critical to ascertain the correct combination and concentration of probiotics which should be recommended for clinical practice. Results from several randomized controlled trials support the use of select probiotics as an adjunctive treatment to prevent AAD in patients undergoing antibiotic therapy; particularly, *S. boulardii* in both adults and children and *LGG* in children.
One criticism of using the meta-analysis to assess the efficacy of probiotics is that because beneficial effects of probiotics can be strain specific, pooling data across different strains could lead to inaccurate conclusions. There are however, meta-analyses reviewed in this report that focused on single strains of probiotics with significant findings in support of probiotic use. In summary, there continues to exist a need for additional well designed double blind randomized controlled trials to support the efficacy of probiotic use in the prevention and treatment of AAD in both children and adults.
CHAPTER 3 IMPLICATIONS FOR PRACTICE

Introduction

As research progresses in the field of probiotics, new information becomes available which can be used in designing evidenced-based practice treatment guidelines for use by primary care providers. Probiotics are frequently prescribed by physicians in Europe and Asia, but rarely in the United States (Floch, et al., 2006). In response to this situation, a workshop was convened in 1995 at Yale University under the auspices of The Journal of Clinical Gastroenterology to make recommendations for the clinical use of probiotics. Final guidelines were based on a review of current literature, knowledge of expert panel members, and conference presentations (Floch et al.). The guidelines developed for this report draw from the above recommendations and this author's synthesis of the literature in an attempt to reflect the current state of the science.

Product Selection

Based on the meta analysis conducted by Johnston et al. (2007), the best efficacy when using probiotics is obtained when at least 5 billion colony forming units (cfu)/day are provided. Colony forming units refer to the numbers of live organisms per dose. The strains with the strongest evidence for prevention were LGG, L. sporogenes, and S. boulardii. Of all the probiotics investigated, S. Boulardii has demonstrated the most consistently efficacious results in the prevention of AAD and prevention of recurrence of CDAD. Kotowska et al. (2004) recommend 250mg twice daily as an effective dose for children treated with antibiotics for otitis media and respiratory tract infections.
Probiotic products vary widely and good sources of product information are: the individual product manufacturer and their websites, the California Dairy Research Foundation, and Consumerlabs.org. Consumerlabs.org is a non-profit organization dedicated to providing independent testing and certification of supplements and information to consumers and healthcare professionals concerning health, wellness and nutritional products (www.Consumerlab.com, 2006).

Probiotics come in two commercially available options: fermented food products (yogurt or dairy drinks) and manufactured dietary supplements. When purchasing a probiotic food, it is important to look for labels which indicate that the product contains live and active cultures. Several probiotic foods are now on the market: *Activia*, *DanActice*, and *Danimals* by Dannon; Stonyfield Farms yogurt, Attune Foods chocolate and granola bars, Naked Juice smoothie with *B. lactis*, Lifeway foods' *Basics Plus* kefir, Horizon Organic Dairy yogurts, Kashi's probiotic cereal *Vive*, and a variety of Acidophilus milks.

*S. Boulardii* is marketed in the United States as a product called *Florastor*. It is packaged in a powder formulation for children and in capsules which can be swallowed whole or opened and mixed with liquids or sprinkled over other foods (www.Florastor.com, n.d.). Although no adverse effects have been documented with Florastor’s *S. Boulardii*, it should not be taken with oral systemic antifungal medications (e.g., Fluconazole, Nystatin, Ketoconazole, or Itraconazole) (www.Florastor.com).

When choosing a supplement it is helpful to know the type of bacteria, potency (number of viable bacteria per dose), purity, and relevant research for a particular strain
Because of their fragility, exposure to heat, moisture, and oxygen can all negatively affect product viability. Therefore, expiration dates are particularly important. Certain species of bacteria cannot survive the acidic stomach environment and must be protected until reaching the small intestines where they will colonize. Once located in the intestines the products must properly disintegrate and release the bacteria so that they do not pass through the body intact and unabsorbed.

Practice Guidelines

No published or recommended guidelines exist for the general use of probiotics in primary care practice. Therefore, practitioners must rely on evidence supported by meta-analyses and randomized controlled trials, as well as expert judgment and opinion to build practice applications. Experts in the field of probiotics form an eclectic group of practitioners representing: traditional medicine, gastroenterology, microbiology, oncology, naturopathy, and other complementary and alternative forms of medicine. Based on this author's clinical experience with probiotics over the past 18 years, as a complementary and alternative clinician, the numerous positive benefits and minimal risk profiles support their use by both children and adults. Listed below are a summary of practice guidelines developed for this report:

1) Fermented food products and manufactured dietary supplements, though safe, offer different relative advantages and disadvantages (see Table 1.2).

2) Because of the potential detrimental effects of terminating a course of antibiotics before treatment is completed due to AAD, probiotic use is suggested in all outpatient, non-immuno-compromised patients.
3) To prevent or treat incidences of AAD, it is recommended that probiotic use begin concurrently with antibiotic therapy and continue for two weeks after its conclusion.

4) It is best to take probiotics at least two hours after antibiotic administration to reduce the possibility that the antibiotic destroy the probiotic bacteria.

5) In order to reduce the possibility of their destruction, protect probiotics from heat and light.

6) It is advisable to refrigerate probiotics to extend their shelf life and further protect them, although, there are currently several shelf stable products on the market.

7) LGG and S. boulardii are the two probiotic species that showed the highest efficacy in trials for AAD. Floch et al. (2006) give an "A" recommendation for use of LGG and S. boulardii in the treatment of AAD in outpatient, ambulatory patients. An "A" recommendation is based on strong positive controlled studies in the literature (Floch et al.).

8) The highest quality recommended food product for LGG is Culturelle or Danimals and the recommended product for dietary preparations of S. boulardii is Florastor (www.USProbiotics.org, 2007). (See Appendix F for specific product ratings.)

9) When selecting a probiotic product there are several important considerations: viability of organisms in the product, absence of contamination, enteric protection of the product, and bioavailability (www.Consumerlab.com, 2006).
10) It is the practitioner’s judgment as to the delivery vehicle (food products or dietary preparation), and that decision is case specific and each method of treatment delivery has its advantages and disadvantages to weigh and be tailored to a specific patient.

Implementation of Pilot Study

Following University IRB approval, the practice guidelines developed for this project initially will be distributed at one adult primary care medical practice and one pediatric medical practice in Tucson for use over a period of six months. Providers at these practices will recommend probiotics to their patients who are taking a course of antibiotics. They will provide them with a handout (see Appendix A) which briefly explains what probiotics are, their benefits, product suggestions, and recommendations for daily use. Providers will be encouraged to elicit feedback from their patients regarding any AAD that might develop and any beneficial effects they experience while taking the probiotics.

Summary

Recommendations for use of probiotics need to be specifically referenced to the particular species clinically trialed for the particular disease or indication. It is not clear that species are readily substitutable and efficacy is dependent on adequate dose and duration of intake for colonization to have an effect. Because of a lack of standardization and quality control, many products on the market have not been proven to be effective. According to independent testing, many products do not have the numbers of viable organisms claimed on their labels, may have other microbial contaminants, and may not
be bioavailable due to destruction in the stomach (www.Consumerlab.com, 2008). Therefore when recommending a particular product, it is critical to rely on independent quality testing (see Appendix F) and use products only as they are referenced. For recommendations of probiotic use for conditions other than AAD, see Appendix C and E.
CHAPTER 4 EVALUATION

Introduction

Evidenced-based practice is the gold standard for improving patient care and treatment outcomes. However, there is a huge time lag between the generation of research findings and the translation of those findings into clinical practice resulting in many efficacious interventions not being used in clinical practice (Melnyk et al., 2007). In an attempt to address this deficit in relationship to the treatment of ADD, practice guidelines were developed to help direct primary care providers in their use of probiotics. Nurse Practitioners must be at the forefront of evaluation and implementation into practice new research findings in the form of evidence-based care.

Evaluation

In order to assess provider satisfaction with the guidelines, after six months of use a short survey will be distributed requesting provider feedback concerning their patient's use of probiotics and their satisfaction with using the guidelines to recommend probiotics to their patients (see Appendix B). Based on input from this survey the practice guidelines will be evaluated and revised in the hope of making them more user friendly and useful to practitioners. The AGREE instrument, an objective measure of guideline quality, will be used in the analysis and evaluation of the practice guidelines (Cluzeau and Burgers, 2001).

Strengths of Project

This report presents the most current evidence from research in the field of probiotics and AAD. Over 70 research trials spanning the past 10 years were reviewed
with the most current and relevant being included. The information provided gives primary care providers an evidenced based practice tool and an additional treatment method to better address and treat the common problem of AAD in their patients.

The risk to benefit ratio is clearly in favor of prescribing probiotics to patients who are taking antibiotics. In the majority of controlled studies with probiotics performed with children and adults, no adverse effects have been observed. In addition, probiotics have not been found to have any toxic effects in animal tests (Zhou et al., 2000). Most probiotic supplements contain approximately $1-5 \times 10^9$ viable bacteria per daily portion. Comparing this figure with the number of bacteria in the intestines ($10^{14}$), clearly there is no risk of overdose (Tijsselina, Pekelharinga, Romboutsb, 2005). In fact, a small portion of yogurt can also contain a similar number of bacteria. Salminen et al. (2002) found no increase in the risk of adverse effects with the additional public consumption of probiotics in Finland over a period of five years.

The cost to patients of prescribing probiotics is minimal with potential huge cost savings due to the elimination of potentially serious consequences of AAD. Probiotics are easily accessible, readily available and simple to use. They can be taken by people across the age span from infants to the elderly with no adverse effects.

Limitations of Project

Despite the existence of a large body of research on probiotics and AAD, there is still no consensus in the scientific community regarding recommendations for wide-scale use. Because of the varying properties of different probiotics, the efficacy of each probiotic for a particular condition must be clearly documented before use can be
extensively advised. Until this occurs, the availability of more anecdotal information in
the literature would be helpful. Additionally, future research must be reported in venues
which are readily reviewed and accessible to primary care practitioners. Currently, there
is a lack of research available for review in either print or online nursing journals or
family practice journals. Most of the research is being conducted and reported on by
gastroenterology researchers, which implies that primary care providers may not be
gaining access to this important information.

Significance for Nurse Practitioners

Nurse Practitioners (NPs) employ a holistic approach to patient care. They
consider the whole individual, not just the disease, when diagnosing and treating their
patients. Through a combination of expertise and knowledge of evidenced based practice
and appreciation for their patient's individual preferences, they are in a unique position to
guide their patients to an understanding of how to maintain balance and achieve a state of
health.

Nursing’s Agenda for Health Care Reform (ANA, 2005) called for a shift from an
illness orientation towards one of wellness and prevention, to “use health resources
effectively and efficiently by balancing efforts to promote health with the capacity to cure
disease.” It also called upon nursing to foster consumer responsibility for personal health,
self care and informed decision making. By taking a proactive approach in preventing
AAD through the prescribing of probiotics, NPs are assisting their patients to take control
of their health by restoring their bodies to a more natural state of equilibrium.
Summary

There is still a lack of consensus in the literature regarding the safety and efficacy of probiotics. This limits their routine acceptance and use in clinical practice. Given the large amounts of probiotics that have already been consumed for many years without any adverse effects and the numerous studies that have demonstrated their health benefits, it can be confidently stated that the advantages of consuming probiotics far outweigh any risks (Tijselinga et al., 2005). In the opinion of this author, the overall evidence is sufficient to recommend use of probiotics in the prevention and treatment of AAD.
### TABLE 1.1 – DIAGNOSIS OF AAD AND CDAD

<table>
<thead>
<tr>
<th>General</th>
<th>Check for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical History</td>
<td>History of recent antibiotics (&lt;2 months)</td>
</tr>
<tr>
<td></td>
<td>History of recent hospitalization</td>
</tr>
<tr>
<td>Exclude other diarrhea causes</td>
<td>Medications resulting in diarrhea</td>
</tr>
<tr>
<td></td>
<td>Chronic intestinal conditions</td>
</tr>
<tr>
<td></td>
<td>(inflammatory bowel disease, Crohn's ischemic colitis, short bowel syndrome)</td>
</tr>
<tr>
<td></td>
<td>Food intolerances</td>
</tr>
<tr>
<td>Exclude non-antibiotic enteric pathogens</td>
<td>Salmonella, Shigella, Campylobacter, Aeroionas, Yersinia, E. Coli 0157:H7</td>
</tr>
<tr>
<td>Specific etiologies</td>
<td>C. difficile cell cytotoxin B assay (best) or ELISA kits for toxin A and B</td>
</tr>
<tr>
<td></td>
<td>If negative for C. difficile suspect other etiologies</td>
</tr>
<tr>
<td>If diarrhea persists or serious symptoms</td>
<td>Repeat C. difficile assay</td>
</tr>
<tr>
<td>develop</td>
<td>Consider sigmoidoscopy or colonoscopy</td>
</tr>
<tr>
<td></td>
<td>Consider computerized tomography (CT) scan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fermented Food Products (e.g. Yogurt or Dairy drinks)</th>
<th>Dietary Supplements (e.g. Capsules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>Promotes corrective gastrointestinal health during extended antibiotic treatment</td>
<td>Require refrigeration and protection from light to reduce degradation and extend shelf life</td>
</tr>
<tr>
<td>Buffering effect of dairy products increases chance that bacteria will survive into the intestine</td>
<td>Must check for labels which indicate live and active cultures present in product</td>
</tr>
<tr>
<td>Good sources of calcium, riboflavin, vitamin B12, potassium, and amino acids</td>
<td>During episodes of diarrhea, dairy products can be hard on an inflamed and irritated digestive tract</td>
</tr>
<tr>
<td>Probiotic foods are becoming more commercially available in grocery stores: e.g. Activia, DanActive, Acidophilus milks</td>
<td>Is important to understand the type of bacteria, potency (bacteria per dose), purity, for a particular strain. An average consumer may lack such understanding</td>
</tr>
<tr>
<td>Minimal risk profile to children as well as and adults.</td>
<td>Minimal risk profile to children as well as and adults</td>
</tr>
<tr>
<td>Fermentation process assists in formation of functional peptides and butyric acid which may also have beneficial effects</td>
<td></td>
</tr>
</tbody>
</table>
What are probiotics?

Probiotics are "good bacteria", living microbial organisms that can benefit our health. Literally, the word means "for life". Some examples are: the yeast Saccharomyces boulardii and the following bacteria: Lactobacillus acidophilus, L. bulgaricus, L. reuteri, Lactobacillus G.G, L. plantarum, L. casei, B. bifidus, Saccharomyces salivarius, Streptococcus thermophilus.

Why are they beneficial?

When the gastrointestinal tract becomes out-of-balance due to stress, illness, improper diet, or as a result of the use of antibiotics, there is a risk that the beneficial intestinal bacteria will be suppressed and that the pathogenic (disease causing) bacteria will become dominant. Probiotics work to support and restore the healthy balance of the good and bad bacteria in the intestines. They help maintain health by stimulating our bodies' immune responses and controlling disease causing mechanisms. They protect the body against infections, assist digestion, produce nutrients, and play an important role in the immune system.

Why are they being recommended to me?

Antibiotics stress the intestines and can kill some of the good bacteria the body needs to function along with the bad bacteria causing your infection. This can cause diarrhea. Probiotics, by restoring balance, can help prevent antibiotic associated diarrhea and other stomach upsets caused by antibiotics.
**Where can I purchase them?**

In supermarkets (Frys, Bashas, Safeway, Albertsons), health food stores (Wild Oats, Trader Joes, Sunflower, New Life), and pharmacies (Walgreens, CVS, Osos, Costco, Walmarts, Target).

**What are some quality brands?**

Dannon Activa yogurt or DanActive milk, Yoplait Yo-Plus, Stoneyfield farms yogurt, Horizon yogurt, Culturelle, Florastor, Jarrow, Kal, Kyo-Dophilus, Nature's Sunshine, Natures Way, Webber Naturals, Natural Factors (for children)

$LGG$ and $S. boulardii$ are the two probiotic species which showed the highest efficacy in trials for AAD. The recommended product for $LGG$ is Culturelle or Danimals and the recommended product for $S. boulardii$ is Florastor (www.USProbiotics.org, 2007).

**How much will they cost?**

They range in price from under $10.00 to up to $40.00 depending on the brand and the amount of capsules per bottle. They can also be purchased in foods such as yogurt, kefir or fermented milk which range in price from under $1.00 to $10.00.

**How often should I take them?**

Follow the instructions on the label of the product you purchase. Generally, one to three times a day, preferably on an empty stomach and two hours after or before taking your antibiotic.
APPENDIX B – PROVIDER SURVEY

1. Are the guidelines clear and easy to use?

2. How valuable or helpful do you find them in your practice?

3. Are they applicable for primary care?

4. Has it been easy or difficult to recommend probiotics to patients?

5. Approximately how many times per week have you recommended probiotics to your patients? (How many prescriptions given?)

6. Are you aware of either positive or negative patient outcomes with probiotic use?

7. Suggestions for improvement of the guidelines?
APPENDIX C – GUIDELINES FOR PROBIOTIC USE

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Clinical Effectiveness</th>
<th>Organisms**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult and childhood diarrhea</td>
<td>B</td>
<td><em>Lactobacillus reuteri</em>¹³,¹⁴</td>
</tr>
<tr>
<td>Prevention</td>
<td></td>
<td><em>Lactobacillus GG</em>¹⁵,¹⁶ *L. casei,<em>¹⁷,¹⁸</em> *L. acidophilus,*¹⁹–²¹ <em>S. boulardii</em>²¹,²²</td>
</tr>
<tr>
<td>Treatment</td>
<td>A</td>
<td><em>Bifidobacteria</em>¹⁴,²⁵</td>
</tr>
<tr>
<td>Antibiotic-associated diarrhea</td>
<td>A</td>
<td><em>S. boulardii</em>²²–²⁷ <em>L GG</em>²⁸–³⁰</td>
</tr>
<tr>
<td>Radiation</td>
<td>C</td>
<td><em>VSL no. 3</em>³¹</td>
</tr>
<tr>
<td>Vaginosis</td>
<td>C</td>
<td><em>Lactobacillus acidophilus</em>³²,³³</td>
</tr>
<tr>
<td>H pylori</td>
<td>C</td>
<td><em>L. johnsonii</em>²⁴,³⁵</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>C</td>
<td><em>E. coli</em> (Nissle),³⁶,³⁷ *Bifidobacteria and Lactobacillus,*³⁸ <em>VSL no. 3</em>³⁹,⁴⁰</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>C</td>
<td><em>E. coli</em> (Nissle),⁴¹ *S. Boulardii,*⁴²,⁴³ *L GG (variable)*⁴⁴</td>
</tr>
<tr>
<td>Pouchitis</td>
<td>A</td>
<td><em>VSL no. 3</em>⁴⁵–⁴⁷</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>C</td>
<td><em>L. plantarum</em>⁴⁸,⁴⁹ *VSL no. 3,*³⁰ <em>B. infantis</em>⁴¹</td>
</tr>
<tr>
<td>Prevention of cardiovascular disease</td>
<td>C</td>
<td><em>Lactobacillus in milk and yoghurt</em>⁴²,⁴³</td>
</tr>
<tr>
<td>To improve immune response</td>
<td>B</td>
<td><em>L. acidophilus</em>⁵⁴ *L. Plantarum,*⁵⁵ *B. Lactis,*⁵⁶,⁵⁷ *L GG,*³⁸,³⁹ <em>L. Johnsonii</em>⁵⁹,⁶¹</td>
</tr>
</tbody>
</table>

* A indicates strong evidence; B, suggestive evidence; C, inadequate studies to be certain.
** Exact dosage used is in appropriate reference.

VSL no. 3 indicates *Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, and *Streptococcus salivarius*.

Source: Floch et al. (2006, p. 276)
### APPENDIX D – COMMERCIAL PROBIOTIC STRAINS

This table lists some commercial probiotic strains currently available. Probiotic species are listed as reported by manufacturer.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Commercial products</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>L. acidophilus</em> NCFM®</td>
<td>Sold as ingredient</td>
<td>Danisco (Madison WI)</td>
</tr>
<tr>
<td><em>B. lactis</em> HN019 (DR10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. rhamnosus</em> HN001 (DR20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Saccharomyces cerevisiae</em></td>
<td>Florastor</td>
<td>Biocodex (Creswell OR)</td>
</tr>
<tr>
<td>(boulardii)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>B. infantis</em> 35264</td>
<td>Align®</td>
<td>Procter &amp; Gamble (Mason OH)</td>
</tr>
<tr>
<td><em>L. fermentum</em> VR003 (PCC)</td>
<td>Sold as ingredient</td>
<td>Probiomics (Eveleigh, Australia)</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> R0011</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em> R0052</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em> LA5</td>
<td>Sold as ingredient</td>
<td></td>
</tr>
<tr>
<td><em>L. paracasei</em> CRL 431</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>B. lactis</em> Bb-12</td>
<td>Good Start Natural Cultures® infant formula</td>
<td>Nestle (Glendale, CA)</td>
</tr>
<tr>
<td><em>L. casei</em> Shirota</td>
<td>Yakult®</td>
<td>Yakult (Tokyo, Japan)</td>
</tr>
<tr>
<td><em>B. breve</em> strain Yakult</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. casei</em> DN-114 001 (&quot;L. casei Immunitas™&quot;)</td>
<td>DanActive® fermented milk</td>
<td>Danone (Paris, France)</td>
</tr>
<tr>
<td><em>B. animalis</em> DN173 010 (&quot;Bifidis regularis™&quot;)</td>
<td>Activia® yogurt</td>
<td>Dannon (Tarrytown, NY)</td>
</tr>
<tr>
<td><em>L. reuteri</em> RC-14™</td>
<td>Femdophilus®</td>
<td>Chr. Hansens (Milwaukee WI)</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> GR-1™</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. johnsonii</em> Lj-1 (same as NCC533 and formerly <em>L. acidophilus</em> La-1)</td>
<td>LC1®</td>
<td>Nestlé (Lausanne, Switzerland)</td>
</tr>
<tr>
<td><em>L. plantarum</em> 299V</td>
<td>Sold as ingredient</td>
<td>Probi AB (Lund, Sweden)</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> 271</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. reuteri</em> ATCC 55730 (&quot;Protectis&quot;)</td>
<td>Stonyfield Farms yogurts</td>
<td>Biogaia (Stockholm, Sweden)</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> GG (&quot;LGG&quot;)</td>
<td>Culturelle®; Dannon Danimals®</td>
<td>Valio Dairy (Helsinki, Finland)</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> LB21</td>
<td>Sold as ingredient</td>
<td>Essum AB (Umeå, Sweden)</td>
</tr>
<tr>
<td><em>Lactococcus lactis</em> L1A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strain</td>
<td>Manufacturer</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------</td>
<td></td>
</tr>
<tr>
<td><em>L. salivarius</em> UCC118</td>
<td>University College (Cork, Ireland)</td>
<td></td>
</tr>
<tr>
<td><em>B. longum</em> BB536</td>
<td>Morinaga Milk Industry Co., Ltd. (Zama-City, Japan)</td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em> LB</td>
<td>Lacteol Laboratory (Houdan, France)</td>
<td></td>
</tr>
<tr>
<td><em>L. paracasei</em> F19</td>
<td>Medipharm (Des Moines, Iowa)</td>
<td></td>
</tr>
<tr>
<td><em>L. paracasei</em> LP-33</td>
<td>GenMont Biotech (Taiwan)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Probiotics Basics (2007)
## APPENDIX E – PROBIOTIC PRODUCTS WITH TARGETED HEALTH BENEFITS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Strain</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant diarrhea</td>
<td><em>L. rhamnosus</em> GG</td>
<td>Culturelle (capsule) (<a href="http://www.culturelle.com">www.culturelle.com</a>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Danimals (drinkable yogurt) (<a href="http://www.danimals.com">www.danimals.com</a>)</td>
</tr>
<tr>
<td></td>
<td><em>L. casei</em> DN-114001 (aka &quot;Immunitas™&quot;)</td>
<td>DanActive (fermented milk) (<a href="http://www.danactive.com">www.danactive.com</a>)</td>
</tr>
<tr>
<td>Inflammatory bowel conditions</td>
<td>8-strain combination of 3 <em>Bifidobacterium</em> strains, 4 <em>Lactobacillus</em> strains and <em>S. thermophilus</em></td>
<td>VSL#3 (powder) (<a href="http://www.vsl3.com">www.vsl3.com</a>)</td>
</tr>
<tr>
<td>Antibiotic associated diarrhea; <em>C. difficile</em></td>
<td><em>S. boulardii</em></td>
<td>Florastor (powder) (<a href="http://www.florastor.com">www.florastor.com</a>)</td>
</tr>
<tr>
<td></td>
<td><em>L. rhamnosus</em> GG</td>
<td>Culturelle (capsule) (<a href="http://www.culturelle.com">www.culturelle.com</a>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Danimals (drinkable yogurt) (<a href="http://www.danimals.com">www.danimals.com</a>)</td>
</tr>
<tr>
<td></td>
<td><em>L. casei</em> DN114001</td>
<td>DanActive (fermented milk) (<a href="http://www.danactive.com">www.danactive.com</a>)</td>
</tr>
<tr>
<td>Gut transit time</td>
<td><em>B. animalis</em> DN-173 010 (aka &quot;Bifidus regularis™&quot;)</td>
<td>Activia (yogurt) (<a href="http://www.activia.com">www.activia.com</a>)</td>
</tr>
<tr>
<td>Keeping healthy</td>
<td><em>L. reuteri</em> ATCC 55730</td>
<td>Stonyfield yogurt (<a href="http://www.stonyfield.com">www.stonyfield.com</a>; <a href="http://www.biogaia.com">www.biogaia.com</a>)</td>
</tr>
<tr>
<td></td>
<td><em>L. casei</em> DN-114001</td>
<td>DanActive (fermented milk) (<a href="http://www.danactive.com">www.danactive.com</a>)</td>
</tr>
<tr>
<td></td>
<td><em>L. casei</em> Shirota</td>
<td>Yakult (<a href="http://www.yakultusa.com">www.yakultusa.com</a>)</td>
</tr>
<tr>
<td>Allergy (primary evidence in prevention of atopic dermatitis in infants)</td>
<td><em>L. rhamnosus</em> GG</td>
<td>Culturelle (capsule) (<a href="http://www.culturelle.com">www.culturelle.com</a>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Danimals (drinkable yogurt) (<a href="http://www.danimals.com">www.danimals.com</a>)</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td><em>L. bulgaricus</em> and/or <em>S. thermophilus</em> (most strains)</td>
<td>All yogurts with live, active cultures</td>
</tr>
<tr>
<td>Colic in infants</td>
<td><em>L. reuteri</em> ATCC 55730</td>
<td>Reuteri drops (<a href="http://www.biogaia.com">www.biogaia.com</a>)</td>
</tr>
<tr>
<td>Immune support</td>
<td><em>B. lactis</em> HN019 (aka HOWARUTM or DR10)</td>
<td>Naked Juice Probiotic Juice Smoothie Strain sold as an ingredient for dairy and supplement products - contact Danisco (<a href="http://www.danisco.com">www.danisco.com</a>)</td>
</tr>
<tr>
<td></td>
<td><em>B. lactis</em> Bb-12</td>
<td>Good Start Natural Cultures (infant formula) Nestle; <a href="http://www.verybestbaby.com">www.verybestbaby.com</a>/</td>
</tr>
<tr>
<td>Strain</td>
<td>Product Description</td>
<td>Source</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------</td>
<td>--------</td>
</tr>
<tr>
<td>L. casei DN114001</td>
<td>DanActive (fermented milk) (<a href="http://www.danactive.com">www.danactive.com</a>)</td>
<td></td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>Culturelle (capsule) (<a href="http://www.culturelle.com">www.culturelle.com</a>) Danimals (drikable yogurt) (<a href="http://www.danimals.com">www.danimals.com</a>)</td>
<td></td>
</tr>
<tr>
<td>L. reuteri ATCC 55730</td>
<td>Stonyfield yogurt (<a href="http://www.stonyfield.com">www.stonyfield.com</a>; <a href="http://www.biogaia.com">www.biogaia.com</a>)</td>
<td></td>
</tr>
<tr>
<td>Vaginal applications</td>
<td>L. rhamnosus GR-1, L. reuteri RC-14 Fem-Dophilus (capsules) (<a href="http://www.urexbiotech.com">www.urexbiotech.com</a>; <a href="http://www.jarrow.com">www.jarrow.com</a>)</td>
<td></td>
</tr>
<tr>
<td>Irritable bowel syndrome symptoms</td>
<td>B. infantis 35264 (aka &quot;Bifantis™&quot;) Align (capsules) (<a href="http://www.aligngi.com">www.aligngi.com</a>)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Probiotics Basics (2007)
### RESULTS OF CONSUMERLAB.COM TESTING OF PROBIOTIC SUPPLEMENTS

<table>
<thead>
<tr>
<th>Product Name (Suggested Daily Serving)</th>
<th>Manufacturer or Distributor</th>
<th>Types of Organisms Claimed Per Unit (and amounts if specified)</th>
<th>Listed Number of Probiotic Organisms in Maximum Suggested Daily Serving*</th>
<th>— TEST RESULTS —</th>
<th>Provided At Least 1 Billion Bacteria Per Daily Serving**</th>
<th>Free of Microbial Contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advocare® Probiotic Restore™ (2 - 4 capsules per day)</td>
<td>Dist. by Advocare® International</td>
<td>Lactobacillus acidophilus 0.5 billion, Bifidobacterium bifidum 0.5 billion</td>
<td>2-4 billion</td>
<td>No</td>
<td>No (for 2 capsules)</td>
<td>Yes (for 4 capsules)</td>
</tr>
<tr>
<td>Culturelle® with Lactobacillus GG, All Natural (1 capsule per day)</td>
<td>Dist. by Allergy Research Group/Nutricology</td>
<td>Lactobacillus GG</td>
<td>10 billion¹</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DDS® Acidophilus with FOS (1 gram of powder [1/4 tsp]) per day)</td>
<td>Dist. by UAS Laboratories</td>
<td>Lactobacillus acidophilus</td>
<td>2 billion¹</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Enzymatic Therapy™ Acidophilus Pearls™ (1 pearl per day)*</td>
<td>Mfd. by Enzymatic Therapy, Inc.</td>
<td>Lactobacillus acidophilus and Bifidobacterium longum</td>
<td>1 billion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Flora Source™, 15 Billion Viable Cells Per Capsule at Time of Manufacture Guaranteed (2</td>
<td>Dist. by MBA Company</td>
<td>Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis,</td>
<td>30 billion¹</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Capsules per day</td>
<td>Bifidobacterium lactis, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus brevis, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus gasseri, Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus salivarius, Lactobacillus lactis, Streptococcus thermophilus</td>
<td>Dist. by</td>
<td>Saccharomyces boulardii lyo 250 mg (2 capsules per day)*</td>
<td>Florastor® Saccharomyces boulardii lyo 250 mg</td>
<td>10 billion</td>
<td>Yes</td>
</tr>
<tr>
<td>----------------</td>
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<td>--------------------------------------------------</td>
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</tr>
<tr>
<td>Garden of Life® Primal Defense™ HSO™ Probiotic Formula (3 scoops powder per day, 0.9 g each)</td>
<td>Mfd. by Garden of Life, Inc.</td>
<td>Lactobacillus plantarum, Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus rhamnosus, Bifidobacterium breve, Lactobacillus casei, Lactobacillus brevis, Lactobacillus salivarius, Lactobacillus acidophilus, Bacillus</td>
<td>Not listed</td>
<td>NA</td>
<td>Yes</td>
<td>Found 1.44 billion** per scoop (4.3 billion/day)</td>
</tr>
<tr>
<td>Brand</td>
<td>Manufacturer</td>
<td>Strains/Organisms</td>
<td>Desired CFU (Billion)</td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
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<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Kal® Acidophilus ProBiotic-5, 3 Billion Viable Organisms, 5 Strains (1 capsule per day)</td>
<td>Mfd. by Nutraceutical Corp.</td>
<td>L. Acidophilus, Lactobacillus spp., L. Bulgaricus, S. Thermophilus, B. Bifidum</td>
<td>3 billion¹</td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Kyo-Dophilus® 1.5 Billion Live Cells Per Capsule (2 capsules per day)*</td>
<td>Mfd. by Wakunaga of America Co. Ltd</td>
<td>L. acidophilus Ks-13, B. bifidum G9-1 and B. longum MM-2</td>
<td>3 billion</td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Nature Made® Acidophilus 500 Million Live Cells per Tablet (2 tablets per day)*</td>
<td>Dist. by Nature Made Nutritional Products</td>
<td>Lactobacillus acidophilus 500 million</td>
<td>1 billion</td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong> (for 2 tablets)</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Nature's Secret Ultimate Probiotic 4-Billion™ (1 tablet per day)</td>
<td>Dist. by Nature's Secret®</td>
<td>Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus rhamnosus, Lactobacillus salivarius, Bifidobacterium infantis, Bifidobacterium longum, Lactobacillus bulgaricus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus paracasei, Streptococcus thermophilus, Lactobacillus brevis, Lactobacillus reuteri, Lactobacillus lactis, Lactobacillus SP lactis, Lactobacillus fermentum, Lactobacillus helveticus, Enterococcus faecium, Lactobacillus keferi</td>
<td>4 billion</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nature's Sunshine® Bifidophilus Flora Force®, 4 billion total microorganisms per capsule (2 capsules per day)</td>
<td>Dist. by Nature's Sunshine Products, Inc.</td>
<td>Lactobacillus rhamnosus 1.25 billion, Lactobacillus casei 1 billion, Lactobacillus acidophilus 1.25 billion, Bifidobacterium longum 0.5 billion</td>
<td>8 billion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nature's Way® Primadophilus®</td>
<td>Dist. by Nature's</td>
<td>Lactobacillus casei-108,</td>
<td>35 billion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Product</td>
<td>Manufacturer</td>
<td>Strains Listed</td>
<td>Amount</td>
<td>Enteric-Coated</td>
<td>Probiotic Strains Plus</td>
<td>NutraFlora®, 35 Billion CFU, Enteric-Coated (1 capsule per day)*</td>
</tr>
<tr>
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<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Optima, 14 Probiotic Strains Plus NutraFlora®, 35 Billion CFU, Enteric-Coated (1 capsule per day)*</td>
<td>Way Products, Inc.</td>
<td>Bifidobacterium longum-135, Lactobacillus acidophilus-122, Lactobacillus plantarum-119, Lactobacillus rhamnosus-111, Lactobacillus rhamnosus-114, Bifidobacterium breve-129, Bifidobacterium bifidum-132, Lactococcus lactis-136 [sic], Streptococcus thermophilus-110, Bifidobacterium infantis-116, Lactobacillus bulgaricus-137, Lactobacillus salivarius-118, Lactobacillus helveticus-128</td>
<td>2.8 billion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nutravite Acidophilus Plus, Heat Resistant (2 capsules per day)</td>
<td>Dist. by Nutravite Pharmaceutical Inc.</td>
<td>L. acidophilus, L. rhamnosus and B. longum</td>
<td>2.8 billion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PB 8® Probiotic Acidophilus For Life™ (2 capsules per day)</td>
<td>Dist. by Nutrition Now® Inc.</td>
<td>Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus paracasei, Lactobacillus salivarius, Bifidobacterium bifidum and Bifidobacterium longum</td>
<td>Amount not stated</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pharmanex®</td>
<td>Dist. by Lactobacillus</td>
<td>Lactobacillus</td>
<td>Amount</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Product</td>
<td>Manufacturer/Supplier</td>
<td>Probiotic Strains/Amounts</td>
<td>Source Found per Capsule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProBio PCC™ Live Probiotics</td>
<td>Pharmanex, a division of NSE Products, Inc.</td>
<td>fermentation not stated</td>
<td>1.2 billion** per capsule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotic Gut Buddies®</td>
<td>Mfd. by Tishcon Corp.</td>
<td>Bifidobacterium longum ME 0.4 billion, Lactobacillus rhamnosus ME 0.4 billion, Lactobacillus acidophilus ME 1.2 billion</td>
<td>Yes Yes Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rite Aid Acidophilus, Milk Free, Natural (1 capsule per day)</td>
<td>Dist. by Rite Aid Corporation</td>
<td>Lactobacillus acidophilus, Bifidobacterium bifidum and L. bulgaricus</td>
<td>NA No Yes</td>
<td></td>
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<tr>
<td>webber naturals™ Acidophilus with Bifidus, Non Dairy (3 capsules per day)</td>
<td>Dist. by wn pharmaceuticals, ltd.</td>
<td>Lactobacillus rhamnosus 3 billion, Lactobacillus paracasei 1.8 billion, Lactobacillus acidophilus 0.6 billion, Bifidobacterium longum 0.6 billion</td>
<td>18 billion¹ Yes Yes Yes</td>
<td></td>
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<tr>
<td>Children's Products</td>
<td>Dist. by Natural Factors</td>
<td>L. rhamnosus 1.3 billion, B. infantis 0.4 billion, S. thermophilus 0.19 billion, L. acidophilus 0.10 billion, L. delbrueckii subsp. bulgaricus 0.01 billion</td>
<td>2-6 billion¹ Yes Yes Yes</td>
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REFERENCES


Salminen, M. K., Tynkkynen, S., Rautelin, H., Saxelin, M., Vaara, M., Ruutu, P., et al. (2002). Lactobacillus Bacteremia during a Rapid Increase in Probiotic Use of Lactobacillus rhamnosus GG in Finland. Clinical Infectious Disease, 15(35), 1155-60.


