suggest that the clinical conditions of the children could be responsible for the difference (more severe condition in almost of the positive studies and mild-to-moderate diarrhoea in the fifth trial). In our experience, we have recently determined whether an oral treatment with *S. boulardii* would reduce the duration of diarrhoea in infants with acute diarrhoea[20]. In this double-blind, placebo-controlled study, 186 infants, 6- to 48-months old and hospitalized within 72 hours after the onset of acute diarrhoea in two hospitals in Goiânia, Goiás, Brazil, were randomly assigned to receive twice a day for 5 days 200 mg of a commercial pharmaceutical product containing 4 x 10^9 viable cells of *S boulardii* or a placebo. Stool samples were submitted to search for rotavirus. Among the 176 infants who completed the trial, the patients treated with *S boulardii* (90) showed a 50% reduction of diarrhoea (P<0.05) since the second day after the beginning of the intervention when compared with a placebo group (86). Additionally, when, in an exploratory analysis, the children pertaining to the two types of intervention were separated into rotavirus-infected patients and non-rotavirus patients, the beneficial effect due to the probiotic treatment was observed essentially for patients presenting a rotaviral diarrhoea. However, the timing of the first administration of the probiotic appears to be critical, as the earlier the first administration of *S. boulardii* the greater the efficacy (no more than 72 hours after the onset of diarrhoea).

Safety of *S. boulardii* in infant

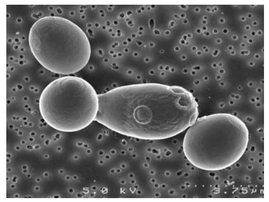
Although no adverse effects were observed in any of the clinical trials with *S. boulardii* in infants, the administration of this yeast is not absolutely without risk[12]. As for other probiotics, its use is not recommended in patients immunocompromised or with severe general or intestinal disease. Up to now, almost 100 cases of *S. boulardii*-associated fungemia have been reported, which is thought to be due to translocation or a contamination by the colonized hands of health workers[22]. Fungemia with *S. boulardii* can be effectively treated with antimycotic medication or sometimes only by stopping the probiotic administration.

Probiotic mechanisms of *S. boulardii*

Many mechanisms of action have been proposed to explain *S. boulardii* protection, such as modulation of the immune system[23], degradation of bacterial toxins and their respective receptors on colonic mucosa[24], inhibition of cholera toxin action[25,26], modulation of the transduction pathway induced by enteropathogenic and enterohemorrhagic *Escherichia coli*[27] and by *Salmonella* Typhimurium[28,29], anti-inflammatory capacity[30] and trapping of some enteropathogenic bacteria on yeast surface[31].

Conclusion

Concluding, the best evidence obtained from biological and clinical trials for the reduction of the duration of acute diarrhoea (approximately 24 hours) using probiotic preparations has been accumulated for some bacterial and yeast strains. For this reason, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Pediatric Infectious Diseases (ESPID) guidelines make a stronger recommendation for the use of probiotics for the management of acute diarrhoea, particularly those with documented efficacy such as *S. boulardii*[32].



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The Probiotics news

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Think BIG, Think micro

An educational project by MD Pharmaceuticals Pte Ltd

Message from the Editor

As our newsletter enters its sixth year, we wish to convey our heartfelt thanks and appreciation to our panel of medical advisors and the many articles contributed by the local and foreign doctors on probiotics.

In this 12th issue, we would like to thank Prof Satya Prakash, for graciously written an article on the **possible role of probiotics in lipid lowering level.**

Our readers would also benefit from an educational article by Dr Jarrod Lee on the **role of probiotics for the gut.**

Adding on, we have also for you, an insightful write up by Professor Jacques Robert Nicoli on the **use of probiotic in infant acute diarrhoea.**

The articles are informative as these good bacteria continue to be well received, recognized and prescribed globally due to its numerous scientific and clinical back-ups.

We hope that you will enjoy reading this newsletter as much as we prepare it.

The editorial team wishes one and all a joyful Lunar New Year and a successful, healthy and blessed 2014.

God Bless !

Melvin Wong
Editor-in chief

Probiotic *Lactobacillus reuteri* (NCIMB 30242) shows promise in lipid lowering effect

Dr. Satya Prakash
Professor, Faculty of Medicine, McGill University, Director, Biomedical Technology and Cell Therapy Research Laboratory Professor, Biomedical Engineering Professor, Artificial Cells and Organs Research Center Member, Physiology and Experimental Medicine

Dyslipidemia and hypercholesterolemia

Dyslipidemia is elevation of plasma total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglycerides (TGs), or low high-density lipoprotein cholesterol (HDL-C) level that contributes to the development of atherosclerosis, cardiovascular disease and cerebrovascular disease. The causes may be primary (inherited) or secondary (sedentary lifestyle and excessive dietary intake of saturated fat, cholesterol, and trans-fats). Diagnosis is by measuring plasma levels of lipids: TC, LDL-C, TGs and low HDL-C. There is no natural cutoff between normal and abnormal lipid levels because lipid measurements are continuous. As a linear relation likely exists between lipid levels and cardiovascular risk, many people with "normal" cholesterol levels still benefit from achieving lower levels. Consequently, there are no numeric definitions of dyslipidemia and the term is applied to lipid levels for which treatment has proven beneficial. Proof of benefit is strongest for lowering elevated LDL-C levels.

What is *Lactobacillus reuteri* (NCIMB 30242)?

Lactobacillus reuteri (L.reuteri) NCIMB 30242 (marketed as Cardioviva or Pro-lipid) is the only natural probiotic that has been shown in peer reviewed and published clinical trials to safely reduce LDL ("bad") cholesterol by 11.6% in adults with moderately elevated cholesterol. *L.reuteri* NCIMB 30242 healthy bacteria help to reduce LDL and TC levels, risk factors for heart disease, in two ways: by reducing the amount of cholesterol your body produces and by reducing the amount absorbed from food.

L.reuteri NCIMB 30242 represents the first of a new generation of probiotics that have targeted and proven mechanisms of action and are supported by gold standard clinical evidence. *L.reuteri* NCIMB 30242 was developed by Micropharma, a Canadian company and a leader in the development of targeted, highly functional probiotics. *L.reuteri* NCIMB 30242 was carefully selected from hundreds of probiotic strains for a specific ability to effect cholesterol absorption and production.

The probiotic strain is produced under the highest standards. The strain is well characterized and its safety is supported by peer-reviewed clinical publications and regulatory agencies in the US (FDA), Canada (Health Canada), Europe (EFSA), Australia and New Zealand and the People's Republic of China.

How does *L.reuteri* NCIMB 30242 work?

Cholesterol is a sterol or "fat-like" molecule that is synthesized in the body (~75%) and absorbed from ingested food (~15%). The exclusive pathway for removing cholesterol from the body and limiting its absorption from food is provided by the enzymatic activity of bacteria that live in the small intestine. The responsible enzyme is called bile salt hydrolase (BSH). The healthy bacteria in the small intestine are the only source of BSH enzyme which is necessary for the natural pathways of cholesterol excretion to function correctly. *L.reuteri* NCIMB 30242 is a probiotic that supplements the amount of BSH enzyme and support the body's natural mechanisms for removing cholesterol from the body.

Lessons from clinical trials

Cholesterol lowering efficacy of *L.reuteri* NCIMB 30242 in yogurt and capsule formulations were evaluated in hyper-cholesterolemic adults in two clinical studies. In the first study, a total of 114 subjects completed a double-blind, placebo-controlled, randomized, parallel-arm, multicenter study. Over the intervention period, subjects consuming *L.reuteri* NCIMB 30242 yogurts attained significant reductions in LDL-C of 8.92% (P=0.016), TC

of 4.81%, (P=0.031), and non-HDL-C of 6.01% (P=0.029) over placebo, and a significant absolute change in apoB-100 of -0.19 (P=0.049) mmol/l. Serum TG and HDL-C concentrations were found unchanged. In a second study, 127 subjects completed similar multi-center study consuming *L. reuteri* NCIMB 30242 in oral capsules. The treatment resulted in significant reductions in serum LDL-C of 11.64% (P<0.001), TC of 9.14%, (P<0.001), non-HDL-C of 11.30% (P<0.001), and apoB- 100 of 8.41% (P=0.002) with no adverse effect. The ratios of LDL-C/HDL-C and apoB- 100/apoA-1 were significantly reduced by 13.39% (P=0.006) and 9.00% (P=0.026) relative to control at the study endpoint respectively. Serum concentrations of TG and HDL-C were unchanged. Serum hs-CRP and plasma fibrinogen were also significantly reduced by 1.05 mg/l (P=0.005) and 14.25% (P=0.004) relative to control at the study endpoint respectively. Mean plasma deconjugated bile acids increased by 1.00 nmol/l (P=0.025) from baseline relative to placebo, whereas campesterol and sitosterol were decreased by 41.5% and 40.7% respectively. These results show that *L.reuteri* NCIMB 30242 can be used to reduce serum LDL-C, likely by inhibiting cholesterol absorption, and indicates its potential as an adjunctive therapy for the treatment of hypercholesterolemia.

Regulatory approval and recommended use:

The probiotic strain *L.reuteri* NCIMB 30242 has obtained significant regulatory approvals based on the safety and efficacy of the strain. The strain has achieved "Generally Recognized as Safe" (GRAS) status with Food and Drug Administration (FDA) (GRN 000440). The strain is one of only about 15 strains to achieve FDA's GRAS approval. The strain has also been launched in supplement form under the Cardioviva brand in the US and Canada where the product obtained a Natural Product Number (NPN) through Health Canada (#80038469) with the following recommended uses:

- Helps to reduce LDL-cholesterol
- Helps to reduce total cholesterol
- Helps to reduce blood C reactive protein levels, a clinical marker of inflammation
- Probiotic to benefit health and/or to confer a health benefit
- Provides live microorganisms to benefit health and/or confer a health benefit
- Helps maintain/support heart health

Probiotics for the Gut: A Guide to Getting Started

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The concept of probiotics was introduced about 100 years ago, when Nobel laureate Elie Metchnikoff, known as the 'Father of Probiotics', proposed that ingesting bacteria could have health benefits for humans and prolong life. In recent years, probiotic have become a multibillion dollar industry, and can be found in many products from yoghurt to granola bars. The world of probiotics is filled with myriad options and long words like *Lactobacillus* and *Bifidobacterium*, and astounding numbers like 10-20 billion CFUs (colony forming units). This article is written as a practical guide to help busy clinicians start navigating this intimidating world of probiotics.

What are probiotics?

Probiotics are defined as: live micro-organisms that confer a health benefit on the host when administered in adequate amounts[1]. This is differentiated from prebiotics, which are dietary substances that nurture a selected group of micro-organisms in the gut, favouring the growth of beneficial bacteria over harmful ones. Synbiotics are products that contain both probiotics and prebiotics, and thus have both effects.

What should I prescribe it for?

There is strong evidence that probiotics are effective in a number of digestive disorders. The more common conditions seen in the community are:

Treatment of infectious diarrhoea
A Cochrane review of 23 studies (n=1,917) showed that probiotics significantly reduced the duration of diarrhoea by a mean of 30.5 hours[2]. Another meta-analyses in children showed that a similar effect in reducing the duration of diarrhoea in children[3].

Prevention of infectious diarrhoea
A meta-analysis of 12 studies (n=4,709) showed a modest decrease in the risk of traveller's diarrhoea when probiotics are taken, with a relative risk of 0.85[4].

Antibiotic associated diarrhoea
A meta-analysis of 19 studies[5] showed that probiotics reduced the risk of antibiotic associated diarrhoea by 52%. The benefit was greatest when the probiotic was started within 72 hours of starting the antibiotic treatment. A meta-analysis of 6 randomised controlled trials in children showed a similar effect in children[6].

Irritable Bowel Syndrome (IBS)
A recent systemic review of 19 randomised controlled trials in IBS showed that probiotics were better than placebo, with a number needed to treat of 4[7]. A meta-analysis of 3 randomised controlled trials showed a similar effect in children[8]. Probiotics appear to be particularly useful for abdominal pain, bloating and global improvement of symptoms in IBS patients.

Are probiotics safe?

Studies suggest that probiotics are safe with few side effects. Flatulence and mild abdominal discomfort have been reported, and are typically mild and self-limited. Long term safety data are limited. Probiotics have no known interactions with medications or other supplements.

There have been rare reports of pathological infection in severely ill or immune-compromised patients, and in children with short gut syndrome. Probiotics should be

Quick Facts

The appendix is not useless - it incubates probiotics. In the past, the appendix was largely thought to be useless. Appendicitis, a life-threatening condition, would call for removal of the appendix. In 2007, Randal *et al.* at Duke University conducted research into the vermiform appendix. The researchers observed that when the body was under attack by pathogens, the appendix would release probiotic bacteria that would perfectly counter the specific type of invaders. The appendix does this by releasing them into the cecum when the body is infected.

avoided in these patients. There have been no such reports in healthy patients.

What probiotic should I use?

Lactobacillus and *Bifidobacterium* species have the most evidence for the above digestive disorders, and are the preferred components in probiotics used to treat these conditions. *Saccharomyces boulardii* is a probiotic yeast strain that has also been proven to be beneficial in diarrhoea conditions, and has the potential advantage of having resistance to most antibiotics.

What dose should I use?

A wide range of dosages have been studied, mostly from 1 to 20 billion CFUs per day. In general, higher dosages of more than 5 billion CFUs per day in children, and 10 billion CFUs per day in adults were associated with better study outcomes for the various clinical conditions. Studies with *Saccharomyces boulardii* use a dose of 250 to 500 mg per day. Although there is no evidence that even higher dosages are unsafe, they may be more expensive and unnecessary.

Conclusion

The use of probiotics is increasing, and they are becoming widely available. It is important for clinicians to be familiar with the basics of probiotics, so that they may be able to address the concerns of patients about these drugs. From a scientific viewpoint, probiotics are proven to be safe and effective for treating infectious and antibiotic associated diarrhoea. They are also possibly effective for IBS symptoms. When used for these purposes, probiotics can be prescribed using the simple steps outlined in this article.

Use of yeast (Saccharomyces boulardii) as probiotic to treat infant acute diarrhoea

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Introduction

Probiotics are defined as live microorganisms, which when administered in adequate amounts confer a health benefit to the host[9]. These microorganisms are widely used in pharmaceutical preparations or fermented dairy products. Lactobacilli and bifidobacteria are typically found in numerous probiotic products for humans, whereas only few types of yeast, such as *Saccharomyces boulardii*, are used. *S boulardii*, a non-pathogenic yeast, has been used for treatment of different types of diarrhoea diseases, such as antibiotic-associated diarrhoea, acute infectious diarrhoea and *Clostridium difficile*-associated intestinal disease[10,11,12]. More recently, its use has been evaluated for the treatment of inflammatory bowel diseases[13].

Efficacy of *S. boulardii* in the treatment of infant acute diarrhoea

In the case of infectious diarrhoea, administration of *S boulardii* provides protection against intestinal lesions caused by several diarrhoea pathogens[14]. Seven single- or double-blind controlled clinical trials using *S boulardii* as probiotic have been conducted for the treatment of acute diarrhoea in children[15,16,17,18,19,20,21]. Six among the seven trials with the yeast showed it to be beneficial in children admitted to hospital for diarrhoea. In the seventh trial, which compared five different probiotic preparations, *S boulardii* had no clinical effect. To explain these contradictory results, the authors of this last study