Practical Insights:

Probiotics & Constipation

In our last issue, we explored the widely-accepted usage of probiotics in diarrhoea. "What about constipation?" Many have asked. Our editorial team will take a bold step to uncover the wonders of probiotics on the other side.

Many have identified with this common gastrointestinal condition. Occurring more in females, elderly and children, it is the cause of morbidity in both young and old. The causative factors include metabolic disorders, lifestyle and occupation, drugs such as anticholinergic and other structural and non-structural problems. Worse are those with chronic functional constipation, which includes constipation- predominant irritable bowel syndrome (IBS-C), dyssynergic defecation and slow-transit constipation. **The prevalence of functional constipation in the general population stands at 12% to 30%**. On top of the usual laxatives like polyethylene glycol, newer treatment options include 5-HT_4 agonists such as tegaserod and prucalopride, selective chloride channel activator (lubiprostone) and probiotics. It is noteworthy that there is a lack of large, randomised, double-blind and placebo-controlled trials done on children with chronic constipation. Most agents used for such cases are based on clinical experience. With about 50% of children still being plagued with symptoms after 1 year of treatment and 30% of them suffering with constipation beyond puberty, a safe and long-term treatment option is needed. Therefore, the indisputably safe probiotics could potentially be the answer.

Lactulose

Lactulose is commonly prescribed as an osmotic laxative. It is also a commonly used prebiotic. Its mechanism of action will probably shed some light on how probiotics may work for constipation. Lactulose is not broken down by intestinal enzymes but by the intestinal bacteria, such as lactobacilli and bifidobacteria. Their breakdown produces several short chain fatty acids. As such, with the increase in total biomass and osmotic pressure and the decrease in pH, bowel motility is increased. Therefore, the prebiotic effect on the 'friendly' bacteria has already been experienced among the many constipated patients. The incorporation of probiotics may enhance their effect and shorten bowel transit time.

Clinical Evidence on probiotics and synbiotics

Many trials have used either probiotics alone or in combination with prebiotics on the treatment and prevention of constipation among different age groups of patients. A study was done using *Lactobacillus casei rhamnosus* Lcr35 to treat children with chronic constipation. Results showed it to be effective, with lesser abdominal pain observed. Another study also showed how *L. rhamnosus* and *Propioniibacterium freudenreichii* relief constipation in elderly.

Many trials have also used a combination of bifidobacteria and FOS for constipation treatment. A recently published study used *Bifidobacteria animalis* and FOS on women with functional constipation (based on the Rome II criteria). Higher bowel evacuation rate, improvement in stool quality (based on the Bristol scale) and reduced pain and effort in defaecation were observed. Another trial also reported that a combination of *Bifidobacterium longum* W22 and FOS increased stool-passing frequency and reduced abdominal pain and bloating in constipation –predominant IBS patients. **However, not all probiotic strains are effective for constipation**. Published in the Journal of Pediatrics in 2005. *Lactobacillus* GG was shown to be ineffective as an adjunct to lactulose in treating constipation in children. Such an observation is similar to the acceptance that the benefits observed in probiotics are specific to the strains.

Moving On...

Similar to how prebiotics works in the treatment of constipation, probiotics is believed to modulate the intestinal microflora, breaking down the indigestible carbohydrates, thus leading to decreased pH and increased osmotic pressure. Whether used by itself or in combination, they have been shown to soften stool and increase bowel movement. Although the studies varied in the strains and combination used, the evidence certainly reveals that probiotics aid in the treatment of constipation.

Quick Facts

While most probiotics are bacterial in origin, there is a non-pathogenic and health positive yeast named *Saccharomyces boulardii*. In fact, it is one of the most documented probiotic strains in the world!

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26. Pictures used are by the courtesy of Chr. Hansen.

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Editor's note

The scientific and clinical research in the probiotics field is constantly challenging frontiers. There is just so much to write on the clinical evidences of using probiotics in human health and diseases. Our editorial team had to painfully select the best articles and compact them into this second issue.

In this issue, we are privileged to have Dr. Mark Wong and Prof. Eu Kong Weng to write on the current trends and advances in colorectal cancer. In our scientific updates section, we discuss and present the use of probiotics in postnatal development of the immune system. This issue concludes with the practical insights of using probiotics in constipation.

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

Thank you & God Bless!

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Colorectal Cancer:
Current Trends & Advances

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Introduction

Colorectal cancer is the most prevalent cancer in Singapore today. It is the commonest cancer in males and second in females, after breast cancer. Majority of those afflicted are over the age of 40 years and more than half will succumb from this disease. However, advances in the understanding and management of this disease have led to improved clinical outcomes.

Epidemiology

During the period of 1968-1972, cancer of the large bowel (colon and rectum) was the fourth and fifth commonest cancers amongst Singaporean males and females, respectively. This has risen steadily through the decades and according to the latest figures released by the Singapore Cancer Registry, **colorectal cancer now ranks as the leading cause of cancer in males at 18.0%, and is only second to breast cancer in females, at 14.4%.** It is the most frequent cancer when both genders are combined (6996 cases in 2002-2006 compared to 5497 cases of lung cancer in the same period).

In Singapore, cancer has increased in importance as a cause of death over the past 35 years, with a rise in proportion of cancer deaths among all causes of death in the population, from 14.8% (1968-1972) to 27.1% (1998-2002). In the latter period, deaths from colorectal cancer constituted 19% of all cancer mortalities in males and 14% in females, accounting for the second highest cause of cancer mortality in both genders. Between 1998 to 2002, more than three-quarters (75.6%) of colorectal cancers occurred in the distal colon (including splenic flexure, descending, sigmoid colon and rectum). The predominant histological subtype has remained adenocarcinoma over the last decade (approximately 90%), with mucinous adenocarcinoma a distant second (approximately 5%).

In a local population-based study by Du et al in 2002, it was shown that from 1968-1992, there was significant progress in survival of colorectal cancer patients with localized disease (limited to large bowel). The 5-year age-standardized relative survival figures for colon cancer improved from 36% to 66% in males and 32% to 71% in females; in rectal cancer, improvements from 25% to 66% in males and 23% to 66% in females were observed. Similar improvements were noted in patients with regional disease (lymph node involvement), but not with distant metastases.

The progress made in colorectal cancer survival in Singapore has paralleled the dramatic national development in socioeconomic and healthcare services. Standard therapeutic protocols are adopted in the several tertiary care centers, based upon best-available clinical evidence, thereby providing the latest in surgical and adjuvant treatment modalities. However, Welch et al demonstrated that increasing 5-year survival rates need not be due solely to improvements in treatment, with factors like changes in diagnostic capabilities, lead-time bias, stage migration and change in stage distribution also contributing a significant role.

Aetiology of Clorectal Cancer

The causes of colorectal cancer are still not fully understood. **Based on the available evidence, the most important factors appear to be environmental (dietary and smoking in particular) and hereditary causes.** In the past 50 years, Singapore has experienced dramatic improvements in socioeconomic development, bringing with it changes in dietary habits and a more sedentary lifestyle. In the context of worldwide colorectal carcinoma incidence, Singapore's rates have seen a rapid rise to rates comparable to those of developed Western nations and have amongst the highest incidence rates in Asia (between two to nine times that of China).

Epidemiological studies have generally shown a direct association between fat intake and colorectal cancer risk. This is thought to be due to raised levels of bile acids, involved in fat digestion, within the colon, which are believed to be toxic to the colonic mucosa. **Probiotic modulation of the intestinal microflora may affect the activity of enzymes (eg. 7a-dehydroxylase) forming these toxic products, and may also reduce the toxicity of bile salts by binding to them.** Probiotics are 'live microbial' food ingredients that, when administered in adequate amounts, confer a health benefit on a host (WHO 2002). Most probiotics are species of lactobacilli and bifidobacteria that reside within the colon and so compete with harmful bacteria for nutrients and help suppress their proliferation. **Some probiotics also produce antibacterial agents, such as lactic acid and similar short chain fatty acids, favouring the growth of colonocytes; this concurrently acidifies the gut lumen making it inhospitable for the growth of harmful bacteria.** Dietary fibre further supports the growth of probiotic species. There is, as yet, no concrete evidence for probiotics in prevention of cancer in humans, but encouraging results from animal studies suggest a role in preventing DNA damage, cellular changes and even tumour suppression.

Smoking has been shown to increase the risk of colorectal cancer by 50%, while individuals with long-standing ulcerative colitis (especially more than 10 years) have also been identified as being at higher risk. Further trials have suggested that non-steroidal anti-inflammatory drugs (NSAID) may protect against colonic neoplasia; evidence suggests that there is an over-expression of cyclo-oxygenase (COX) receptors in neoplastic colonic tissues (such as polyps) and by inhibiting these receptors, they have been shown to interrupt chemically-induced tumour signaling in animal models.

Majority of colorectal cancers are sporadic in nature with no known genetic predisposition. Approximately 5% of colorectal cancers, however, arise on the background of Familial Cancer Syndromes with known hereditary genetic mutations. The most common of these are Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colorectal Cancer (HNPCC), with affected individuals having a 100% and 80% lifetime risk of developing colorectal cancer, respectively. Members of these families are themselves at high risk of colorectal cancer and require close surveillance and should be counseled for genetic testing.

Known risk factors include age above 50 years, a personal or family history of colorectal cancer or adenoma and a long-standing history of ulcerative colitis. The average population risk for an individual without any risk factors is about 1 in 50. This rises dramatically for an individual with 2 first degree family members where the risk is about 1 in 5. Herein lies the basis behind recommendations for population screening for colorectal cancer.

Screening for Colorectal Cancer

In addition to modifying environment influences, such as adopting a more active lifestyle, increasing public awareness about the risks of colorectal cancer and its symptoms is crucial. Patients who understand the nature of the disease are more likely to feel that they may be at risk, perceive fewer barriers to testing, and be more likely to participate in screening. **Population-based studies have shown reductions in colorectal cancer mortality by screening for either faecal occult blood or with endoscopy.** Although the cost-effectiveness of screening colonoscopy in the average-risk population has not been formally demonstrated, there is indirect evidence for its efficacy, and it has the advantage of resection of pre-malignant lesions from all parts of the colon. Furthermore, the value of a negative colonoscopy exceeds that of other tests and may permit wider screening intervals. Double-contrast barium enema and virtual colonoscopy are potential alternatives in the same risk population, but their role remains to be determined.

Treatment

Surgery remains the mainstay of treatment in colorectal cancer. Surgical principles mandate the wide resection of the tumour with adequate margins, en-bloc resection of its regional lymphatics and proximal ligation of the feeding arteries at their origin. Along with advances in surgical techniques and medical technology, minimally-invasive surgery has now become an essential tool in the armamentarium of the modern-day colorectal surgeon. **Recent data from the Cochrane Database of Systematic Reviews confirms the long-term safety of laparoscopic surgery for colorectal cancer**, while reaffirming the short term benefits of less pain and quicker recovery. Furthermore, there are available Robotic-assisted surgery for rectal cancers, with the aim of enhancing outcomes through the benefits of improved multi-dimensional dexterity and better visualization of critical pelvic neurovascular structures.

Laparoscopic colorectal cancer resection

The subsequent need for adjuvant treatment, either in the form of chemotherapy, radiotherapy or in combination, depends upon the final histology and stage of the cancer. These modalities essentially seek to reduce local recurrence and improve overall survival in selected groups of patients with advanced disease. In some cases of locally-advanced disease, such as a bulky low-rectal tumour, neoadjuvant therapy may play a role in down-staging the disease, so as to improve resectability and sphincter preservation. Finally, biological agents such as interferon and monoclonal antibodies, have also been developed in an attempt to specifically target cancer cells, so as to lessen the side effects of conventional chemotherapeutic agents; however, these are still used within the confines of clinical trials.

Stemming the tide

Evidence suggests that colorectal cancer trends will continue to rise worldwide, with estimates reaching a staggering 15 million new cases by 2020. Strong governmental support of health education and screening programs are vital to stemming the tide of colorectal cancer, as well as the modification of environmental influences and continued cancer research and training into the latest surgical techniques.

What of the future? Unraveling the molecular pathogenesis of colorectal cancer offers opportunities for improvements in genetic testing, targeted intervention including gene therapy, chemotherapy, immunotherapy and patient selection for different therapeutic strategies based on tumour genotype-phenotype correlations. The challenge that we face in the eradication of this modern world scourge will be the integration of molecular medicine, epidemiology and public health policy.

What's New?

Prebiotics has positive effects on the postnatal development of the immune system

"Superior formula fortified with prebiotics for your child's digestive health." This is a common message that many milk formula companies have bombarded us with through the media. Many health care professionals and mothers who are vexed about their beloved's nutritional health have asked about the benefits of having prebiotics in milk formula. For the scientific update in this issue, we have decided to dig deep and present a recent article published in the Journal of Nutrition that reviews the structural and functional effects of prebiotics on infants' immune development.

Studies have shown that breast-fed infants have lesser allergies and infections than bottle-fed infants. There are many benefits that breast milk can contribute to an infant's immune system. In particular, there is increasing evidence showing that the effects of human milk oligosaccharides (HMOS) on intestinal microflora have played a significant role in the immune health of infants. The article speaks about how HMOS affects the intestinal microflora. Thereafter, we will learn about how prebiotics are able to emulate the similar benefits of human milk, especially during postnatal development of the immune system.

Clinical Benefits of HMOS

Human milk has a diverse formulation of oligosaccharides. These chains of sugar make up about 10g/L of human milk. HMOS are hydrolysed products of lactose and comprise of different monomers linked together by α & β glycosidic bonds. Among the many functions of HMOS the following are discussed - the stimulation of growth and/or activity of health positive bacteria and the binding to pathogens and interaction with immune cells.

HMOS are bifidogenic. Studies have shown that HMOS increase the fermentation activity and growth of bifidobacteria. These friendly bacteria produce glycohydrolases that acts on the α & β glycosidic bonds thus utilising HMOS as food. The enzymes are specific to the bifidobacteria and not secreted by the human intestines.

There are direct interactions between HMOS and both the immune cells and bacteria. HMOS can bind directly to pathogens and prevent them from adhering to the intestinal wall. Furthermore, studies have shown that HMOS also bind to immune cells via integrins and Toll-like receptors.

Prebiotics

Non-human milk oligosaccharides used are hardly from animal milk but from natural sources or that are synthesized from monomers. Certain clinically tested ones include galacto-oligosaccharides (GOS), inulin, short-chain fructo-oligosaccharides (scFOS), lactulose and combinations of the above. One may argue that the medium or food used as a delivery for oligosaccharides might affect the efficacy of HMOS. However, based on the numerous studies done using prebiotics in various media (such as milk, cereal, etc.), it is certain that the effects of prebiotics are independent of the delivery medium.

Clinical Benefits of Prebiotics

To determine and measure the effect of prebiotics, markers such as short chain fatty acid (SCFA) profile, faecal pH and the count and percentage of faecal bifidobacteria can be used. The fermentation of oligosaccharides in the colon produces SCFA. Lower faecal pH has also been observed in studies using GOS and combination of scGOS/lcFOS. In addition to the above observations, it has been proven that SCFA and pH affect the intestinal cells physiologically. Studies have shown that SCFA, at pH of 5.5 only (vs. pH of 7.5), inhibits pathogenic growth in a dose-dependent manner.

Furthermore, the application of prebiotics can specifically modulate the composition of the intestinal microflora and this translates to functional benefits on the immune health. It has been demonstrated in some studies that prebiotics can specifically affect the growth of different bifidobacteria. For instance, the application of scGOS/lcFOS increased the growth of *B. infantis* but suppressed the counts of *B. adolescentis*. Such alteration is not observed in the non-prebiotic control group. In the same light, we have seen how infants of different immune health have different composition of the microbiota. Studies have shown that the intestinal microflora of allergic infants have adult-like faecal microflora like *B. adolescentis*, whereas the healthy infants have more species such as *B. infantis* and *B. bifidum*.

One thing that we can be sure...

Regardless of whether we are standing from the position of a breast-feeding advocate or a milk formula company, we are certain that prebiotics are beneficial to the post-natal development of the immune system. This is not considering other positive effects such as the prevention and treatment of diarrhoea and abdominal bloating. Maybe it is now worthy to pay more attention to this faithful prebiotic support, on top of the probiotic warriors.