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Volume 6.05 - March 10th 2016

PROBIOTICS AND NUTRITION IN PAEDIATRIC SURGERY

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This article reviews the current evidence for the use of probiotics in paediatric surgical care and examines the important nutritional considerations for these patients.

Our bodies are host to an astonishing 100 trillion bacteria,[1] a number that exceeds that of our own cells by 10 times. The entire population of these micro-organisms is commonly referred to as the 'microbiota'. The human gut microbiota is incredibly diverse and is estimated to consist of over 1,000 different bacterial species, with each individual harbouring approximately 160 species.[2] Our gut flora has been the subject of intense study over the last 20 years and more and more evidence is published every day detailing the profound impact that these tiny organisms have on almost every aspect of our health. Immune system maturation and activity,[3] nutrition,[4] tumour inhibition[5] and even psychological functioning[6] are to name a few of the roles detailed in available research (Table 1 overleaf).

The complex microbial community of the gut may become imbalanced by multiple factors such as infections, analgesic ingestion and antibiotic treatment. All of these intestinal insults may be experienced by the surgical patient and children are particularly vulnerable. The days and weeks leading up to a surgical procedure can be stressful for children and this may impact negatively on their diet and nutrition. Inadequate nutrition in combination with the complications of surgery can deliver a huge physiological blow to the gastrointestinal ecosystem and, consequently, the body as a whole, which risks impeding recovery from surgery.

Attempts to prevent the microbial imbalance or, 'dysbiosis' as it is referred to, have seen the utilisation of probiotics. A collaborative definition of probiotics was decided in 2001 by the Food and Agriculture Organisation and the World Health Organisation as 'live microorganisms, which when administered in adequate amounts confer a health benefit on the host'.[3] Many studies have investigated the use of probiotics in numerous surgical domains from paediatrics to geriatrics and in preventative applications to augmenting post-operative recovery.

Table 1: Microbiota functions

Function	Mechanism
Immune system	• Regulate innate immunity • Regulate adaptive immunity
Enhance barrier function	• Goblet cells - mucus production • Promote epithelial cell survival
Antibacterial	• Produce bacteriocins • Competitive inhibition of pathogenic bacteria • Bind bacterial toxins
Vitamin activation and synthesis	• B vitamins • Vitamin A • Vitamin K

NUTRITIONAL CONSIDERATIONS FOR CHILDREN IN SURGERY

Good nutrition is paramount in supporting all physiological processes and thus promoting a healthy body. The complex course of wound healing is divided into three phases: inflammation, proliferation and remodelling. The efficiency of this process requires an optimal supply of energy, protein, vitamins and micronutrients. Malnutrition, which is prevalent in 9-47% of patients in paediatric hospitals,[7] and nutrient deficiencies have been implicated in delayed and inadequate wound healing.[8] Inappropriate nutrition will decrease the immune system's ability to defend against infection by impairing the function of white blood cells and thus lead to wound infections.[8] The route of nutrition is also important in the context of surgery with substantial evidence demonstrating that parenteral feeding quickly leads to gut atrophy.[9] This process may compromise intestinal barrier function predisposing to septic complications resulting from bacterial translocation.

Glucose is the predominant and most efficient source of fuel for synthesis of collagen; the key protein involved in all stages of wound healing. Other carbohydrates, including resistant starches and dietary fibre, are fermented by colonic microflora to produce short-chain fatty acids (SCFA) such as butyrate, the principal energy source for colonocytes (colonic epithelial cells).[8] Butyrate has been shown in animal models to increase the mechanical strength of healing scars in the colon.[10]

Protein is an essential constituent of our diet and adequate amounts are vital for all stages of wound healing. In healthy children, protein requirements vary with age and weight (reference ranges may be found in the WHO/FAO/UNU 2007 publication[11]). Children under surgical care may experience fever, trauma and wound healing. These factors increase energy expenditure and utilisation of protein,[12] which will necessitate increased dietary provision above base line requirements.

A number of vitamins and micronutrients are also important for efficient recovery from surgery. Vitamin A plays a crucial role in the inflammation and proliferation stages of wound healing.[8] Research has shown that commensal bacteria is capable of stimulating the host to generate the active form of vitamin A (retinoic acid).[13] Rich dietary sources of this vitamin include cheese, eggs and yoghurt. Vitamin C is essential for the synthesis of collagen and thus vital for wound healing. The classic dietary source of this vitamin are citrus fruit; however, guavas and bell peppers are amongst the most concentrated sources in nature. Zinc is an essential micronutrient involved in a range of metabolic functions including protein and collagen synthesis, and thus plays an active role in wound healing.[8] Dietary sources rich in zinc include meat, shellfish and baked beans.

PROBIOTICS FOR CHILDREN IN SURGICAL CARE

The impact of medications

Surgical patients, regardless of age, are regularly exposed to a barrage of medications during their treatment. These may include pain killers, anaesthetic drugs and antibiotics and, depending on the individual case,

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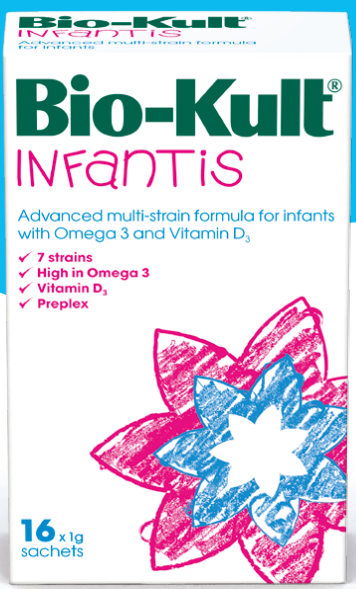

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patients may be exposed to these agents before, during and even weeks after surgery. All of these medicines come with their own list of side effects, which commonly include gastrointestinal upset attributed in numerous studies to their impact on the gut microbiota.

Antibiotic Associated Diarrhoea (AAD)

Antibiotics can have a detrimental impact on the microbial balance within the gut of both children and adults alike and may cause a condition known as Antibiotic Associated Diarrhoea (AAD). Frequent loose bowel motions and abdominal cramps are experienced by most, and in severe cases patients may suffer from electrolyte disturbances and occasional life-threatening intestinal inflammation associated with the 'superbug' *Clostridium difficile*.[14]

The incidence of AAD ranges from 5-62% and may occur up to two months following completion of therapy.[14] A recent comprehensive review of 23 studies involving nearly 4,000 children concluded that probiotics have a protective effect in preventing AAD.[14] In one multi-strain probiotic trial AAD and nausea and vomiting symptoms, associated with antibiotic treatment, were significantly reduced.[15]

Post-operative constipation

Surgery has a physiological impact on the body which may increase the risk of post-operative constipation. Various medications can also contribute to this risk. Anaesthetic agents, such as benzodiazepines and opiate-based pain killers, such as codeine and morphine, may reduce colonic motility causing constipation. The use of probiotics to treat post-operative constipation in children has not been investigated yet; however, data from a number of small trials has demonstrated positive effects of probiotics in treating childhood constipation,[16-18] which will hopefully lead to future studies into this application.

Post-operative infection and bacterial translocation

Post-operative infections may affect numerous sites in the body such as urinary tract infections, pneumonia and Surgical Site Infections (SSI). They are complications of surgery responsible for significant morbidity and mortality worldwide. SSIs have a substantial financial impact on healthcare systems with recent estimates from UK data of over £5,000 per patient to treat.[19] Affected patients also have an increased length of hospital stay and twice the mortality risk.

A significant cause of post-operative infections is thought to be due to disruption in the barrier function of the intestine known as the 'gut origin of sepsis' hypothesis or bacterial translocation.[9] Probiotics have been shown to maintain and enhance the gut barrier function through a variety of mechanisms involving receptor stimulation and cell signalling pathways.[20] A comprehensive review of evidence from 20 human trials, which investigated the treatment of post-operative infections with various probiotics, was published in 2015 and concluded that probiotics significantly reduced SSIs and Urinary Tract Infections (UTIs) attributable to abdominal surgeries.[21]

PROBIOTIC APPLICATIONS FOR SURGICAL PROCEDURES AND PREVENTION

Caesarean section

There is substantial evidence to suggest that the mode of delivery may have a significant impact on the development of a baby's immune system and subsequent risk of disease. Infants born by vaginal delivery have a 'healthy' microbiota, which seems to protect against dysfunctional immune responses that are more common in children born by caesarean section.[22] In a large study involving more than 1,200 mothers, a multi-strain probiotic was found to significantly reduce

the rate of allergic disease in caesarean-delivered children.[23]

Necrotising enterocolitis (NEC)

Necrotising enterocolitis (NEC) is the most frequent surgical emergency in new born babies, affecting ~6-7% of very-low-birth-weight infants.[24] It is a condition in which the intestines become inflamed and, in severe cases, where this causes an interruption to the blood supply, the bowel starves and dies. Dead bowel is weak and holes may form which permit intestinal contents to spill into the abdominal cavity, leading to peritonitis and sepsis (severe infection). If this occurs, the child will require surgery under general anaesthetic to remove the dead bowel and any source of infection. This is obviously a last resort option and all attempts should be made to revive the inflamed gut by conservative means, such as resting the bowel and administering fluids and food via the veins.

The pathogenesis of NEC is thought to involve abnormal bacterial colonisation (dysbiosis), a finding which has stimulated research into probiotic treatment for this deadly disease. A 2015 publication reviewed 20 randomised controlled trials involving nearly 6,000 infants on probiotics for NEC and concluded that their use was associated with an impressive 49.1% reduction in risk of NEC, a 26.9% reduction in mortality and a significantly reduced time to reach full feeds.[24]

Helicobacter pylori (stomach ulcers)

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that colonizes the stomach of the infected host and is generally acquired in childhood.[25] Worldwide *H. pylori* is the most infectious pathogen in humans infecting approximately one third of Western populations and more than half of those residing in developing countries.[26]

Infection is associated with a broad spectrum of diseases such as gastritis (inflammation of the stomach wall), peptic ulceration, lymphoma, stomach cancer and a number of haematological disorders in children.[26] Research has shown that in children with Duodenal Ulcers (DU) over 90% were infected with *H. pylori*. Gastrointestinal

ulceration may require emergency surgical intervention in severe cases. *H. pylori* has also implicated in reflux oesophagitis in children where a study in the US including 420 children (age range 0 – 20 yrs) identified that those infected with *H pylori* had a significantly higher prevalence of the disease.[27] Reflux oesophagitis in some instances may require a surgical procedure (fundoplication) where the stomach is wrapped around the lower part of the oesophagus to reduce acid reflux.

Surgery for both ulceration and reflux is typically a last resort after a trial of medical management, termed 'triple therapy' which consists of an acid suppressing medication and two different antibiotics, is used to eradicate the infection. The effectiveness of triple therapy is however increasingly compromised by the global rise of antibiotic resistance, which is the major cause of failure in the treatment of this disease.[25] A 2015 publication reviewing 143 studies on treatment of *H. pylori* concluded that the addition of probiotics to standard triple therapy enhanced the efficacy of treatment with the added benefit of improving tolerance to the medication.[26] In a recently published double blind, randomised clinical trial the addition of a multi-strain probiotic (*Lactobacillus*, *Bifidobacterium* and *Streptococcus* species), to standard treatment, led to significantly higher rates of eradication of *H. pylori*.[15]

Inflammatory Bowel Disease (IBD)

Inflammatory Bowel Disease (IBD) is a condition characterised by chronic relapsing intestinal inflammation[28] which commonly requires surgical intervention. IBD is an umbrella term that includes both Ulcerative Colitis (UC), in which disease

is limited to the colon, and Crohn's Disease (CD), which involves transmural (full-thickness) inflammation that may affect any part of the gastrointestinal tract from the mouth to the anus.

Multiple factors have been implicated in the origins of this common idiopathic disease such as an abnormal immune response to intestinal microbiota and an imbalance in the bacterial populations within the gut, termed dysbiosis.[29] Probiotics seem a logical treatment option for a condition that involves an imbalance in the intestinal microbiota.

A wealth of trial evidence exists showing the advantages of probiotics in the management of UC. However, trials in CD are currently lacking.[29] A recently published review on the subject concluded that probiotics significantly increased the remission (period without disease) rates in patients with UC, and sub-group analysis found that only probiotic mixtures had a significant benefit.[30] The efficacy of multi-strain probiotic in maintaining remission in UC has also been shown in children.[31] Interestingly, multi-strain probiotics have been shown to significantly reduce markers of intestinal inflammation in children with cystic fibrosis;[32] also, a promising finding that suggests probiotics may have a role in treating a range of pathologies that involve damage to the bowel.

CONCLUSION

Paying close attention to a child's diet and considering the use of probiotics to protect the delicate balance of their microbiota, both before and after surgery, may help to cushion the blow that surgery has on their gastrointestinal and immune systems.

Evidence for novel applications of probiotics in surgical sciences is being published regularly. It is likely that the future will see probiotics being used increasingly often for numerous medical applications as we learn more about their promising mechanisms.

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Volume 6.05 - March 10th 2016

Questions relating to: *Probiotics and nutrition in paediatric surgery* Type your answers below and then **print for your records** or print and complete answers by hand.	
Q.1	Which of these statements are true? a. On average there are less than 100 bacterial species in the adult intestine. b. There are more human cells than bacterial cells in the body. c. On average the human gastrointestinal system contains 100 billion bacteria. d. Gut bacteria influence our nutrition only
A	
Q.2	What is the current formal definition of a probiotic?
A	
Q.3	Detail the consequences of malnutrition in surgical patients.
A	
Q.4	Name 2 important vitamins involved in wound healing.
A	
Q.5	What are the functions of these vitamins specific to wound healing?
A	
Q.6	Name an important micronutrient involved in wound healing. Detail 2 rich dietary sources.
A	
Q.7	What is AAD and how frequently does it occur?
A	
Q.8	The gut microbiome of babies born by caesarean section tend to be ‘healthier’. True or false?
A	
Q.9	Describe the evidence for the benefit of probiotics in treating NEC.
A	
Q.10	Describe some of the factors thought to be implicated in the development of IBD. What is the evidence for the use of probiotics in IBD?
A	
Please type additional notes here . . .	