Chronic Enteropathy and Feeding

Silvia Salvatore\textsuperscript{a}, Bruno Hauser\textsuperscript{b}, Yvan Vandenplas\textsuperscript{b}

\textsuperscript{a}Clinica Pediatrica di Varese, Università dell'Insubria, Varese, Italy; \textsuperscript{b}Academisch Ziekenhuis Kinderen, Vrije Universiteit Brussel, Brussels, Belgium

Abstract

Enteropathy defines abnormalities of the small intestinal mucosa, visible with the light microscope, of various etiologies, that can be separated into acute versus chronic conditions. This review focuses on these areas in which recent progress has been made. Severe infections increase mucosal permeability and induce local expression of co-stimulatory molecules allowing antigen penetration in the mucosa, T cell activation and possible disruption of oral tolerance. Biotherapeutics are of importance in the prevention and treatment of (chronic) enteropathy of infectious origin. Celiac disease and cow's milk protein allergy are key examples of chronic enteropathy. The dietary approach to allergy has evolved to include active stimulation of the immature immune system in order to support the establishment of tolerance. Supplementation with probiotics may provide maturational signals for the lymphoid tissue and improve the balance of pro- and anti-inflammatory cytokines. Enteral polymeric feeding is effective in Crohn's disease. Dietary nucleotides may improve growth and immunity, optimize maturation, recovery and function of rapidly dividing tissue. Adequate dietary lipids are important not just for caloric value but also for immune-modulatory effects. Lipids may prevent allergic sensitization by downregulating inflammatory response (n-3 but not n-6 fatty acids) whilst protecting the epithelial barrier, regulating immune function and modifying the adherence of microbes to the mucosa, thereby contributing to host-microbe interactions.

Introduction

Enteropathy defines abnormalities of the small intestinal mucosa visible with the light microscope [1]. Clinical entities in children include infection, food hypersensitivity, immune dysregulation, or primary abnormalities of the enterocytes. The overall prevalence of chronic enteropathy in children is difficult to estimate because of the large spectrum of etiologies, patient selection,
and other factors. Herein we will discuss some selected enteropathies focusing on either the causal or the therapeutic role of feeding.

**Infection**

Acute and chronic infections play a key role in the occurrence of enteropathy. Enteropathogenic *Escherichia coli*, rotavirus, *Salmonella*, *Giardia lamblia* and *Cryptosporidium* are pathogens more frequently responsible for persistent small bowel damage with increased severity in case of inadequate initial nutrition and realimentation [2]. Optimal nutritional rehabilitation is consequently considered as the cornerstone of management of (persistent) diarrhea [2]. Malnutrition not only increases the severity of a gastrointestinal infection due to an impaired immunological response but also impairs the recovering of damaged mucosa with secondary intestinal and pancreatic enzymatic reduction [2].

Severe infections increase mucosal permeability and induce local expression of co-stimulatory molecules allowing antigen penetration in the mucosa, T cell activation and possible disruption of oral tolerance. In the last decades, rapid realimentation in acute gastroenteritis has reduced the incidence of postenteritis syndrome with food intolerance and persistent diarrhea. Complex carbohydrates, probiotics and prebiotics, such as maize, green banana fibers and pectin, have been hypothesized to enhance epithelial gut repair and absorption. L-Glutamine, the ‘fuel’ for the intestine, nucleotides, causing proliferation of enterocytes, growth factor(s) with trophic effects on the intestinal mucosa, bovine colostrum and bovine serum concentrate have also been evaluated, without evidence of any substantial benefit [2].

Probiotics, such as some specific lactobacilli (e.g. *Lactobacillus casei* DN-114 001, *Lactobacillus plantarum* 299v) or yeast (*Saccharomyces boulardii*) reduce the invasiveness of intestinal pathogens and beneficially affect the increased intestinal permeability caused by selected bacterial pathogens [3–5]. But not all the literature is in agreement: administration of *Lactobacillus GG* (LGG) during 30 days showed no effect on the intestinal integrity of 3- to 5-year-old Malawian children with tropical enteropathy [6].

Much research has highlighted the possible role of zinc supplementation in reducing both the severity and the duration of diarrhea in immunocompetent and immunocompromised patients [7, 8].

**Enteropathy Caused by Food Hypersensitivity**

*Celiac Disease*

The incidence of celiac disease (CD) is increasing worldwide, with a prevalence as high as 1:300 and even 1:80 children [9]. One of the major reasons
for the increase in prevalence is improved serological screening in subjects without overt gastrointestinal complaints. However, regional differences are emerging. The incidence of histological abnormalities suggestive of CD is lower than 1/250 children undergoing upper endoscopy for various indications (pers. data). Wheat, rye and barley are the predominant grains containing gluten peptides, very rich in proline and glutamine and resistant to digestive enzymes, known to cause CD. Variability exists in the age of onset of symptoms, in extraintestinal and autoimmune manifestations, in serological positivity, and in severity of histological involvement and no clear explanation has emerged despite major advances in the identification of toxic peptides, immune cascade and genetic susceptibility. The incidence of CD in mothers giving birth to preterm or immature babies is higher than in a control population (pers. data); in other words, undiagnosed CD in pregnant women challenges the outcome of pregnancy, and subsequently the nutritional status of the newborn. The variable histological findings of CD include increased intraepithelial lymphocytes (>30 lymphocytes per 100 enterocytes, with a mitotic index >0.2%), inflammatory infiltration into the lamina propria and crypt hyperplasia, decreased height of the epithelial cells (changes from columnar to cuboid to flat epithelium) and decreased villous/crypt ratio, and partial to total villous atrophy. Modern histological (Marsh) classification consists of 4 CD types ranging from a normal preinfiltrative stage (type 0), to infiltrative lesions with increased intraepithelial lymphocytes (type 1), hyperplastic lesions (type 2: type 1 + hyperplastic crypts), destructive lesions (type 3: type 2 + variable degree of villous atrophy), and hypoplastic lesions with total villous atrophy and crypt hypoplasia (type 4). Marsh type 3 was subsequently modified into type 3a (partial villous atrophy), type 3b (subtotal villous atrophy) and type 3c (total villous atrophy). In Marsh type 1 and type 2 lesions, positive celiac antibodies and clinical and serological response to a gluten-free diet support the diagnosis of CD [9]. After diagnosis of CD, a life-long gluten-free diet results in the disappearance of clinical manifestations, mucosal healing and reduction of CD-related complications. However the importance of dietetic compliance in asymptomatic patients, the real risk of complications in patients with only subtle mucosal involvement (Marsh type 1), the individual threshold of gluten sensitivity and the clinical significance of seropositivity in the absence of enteropathy require further clarification [10]. The role of prolonged breastfeeding, timing of introduction and dosing of gluten-containing food especially in subjects with a high genetic risk is under evaluation.

Future therapeutic strategies include peptidase supplementation (from experimental bacterial sources) which cleaves residues next to proline to facilitate proteolysis of immunogenic peptides, transgenic wheat without antigenic peptides, modulation of permeability (by control of the immune cascade and zonulin release) and block of innate and acquired immunity triggered by gluten in celiac patients [10]. Further efforts are needed to clarify
and standardize the definition of a gluten-free diet, to simplify the labeling of ingredients in food products, to improve and support the social life of celiac patients and to increase early identification of celiac patients [10].

Food Allergy

Cow’s milk protein (CMP), soy, wheat, oats, rice, eggs and fish have all been reported to cause enteropathy in selected children [11, 12]. A 30-kD protein in soy cross-reacts with casein [13] and may favor a concomitant soy and cow’s milk hypersensitivity especially in infants with (IgE-negative) CMP enteropathy or enterocolitis. In the last decades an increased number of children has been reported to be sensitized to multiple food antigens, especially (or even) during exclusive breastfeeding, with allergic manifestations early in life due to an impaired development of oral tolerance. In selected infants, acute gastroenteritis increasing permeability and contact of antigens in the lamina propria may provoke sensitization to dietary antigens.

Chronic diarrhea, malabsorption, edema and failure to thrive are the most common clinical manifestations of food-related enteropathy. Other gastrointestinal (abdominal pain, frequent regurgitation or vomiting, constipation, refusal to feed, protein-losing enteropathy), dermatological (atopic dermatitis, napkin rash, swelling of the lips or eye lids), respiratory (runny nose, chronic cough or wheezing, laryngeal edema), and general (persistent distress, colic) manifestations may be additional features. In many patients, the nongastrointestinal manifestations are predominant. Especially regarding CMP, most children will tolerate the offending allergen after the age of 1 year although food enteropathy may persist longer in a minority of them [14].

In food allergy, duodenal, ileal and colonic lymphonodular hyperplasia may be detected [15] as a consequence of immune activation. Histological abnormalities are variable: from total to patchy or even absent villous atrophy, mild to moderately increased intraepithelial CD8 cells, lymphoid follicles, activated lamina propria CD4 cells, activated lamina propria CD4 cells (with increased IFN-γ with or without IL-4 or TNF-α) and decreased regulatory cytokines (especially TGF-β) [16].

Different from CD, enteropathy caused by food allergy presents a thin mucosa, a prominent patchy distribution, only moderate crypt hyperplasia and less intraepithelial lymphocyte infiltration. The infiltration of eosinophils and mast cells is frequent and related to antigen-induced dysmotility and enteric neural dysfunction. The mucosal lesions may cause reduction in brush border disaccharidase expression and secondary exocrine pancreatic impairment, caused by decreased duodenal CCK production, with mild-to-moderate steatorrhea and reduced fecal elastase [17].

As food-related enteropathy is mostly cellular mediated, total and specific serum IgE and skin prick tests are often negative. PATCH tests seem a promising diagnostic tool for T cell (late) response to dietary antigen. Fecal calprotectin has recently been proposed as an (unspecific) noninvasive marker of enteropathy.
Mechanisms inducing oral tolerance are in general not complete at birth but develop postnatally, mainly in response or intimate relation to the gut flora and to activation of specific Toll-like receptors on regulatory T cells [1, 18]. The key role of the luminal bacteria is highlighted by the impaired tolerance in germfree mice [1], by the different intestinal flora in populations that will develop atopy, by the immune-modulatory properties of specific probiotics and by the promising results of interventional studies. Allergic infants showed, even before the appearance of symptoms, a significantly higher prevalence of clostridia, coliforms and Staphylococcus aureus versus lactobacilli and Bifidobacterium (bifidum). Manipulation of the gut flora as early as in the first days or months of life may influence through microenvironment modification and competition subsequent colonization and expression of regulatory cytokines. Specific probiotics including LGG may induce anti-inflammatory IL-10 and TGF-β [19] and possibly exert a tolerogenic effect before sensitization occurs. According to 2 trials using supplementation of LGG and E. coli in the perinatal period, in particular non-IgE-mediated allergies are reduced [19, 20]. Maternal supplementation with LGG during pregnancy and 6 months after delivery increases the concentration of TGF-β in the breast milk of at-risk mothers and confers protection against atopy.

Supplementation of a cow’s milk-based formula with prebiotics has the ability to manipulate the intestinal flora with a bifidogenic effect, but a beneficial prospective effect on food allergy has not been demonstrated so far with prebiotic supplementation. Comparing symptoms suggesting atopic sensitization at the age of 3–4 years in 27 exclusively breastfed babies during 6 months, in 16 infants on oligosaccharide-supplemented formula and in 17 infants on standard infant formula, the incidence was similar in breastfed and standard formula-fed infants (59 vs. 58%) and decreased by 50% in the supplemented formula group (31%) (pers. data).

Prenatal prevention is complex and multifactorial and dietetic intervention during pregnancy is not currently substantiated by scientific evidence [21]. Postnatally, dietetic prevention is actually recommended in high-risk infants only and is based on the promotion of breastfeeding (with no conclusive evidence of inconsistently proposed exclusion of peanuts and nuts), hypoallergenic formulas for bottle-fed infants and late introduction of solid foods. Compared to extensive hydrolysate formulas (eHFs), partial hydrolyzed formulas offer economical and taste advantages and a theoretical benefit in inducing oral tolerance to CMP as they still have enough residual allergenicity to induce tolerance but too low allergenicity to induce allergic reactions.

Up to now, for the treatment of food allergies, guidelines worldwide recommend exclusion of the causative antigen. For the infant who is sensitized while being breastfed, maternal exclusion of the more relevant antigens (CMP, egg white, (pea)nut) is advised. In cow’s milk-sensitive enteropathy,
eHF or, in those refusing to drink eHF or those not responding to the elimination diet, amino acid formulas are recommended. Infants and children with multiple food allergy have often more severe symptoms with possible reactions even to a small quantity of antigens (like those present in breast milk), are unresponsive to eHFs, and have late acquisition of tolerance. The maintenance of a nutritionally adequate diet is not easy especially in the case of compromised absorption or multiple allergies but is mandatory for each child. It is fortunate that manufacturers continue to make efforts to be able to offer new formulas with improved hydrolyzation, amino acid profile, additional beneficial components such as prebiotics, probiotics, nucleotides, medium-chain triglycerides (MCT) and long-chain polyunsaturated fatty acids, and last but not least cost and taste.

**Immune Dysregulation**

Different immune deficiencies have been related to an (often patchy) enteropathy, caused by the primary immune disorder and/or by the increased occurrence of (common and opportunistic) infections.

In α-γ- and hypo-γ-globulinemia, the plasma cells in the lamina propria are absent or reduced, respectively, with an increased rate of intestinal infections and malabsorption. In isolated IgA deficiency, enteropathy may be primary or secondary to (increased coexistence of) CD, food allergy and giardiasis. Reduced plasma cells, nodular hyperplasia and giardiasis have also been described in common variable immunodeficiency. Intractable (even fatal) diarrhea due to autoimmune inflammation and chronic pathogen infections is frequent in severe combined immunodeficiency. AIDS is an important cause of (a variable degree of) enteropathy.

In HIV infection, intestinal biopsy is characterized by increased intraepithelial lymphocytes, proinflammatory cytokines (TNF-α, IL-1β and IFN-γ), and lamina propria mononuclear cells with decreased CD4 cells, villous atrophy, and crypt hyperplasia [22]. In immunodeficiency, infections of common or opportunistic pathogens are frequent and discrimination between primary and secondary enteropathy is often difficult. Nutritional support exerts a positive effect on the immune function with a reduction of serum cytokine levels, a decrease of (opportunistic) infections and HIV replication [22]. Especially micronutrients, including vitamins, antioxidants and trace elements (particularly zinc), play an important role in immunomodulation. Supply of fat and carbohydrate is necessary to satisfy the energy requirements (increased up to 150% of the recommended daily intake) but malabsorption and malnutrition should be closely monitored to avoid further malnutrition [22].

T cell activation defects with a failure of tolerance and/or impaired apoptosis represent the basis of autoimmune enteropathy. Intestinal biopsies are characterized by (variable) villous atrophy, crypt hyperplasia and a marked
infiltration of activated T cells into the lamina propria without a significant increase of intraepithelial lymphocytes. Patients present positive serum antibodies against enterocytes, frequent extraintestinal manifestations of autoimmunity, and diarrhea starting after the first 8 weeks of life with clinical response to potent immune suppression.

Defective central (thymic) or peripheral (i.e. gut) tolerance is also responsible for other rare immune disorders with multiorgan involvement and frequent enteropathy. In the APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy) and Omenn's syndrome there is an abnormal expression of the AIRE thymic factor which is crucial for central deletion of autoreactive T cells. Mutation of the transcription factor Foxp3 which is the pivot molecule in the generation of (peripheral) regulatory lymphocytes induces a specific severe multifocal disease, the IPEX syndrome, which includes immune dysregulation with severe autoimmune enteropathy, polyendocrinopathy, and X-linked inheritance.

Enteral tolerance is present in a minority of patients but most of severe enteropathies require long-term parenteral nutrition. Bone marrow or, more recently, stem cell transplants have recently been suggested for these patients.

In addition to the ‘classic’ immune disorders, more subtle immune dysregulations have been reported both in food-sensitive and in inflammatory bowel disease (see specific paragraphs).

**Eosinophilic Gastroenteropathy**

Eosinophilic enteropathies are rare conditions with eosinophil-rich inflammation in the absence of known causes for eosinophilia (e.g., drug reactions, parasitic infections and malignancy) that may affect part or all of the gut (esophagus, stomach, small and large bowel) and different layers of the intestine, such as the mucosa, submucosa, muscular layer or serosa. The disease often has patchy involvement and normal macroscopic appearance, necessitating the analysis of multiple biopsy specimens and quantification of eosinophil infiltration from each intestinal segment. Clinical manifestations are variable, including vomiting, dysphagia, abdominal pain, diarrhea, blood stools, iron deficiency anemia, malabsorption, protein-losing enteropathy, failure to thrive, obstructive symptoms, and even ascites in the serosal form. A trial of specific food antigen and aeroallergen avoidance is often indicated and in selected cases, an elemental formula is necessary. Glucocorticoids (systemic or topical) have also shown beneficial results, especially in eosinophilic esophagitis. Other treatments, such as cromoglycate, montelukast, ketotifen, suplatast tosilate, mycophenolate mofetil, ‘alternative Chinese medicines’, anti-IL-5, the tyrosine kinase inhibitor imatinib mesylate, CCR3 antagonists, and IL-4/IL-13 inhibitors, have all been used in the attempt to decrease eosinophilic infiltration but without clear evidence. The primary
pathogenic role of eosinophils and of food and inhalant allergens remains to be established [23].

**Crohn’s Disease**

Crohn’s disease may affect any part of the gut (most commonly the ileum and colon) with patchy mucosal ulceration and transmural inflammation due to excess (Th1 and macrophages) immune activation, increased free radicals and overexpression of matrix metalloproteinases. Crohn’s disease results from a complex interaction among immune, genetic and environmental factors producing a dysregulated immune response to the gut flora. Tolerance to autologous flora appears to be lost and thus the luminal ‘content’ represents a persistent driving factor of the cell-mediated inflammatory process further stimulated by a possible defective response to (selected?) pathogens. The concept that the enteric flora is of profound importance in the development of Crohn’s disease is supported by the absence of disease in germ-free conditions, by the recognition that a specific disease-associated gene such as Nod-2 encodes an intracellular molecule important in the inflammatory response to bacterial peptidoglycans and by the production of IFN-γ induced in these patients by extracts of their own commensal flora. Furthermore recent studies showed reduced defensin expression, defective activation of NF-κB and IL-8 secretion and enhanced IL-12 production (due to a failed inhibition of TLR2 signaling). Thus, interaction between the luminal antigens (from dietary products and microorganisms) and the immune system is crucial and beneficial manipulation of diet and selected probiotic supplementation is intriguing. Many diet trials (i.e. with fibers, carbohydrate restriction or PUFA supplementation) have been tried without significant benefit. Conversely, enteral nutrition (EN) with a polymeric formula has a proven therapeutic effect for inducing (clinical and histological) remission in pediatric Crohn’s disease, improves weight gain, and reverses growth failure and nutrient deficiencies. Some progress has been made in understanding the mechanisms by which EN exerts its beneficial influence in Crohn’s disease. Nutritional restitution, modulation of enteric flora and inflammatory cytokines and alteration of the expression of specific genes (with immune effects) within the epithelium have all been considered. A recent report pointed out that the efficacy of EN is significantly dependent on ileal involvement [24]. A profound modification of the fecal microflora after EN (Modulen IBD, Nestlé) has been demonstrated [25] although the mechanisms of the interaction between the formula used and the gut flora still need to be clarified. Selected probiotics could, in theory, restore the luminal balance and exert regulatory or anti-inflammatory effects. However, a recent randomized, placebo-controlled trial of LGG supplements added to standard therapy did not prolong remission in 39 children with Crohn’s disease [26].
Primary Enterocyte Abnormalities

Intestinal Epithelial Dysplasia (Tufting Enteropathy)

Intestinal epithelial dysplasia presents at neonatal age with chronic watery diarrhea, impaired growth and possible facial dysmorphisms. Small bowel biopsies reveal variable villous atrophy, crypt hyperplasia and slightly increased inflammatory activation in the lamina propria without a marked increase of intraepithelial lymphocytes. The characteristic feature of tufting enteropathy is the presence of focal epithelial ‘tufts’ composed of closely packed enterocytes with rounding of the apical plasma membrane which results in a teardrop configuration of the affected epithelial cell likely due to a defect in the basement membrane and in the expression of cellular adhesion molecules. Parenteral nutrition is necessary in most affected patients.

Microvillous Inclusion Disease

Microvillous inclusion disease is a rare (often fatal) enteropathy with severe watery diarrhea starting in the first days of life. Variable villous atrophy with mild crypt hyperplasia, and an absence of marked inflammatory infiltrate in the lamina propria are present in the biopsies. On higher magnification, the surface enterocytes are disorganized, with extensive vacuolization and positive staining for periodic acid-Schiff, alkaline phosphatase and CD10 (a leukemia antigen normally expressed in the brush border of enterocytes) of the apical cytoplasm indicating an internalization or a defective exocytosis of the glycocalyx. On transmission electron microscopy, intracytoplasmic microvillous inclusions and apical secretory granules in surface epithelial are pathognomonic of microvillous inclusion disease. The severity of the secretory diarrhea and the concomitant different alterations of brush-border membrane transport cause the need of long-term parenteral nutrition and eventual intestinal transplant.

Small Intestinal Lymphangiectasia

Small intestinal lymphangiectasia is a rare disease characterized by obstruction of the small bowel lymph drainage with dilated lymphatic vessels and patchy villous distortions and mucosal involvement. Lymphangiectasia may be caused by a congenital malformation or by a secondary lymphatic block (such as in abdominal or retroperitoneal tumors or fibrosis, mesenteric tuberculosis, intestinal malrotation, congestive heart failure, and constrictive pericarditis). Due to lymph stasis an excess loss of protein into the intestinal lumen may occur and peripheral edema (related to hypoalbuminemia) and malnutrition may manifest. Steatorrhea due to malabsorption of chylomicrons and fat-soluble vitamins (T-cells), lymphocytopenia and hypogammaglobulinemia are additional findings. On endoscopy scattered white opaque spots or plaques in the duodenal mucosa represent the dilated enteric lymphatic vessels detected on the biopsies. The mainstay of dietary treatment is a low-fat, high-protein MCT diet.
with additional calcium salt and water-soluble forms of fat-soluble vitamins required in selected patients. EN (with elemental diet or polymeric diet containing MCT) appears to have a similar efficacy to total parenteral nutrition.

**A-β-Lipoproteinemia**

In a-β-lipoproteinemia chylomicron formation is impaired (related to mutations in the MTP gene) and the absorbed dietary fats (chylomicrons, VLDL, LDL) are absent from the plasma and are accumulated, as vacuoles, in the cytoplasm of the enterocytes. Steatorrhea and failure to thrive may be associated with retinitis pigmentosa, progressive neurological manifestations (absent deep tendon reflexes, ataxia, tremors, impaired position and vibration sensitivity), and acanthocytes related to vitamin E deficiency. Large supplements of fat-soluble vitamins and reduced long-chain fat intake replaced by MCT are required.

**Protein-Losing Enteropathy**

Protein-losing enteropathy is a broad term including all the conditions that cause an abnormal loss of plasma proteins from the gut. Three main mechanisms are responsible for protein-losing enteropathy: enhanced mucosal permeability to proteins (as in eosinophilic gastroenteritis and Menetrier’s disease), mucosal erosions or ulceration (as in erosive gastritis and inflammatory bowel disease), and lymphatic obstruction (congenital or secondary). Enteric loss of protein may be revealed noninvasively by an increased stool concentration of \( \alpha_1 \)-antitrypsin or, more expensively, by radioactive methods (intravenous administration of \(^{51}\)Cr albumin or chloride).

**Specific Dietary Interventions**

**Nucleotides**

Dietary nucleotides build blocks of RNA, DNA, ATP, and therefore a supplemented formula may improve growth and immunity, optimize the maturation, recovery and function of rapidly dividing tissue, such as the gastrointestinal tract mucosa. Infant studies have shown that the addition of nucleotides decreases the incidence of diarrhea and upper (but not lower) respiratory tract infections, affects NK cell activity, increases serum IgA, T cell maturation and antibody level after *Haemophilus influenzae* type B (but not hepatitis B) vaccination [27, 28]. ‘Most’ dietary nucleotides are rapidly metabolized and excreted. However, ‘some’ are incorporated in tissue, probably depending on many factors such as age at supplementation. In infants with severe intrauterine growth retardation nucleotides enhance catch-up growth. The supplementation of nucleotides in infant feeding can be regarded as very safe; therefore the cost/benefit ratio is of major importance. As a consequence, the addition of nucleotides in infant feeding should be considered in ‘at risk’
infants such as the preterm and immature infant, or after severe intestinal injury.

**Glutamine**

Glutamine supplementation is reported as safe, and tends to be associated with less infectious morbidity and mortality. However, glutamine-enriched EN did not improve feeding tolerance or short-term outcome in very low birth weight infants and the available data from good quality randomized controlled trials suggest that preterm infants do not clinically significantly benefit from glutamine supplementation [29].

**Lipids**

Increasing evidence has demonstrated that adequate dietary lipids are extremely important not just for their calorific value but also for their immune-modulatory effects. Lipids may prevent allergic sensitization by downregulating inflammatory response (n-3 but not n-6 long-chain fatty acids) whilst protecting the epithelial barrier, regulate immune function and modify the adherence of microbes to the mucosa, thereby contributing to host-microbe interactions. Medium-chain (8–12 carbons) fatty acids (MCT) seem to have more strongly antiviral and antibacterial properties (against Rous sarcoma virus, herpes simplex virus, *H. influenzae* and group B streptococcus) than long-chain triglycerides [30]. According to a recent Cochrane review, there is no evidence of differences between MCT and long-chain triglycerides in short-term growth, gastrointestinal intolerance, or necrotizing enterocolitis [31].

**References**

Discussion

**Dr. Rivera:** This morning I glanced at the *European Journal of Nutrition* and I saw a very interesting topic on the use of probiotics in pancreatitis with apparent good results [1]. I wonder if you have any comments or if you have heard about this study or any particular experience that you may have had with pancreatitis?

**Dr. Vandenplas:** I am not aware of clinical studies on probiotics in human patients with pancreatitis. However, probiotics have been demonstrated to equilibrate the gastrointestinal ecosystem. Also, they have been shown to be beneficial in different infectious diseases, even outside the gastrointestinal tract, such as urinary tract infections and vaginitis. Therefore, it could be possible that probiotics may also have a role in pancreatitis.

**Dr. B. Koletzko:** You cited the paper by Yau et al. [2] from Taiwan who supplemented nucleotides; you interpreted their data as showing a reduction in respiratory disease and respiratory infections with added nucleotides. I think there was a mistake; in fact these authors reported that nucleotide supplementation, at a relatively high level exceeding 10 mg/100 kcal, increased rather than decreased the rate of respiratory infection. Thus this is one of the studies that actually raise the question whether higher levels of nucleotides in infant formulae are appropriate.

**Dr. Saavedra:** When we look specifically at ‘probiotics’ we should use the term as a concept. But when we get to recommendations we should not use the word as a concept, we should use the specific strains that we are talking about. This is a common mistake. In any recommendation paper, not a conceptual paper, that is making recommendations, when we use the word ‘probiotics’ relative to safety or efficacy it is naïve or simplistic to say that antibiotics are safe or efficacious. In the future, if we stick to recommendations regarding the safety or efficacy of these agents, we should talk about the specific agent being studied.

My question refers to the use of some of these microorganisms early in life. Most breastfed babies get nonsterile formula, i.e. breastfeeding, and get it in the least allergenic way (human proteins). What we have done with ‘modern’ formula is to give sterile formula in the most allergenic form we know (cow proteins). What does the inclusion of microorganisms in the diet of babies in early life have to do with regular or constant bacterial stimulation? That is, do you have to keep giving these organisms or is it enough to inoculate a child with potential microorganisms to establish the flora which leads to less necrotizing enterocolitis or diarrhea?

**Dr. Vandenplas:** I fully agree with the proposed definition of probiotics. Recommendations should be strain specific. Probiotics should be separated into groups referred to as ‘food supplements’ and ‘medications’. Whether you call these probiotics simply ‘medication’ or ‘biotherapeutic’ is a question of making agreements and reaching a consensus. Food supplements are clearly different.

It is true that on the one hand we sterilize the formulas for the preterm infants and then we add microbes to it. I do not know if that is good or not. The idea of adding prebiotics to starter formula to develop the infant’s own gastrointestinal flora is also a possibility. In the future we may learn that prebiotics are a good concept for healthy term-born infants, whereas probiotics are a better concept for sick infants. Today, we have no information on this, and every statement is speculation. Most of the time the preterm infant is born by cesarean section and lives in a sterile environment; it gets antibiotics, but may be better off with probiotics. We do not have information on this today.

**Dr. Fuchs:** My question has to do with Modulen and the evidence that suggests it would be advantageous. What is your view of the evidence or just your personal opinion on where Modulen might fit in our treatment approach?
Dr. Vandenplas: Up to now, there is to my knowledge no consensus where exactly Modulen fits into the treatment. Some centers first focus on nutrition and use Modulen almost as first-line treatment. Other centers use Modulen after failure of ‘classic’ medical treatment. Opinions do differ. In our center, we first try medical treatment with corticoids, 5-ASA and Imuran. If this fails, we try nutritional therapy. But whether this is a better approach than starting with nutrition, I do not know. There are not enough randomized data to allow conclusions.

Dr. Fuchs: Specifically as it relates to Modulen, not just any formula, is there a potential role for Modulen as opposed to another elemental or semi-elemental formula?

Dr. Vandenplas: Yes, there are data suggesting that Modulen is effective. It tastes quite good, so most children succeed in drinking it as their only food for a couple of weeks or even months. This is a big advantage. In general tube feeding is very poorly accepted by adolescents, and causes psychological and emotional problems. If patients drink the formula, at least the psychological problem is solved.

Dr. Milla: As Dr. Fuchs said yesterday eosinophilic gastroenteropathy is probably a heterogeneous group of different conditions and mucosal eosinophilic gastroenteropathy seems to be quite different to transmural and serosal eosinophilic gastroenteropathy. Mucosal eosinophilic gastroenteropathy is becoming much more common in Europe and we may catch up with the east coast of the US. There was a paper in Gut showing that Montelukast, a chemokine antagonist, is helpful in mucosal eosinophilic gastroenteropathy but does not seem to help the other two [3]. Could you comment on the place of oats and oat withdrawal in gluten-induced enteropathy and the management of gluten-free resistant celiac disease.

Dr. Vandenplas: Regarding your comment, I fully agree with your statements. The short answer to your question would be no. Although there is no real consensus today on the question if the glutens present in oat are really not toxic or if they have a reduced toxicity compared to the glutens from the 3 other sources. The first thing to do in patients who do not improve on a gluten-free diet would be to reconsider the diagnosis. If the patient does not respond to a gluten-free diet, it is likely not celiac disease.

Dr. Ruemmele: Perhaps I can address some points regarding the question from Dr. Milla. We [4] and also Marti et al. [5] tracked down different peptides in glutens involved in celiac disease, there are immunostimulatory peptides and there are toxic peptides. Therefore, we have to consider different gliadin antigens involved in the pathogenesis of celiac disease. The improved understanding of these antigens may help to explain the varying clinical presentation of celiac disease. Once the immune process is stimulated, and it can be self-perpetuated by cytokines, such as IL-15, these patients no longer respond to glutens so this is the true mechanism on the way to lymphoma. We never saw this in pediatrics but in adult patients it is well known.

In the intestine we know that on one hand there are enterocytes, the epithelium, the mucosal immune system, and on the other hand in the lumen there are antigenic structures and bacteria, which were largely neglected in the past. We are wondering whether Modulen IBD in Crohn's disease patients is not one of those drugs that is very selective in improving this interplay. We know about its anti-inflammatory effects but perhaps this is related to a major impact on the intestinal flora. With the help of Nestlé we are addressing this in a study with Crohn's disease patients using Modulen IBD. There are preliminary data by Paolo Lionetti from Italy who observed a certain degree of change in the intestinal flora in these patients and we want to address this question in a systematic manner. By modifying the diet not only are the nutritional elements changed; the flora might be one of the major aspects modifying Crohn's disease.

Dr. Vandenplas: I would like to add that every one is so focused on gastrointestinal flora that it is now brought in relation to every condition. Many researchers have
shown that the gastrointestinal flora is very important in immune system development and immune response. But it is also likely that the gastrointestinal flora is not the only factor influencing the immune development and response.

Dr. Picaud: As a neonatologist I would like to talk about probiotics in prematurity because it is rarely discussed and it could be interesting because we need something new to improve nutrition in preterm infants. There are some data from Japan showing that there is an improved feeding tolerance with these probiotics. On the other hand the benefits have been clearly shown in areas where there is a high incidence of necrotizing enterocolitis. More than 1,000 infants have been included in this type of study, and there is no problem with safety. Regarding safety, the balance between risks and benefits should be integrated. Indeed, the theoretical risk is bacterial translocation but there are some data showing that the translocation, at least in animals, decreases when probiotics are provided. Furthermore, when there is suspected late-onset sepsis in neonates, antibiotics are used. There could be a benefit from using probiotics in this clinical setting, and there are recent data showing that it is better when two probiotics are given rather than one.

Dr. Vandenplas: This is an interesting area that needs further research. There is laboratory research showing that it should be safe. On the other hand, the clinical studies that have been performed still have a limited number of children. Much more data are needed in sick newborns before we can be really sure that in ‘daily life’ the administration of probiotics is really safe. Side effects, such as septicemia, have been reported in preterms with short bowel. The effect of the introduction of probiotics from the very first day of life on the development of permanent gastrointestinal flora should also be further investigated. It is well known that when given later in life, probiotics do not colonize the gastrointestinal tract. They disappear from the flora a couple of days or weeks after the administration has stopped. But this natural evolution might be different when the probiotic is introduced at birth, because then it is part of the very first flora that will develop. It might be that colonization in this condition with the probiotic becomes more permanent. We do not know. As a consequence, we certainly do not know whether this might be beneficial or potentially dangerous.

Dr. Heine: Could you speculate on the mechanism of Lactobacillus GG that might be detrimental in Crohn’s disease?

Dr. Vandenplas: I would not like the take-home message to be that probiotics in Crohn’s disease are detrimental because the data available are very limited, and for the study I showed the difference was not significant. There was a trend towards more relapses in the group with Lactobacilli. However, several studies in adults with Crohn’s disease did show some benefit from probiotics, especially in pouchitis. Presently the evidence that probiotics in Crohn’s disease are really helpful is weak, except for pouchitis.

Dr. Jacobson: You spoke a little bit about Crohn’s disease and enteral nutrition support, and you indicated that the polymeric diet is as efficacious as the elemental diet. Can you provide us with some thoughts as to why you think the polymeric is equally efficacious given that the theory behind the efficacy of the elemental diet is related to the reduced antigenic load.

Dr. Vandenplas: I do not have enough personal experience with the comparison of different feedings. It can be supposed that an elemental or normal polymeric diet probably approaches different mechanisms involved in Crohn’s disease. One mechanism may be that a sick mucosa has an increased permeability. Elemental feeding would be a logical choice. Another mechanism might be that with normal feeding there is a more balanced effect on gastrointestinal flora. We do not know why both seem to work. I also don’t know of any study showing that elemental feeding is successful after failure of polymeric feeding.
Dr. Nowak-Wegrzyn: We followed a number of children with mucosal eosinophilic gastroenteritis in whom protein-losing gastroenteropathy was seen and on biopsies the only place where eosinophilic infiltrate was found is the stomach [6]. Have you had any patients like that? In your experience, is the stomach a common site for protein loss or have we missed the intestinal eosinophilic infiltrates, which are patchy in nature, or can’t they be detected in the ileum?

Dr. Fuchs: I find it difficult to believe that all your protein loss is just from the stomach with that sort of histology. There are cases with protein loss just from the stomach, but my suspicion is that it probably reflects protein loss further down the small bowel.

Dr. S. Koletzko: The distribution can be very patchy. I have followed a child who has a severe eosinophilic enteropathy for several years and was endoscoped many times. On each occasion the distribution of the lesions was different; at one point the stomach and the next time the colon or the small bowel. So the lesions are probably patchy and that may be misleading in your case.

Dr. Vandenplas: Then you need a capsule which can take multiple biopsies in the small bowel.

Dr. Lentze: You and others have touched upon probiotics. Why do they work, how do they work and where do they work?

Dr. Vandenplas: There is quite a lot of in vitro laboratory research on the mechanisms of action of different microorganisms. Whether you can transpose those mechanisms to the clinical situation is another question. One of the mechanisms may be an increased secretion of IgA at the intestinal mucosa level. This may explain why the duration of diarrhea is shortened, even if dead microorganisms are administered. Maybe this is also the reason why there is less re-infection 1 month later as suggested in an open trial. But you are right, more research in clinical settings is needed on the mechanisms of action.

Dr. Saavedra: I think your question is very valid because it underlines what Dr. Vandenplas was saying earlier, we should not just say ‘probiotics work’, we have to say what we mean by ‘they work’. In other words, maybe this is a bad analogy but it is like saying this particular diet works – it works for certain patients; similarly for probiotics, a particular probiotic has been shown to be safe and efficacious for a specific application. So of course we could say there are many Lactobacilli and they are all excellent for lactose digestion. It has been very well demonstrated and shown mechanically that they improve lactose tolerance in patients with lactose malabsorption [7]. This is very different than saying probiotics may improve or decrease the chances for rotaviral infection [8], or that they can increase specific anti-rotaviral IgA [9]. When we talk about these benefits we need to point out specific agents such as a specific Bifidobacteria for specific purposes, and not say that probiotics in general have this or that effect. We cannot generalize benefits or adverse effects to all probiotics, because we will never come to a conclusion.

References

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