# Pediatric Applications of Inulin and Oligofructose[1–3]

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## Abstract

Inulin-type fructans have been used in infants and children because of their prebiotic potential to modulate the intestinal flora and influence the innate and adaptive immune response favorably. A mixture of long chain inulin (5–60 monomers) in combination with galactooligosaccharides (GOS) (2–7 monomers) has been added to infant formula in Europe in a 10–90% ratio for over 5 y. Clinical studies have demonstrated that these prebiotic formulas have significant effects on flora composition, improve stool consistency, decrease intestinal permeability, and reduce the incidence of gastrointestinal (GI) and respiratory infections and atopic dermatitis. Oligofructose in weaning foods consumed by toddlers increases fecal Bifidobacteria counts and decreases fecal Clostridia counts during consumption, leading to softer stools and fewer fever episodes and other GI symptoms. Synergy, a mixture of oligofructose and long chain inulin, is protective of the Bifidus flora during amoxicillin treatment. Few studies are available in adolescents. Calcium absorption is improved especially by Synergy. The same product, combined with Lactobacillus Rhamnosus and Acidophilus, induces significantly favorable effects on colonic ammonia (NH3) metabolism. The demonstrated bifidogenic effect of inulin and oligofructose on intestinal microbiota is probably not the only mechanism involved but may be the key to important immune mediated effects. J. Nutr. 137: 2585S–2589S, 2007.

## Why inulin and oligofructose are important in pediatrics

Establishment of the intestinal flora soon after birth plays a crucial role in the development of the innate and adaptive immune system (1). In normal circumstances, the newborn baby is inoculated by the mother's flora when passing through the birth canal. A diverse flora residing in the mother's vagina and intestine colonizes her baby. In case of caesarean section, this step obviously does not take place, but consequences, if any, are yet unclear. In the gastrointestinal (GI) system of breast-fed babies, Bifidobacteria are soon selected and become predominant. This situation remains until weaning. The introduction of formula or solid food immediately leads to diversification of the flora, which is reflected by alterations of stool color, consistency, and odor. Formula-fed babies harbor a varied flora consisting of Bifidobacteria, *Escherichia coli*, and Bacteroides (2–5).

Human milk stimulates the growth of Bifidobacteria because of a high oligosaccharide (10–12 g/L) content (6). These oligosaccharides are predominantly neutral, low molecular weight molecules, depending on the Lewis blood group of the mother. They inspired the addition of non digestible oligosaccharides and inulin to infant food to obtain a comparable bifidogenic effect.

The aim of a bifidogenic effect on the infant's intestinal flora is to counteract the current rise of allergic diseases (7) and to protect from GI infections. Human milk is protective against atopy (8) and infections (9).

The immune system of newborns is characterized by a Th 2 profile, meaning that type 2 helper cells and their cytokines predominate. These generate IgE-producing cells and eosinophilic stimulation leading to allergic inflammation (1). In a normal assemblage, intestinal bacteria promote a Th1 response, restoring the balance toward tolerance (10). Bifidobacteria induce a Th 1 response (11). Lack of adequate bacterial stimulation has been incriminated as the culprit for the increased incidence of allergic disease, also called the allergic march (12). However, the hygiene hypothesis does not account for changes related to the earlier, far more significant drop in infectious diseases. Therefore, it is now suggested to rather focus on differences in microbial exposure (12,13).

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[3] In these proceedings, the term inulin-type fructan shall be used as a generic term to cover all $\beta$–(2 ← 1) linear fructans. In any other circumstances that justify the identification of the oligomers vs. the polymers, the terms oligofructose and/or inulin or eventually long-chain/or high molecular weight inulin will be used, respectively. Even though the oligomers obtained by partial hydrolysis of inulin or by enzymatic synthesis have a slightly different $DP_{av}$ (4 and 3.6, respectively), the term oligofructose shall be used to identify both. Synergy will be used to identify the 30:70 mixture (wt:wt) of oligofructose and inulin HP otherwise named oligofructose-enriched inulin.
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Allergic and nonallergic children harbor different types of flora, nonallergic children having higher counts of aerobic bacteria, Lactobacilli, and Bifidobacteria (14). It appears that *Bifidobacterium bifidus* has stronger adhesive properties and may be specifically protective against allergy as opposed to *Bifidobacterium adolescentis* (15).

Inulin and oligofructose may be safe inducers of a Bifidus flora and thereby affect the intestinal and systemic immune balance. We have here reviewed all available information on pediatric applications of oligofructose and inulin, restricted to peer-reviewed publications. Animal studies were deliberately not included in this chapter, because the application of prebiotics in animal nutrition is discussed by J. Van Loo in this supplement issue.

## Effects of inulin and oligofructose in infants

The first prebiotics added to infant food are a combination of 10% inulin with 5–60 fructose monomers and 90% galactooligosaccharides 2–7 monomers (called GOS) (16). The distribution of these formulas targets specific markets; they were introduced in Europe in 2000 but up to this day are not present on the U.S. market. The prebiotic formulas are reported to have multiple positive effects mediated through changes in the flora, the immune system, and other mechanisms (**Table 1**). Several postmarketing studies have clearly demonstrated a beneficial effect on the baby's flora after 28 d of intake: Bifidus counts showed a dose-related increase (with 0.4 g/100 mL and 0.8 g/100 mL) and Lactobacilli also significantly increased from baseline to levels seen in breast-fed babies. Moreover, the types of Bifidobacteria and Lactobacilli corresponded with the patterns seen with breastfeeding (17–20). The shift toward breast-fed type flora is accompanied by a reduction in potential pathogens (21). These changes in the bacterial populations and their metabolic activities led to lower stool pH (18) and production of SCFA profiles comparable to breast-fed infants, with higher acetate and lower propionate levels (22) or higher acetate and lactate levels (23). This last report, however, fails to demonstrate a superior bifidogenic effect compared with standard formula (23).

Addition of the inulin/GOS mixture in weaning foods of 4- to 6-mo-old infants in a daily dose of 4.5 g during 6 wk succeeded in increasing the Bifidus population from 43–57% of the fecal flora. This change was significantly different from the nonsupplemented group (24).

**TABLE 1** Reported effects of inulin 10% + GOS 90% in infants[1]

| |
|---|
| Flora |
| Bifidogenic (0.8 g % > 0.4 g %) to breastfed pattern (18) |
| Bifidogenic in weaning foods (24) |
| + Lactobacilli to breastfed pattern (17–19) |
| Stool SCFA profiles comparable to breastfed (20) |
| − Relative number of potential pathogens (21) |
| Immunity |
| − GI and extra intestinal infections (25) |
| − Atopic dermatitis at 6 mo (26) |
| + Fecal S IgA (28) |
| Other |
| Softer stools (18) |
| Accelerated GI transit (29) |
| + Intestinal barrier (27) |
| Stable growth and water balance (31) |

[1] + or – correspond to significant increase or reduction, respectively.

A consistent clinical effect obtained by prebiotic formula is softer stools (18). It is unclear whether this is due to the flora shift, to an osmotic effect, to SCFA, or to all of the above.

The putative effect of prebiotic formula on the immune system has been demonstrated by 2 recent studies on the incidence of infections during the first year of life and on atopic dermatitis. In a prospective, randomized, placebo-controlled open trial, infants receiving the inulin/GOS mixture during 12 mo had significantly fewer episodes of GI and respiratory tract infections (25). A prospective, double-blind, randomized placebo-controlled study in infants at risk for atopy brilliantly demonstrated a protective effect of the inulin-/GOS-enriched hydrolyzed formula at 6 mo (26). Potential mechanisms of the prebiotic effect may be improved gut barrier, as was shown to be the case (27). The prebiotic mixture also enhanced fecal secretory IgA levels (28).

A similar enrichment of formula for premature infants at 1 g/dL during 2 wk lowered stool viscosity and shortened intestinal transit time measured with carmine red dye (29).

A short prospective, randomized, crossover intervention with 1.5 g and 3 g oligofructose/L formula showed a laxative effect of the higher dose but failed to document alterations in fecal flora. However, 1 wk intervention may have been too short to permit changes in the species composition and metabolic activities of the GI bacteria (30).

Infants fed the prebiotic inulin/GOS mixture (31) or oligofructose alone (32) in formula grow well, have a stable water balance, and show no noted undesirable side effects. The addition of a mixture of 10% inulin and 90% GOS in a concentration of 0.8 g/dL to infant formula was recognized safe by the European Commission in December 2001. This was confirmed in the last EU directives of December 2006 [Commission directive 2006/141/EC on infant formulae and follow-up formulae (33)] with the following wording in Annex 1: "fructo-oligosaccharides and galacto-oligosaccharides may be added to infant formula… their content shall not exceed 0.8g/% in a combination of 90% oligogalactosyl-lactose and 10% high molecular weight fructosylsaccharose. … other combinations may be used." The document further mentions in article 5: " the formula is manufactured from protein sources… and other food ingredients…whose suitability for particular nutritional use by infants from birth has been established by generally accepted scientific data" (33).

Finally, in vitro studies of nutrient availability showed that inulin (0.4 g/dL) supplementation to standard infant formula improves calcium availability (34).

## Effects of inulin and oligofructose in toddlers

Inulin and oligofructose have been studied more often in weaning foods in toddlers. Multiple positive effects have also been reported, especially clinical effects suggesting improved immune response, as indicated by a lower incidence of febrile episodes. Inulin and oligofructose are bifidogenic and decrease the number of some pathogens (an overview of the studies performed in toddlers can be found in **Table 2**).

A study by Saavedra and Tschernia performed in 1999 first reported the effect of oligofructose (up to 3 g/d) in weaning foods consumed by toddlers attending daycare. These otherwise healthy toddlers had softer stools, less emesis, regurgitation, and perceived discomfort and, interestingly, fewer fever episodes (35). A similar recent analysis in toddlers attending daycare and taking 2 g/d oligofructose for 3 wk confirmed a protective effect against fever. These toddlers also had fewer infectious episodes requiring antibiotic treatment, fewer episodes of diarrhea and emesis, and less flatulence. Fecal microbial analysis confirmed the suspected bifidogenic effect during supplementation. Simultaneously,

**TABLE 2** Reported effects of inulin/oligofructose in infants and toddlers[1]

| |
|---|
| Flora |
| + Bifidobacteria, − Clostridia with oligofructose 2 g/d during 3 wk (36) |
| + Bifidobacteria after antibiotics with oligofructose/inulin (70:30) 2.25 g/d during 3 wk (40) |
| minimal effects with oligofructose 1.5 and 3 g/L during 1 wk (30) |
| Immunity |
| − Fever with oligofructose 1.1 g/d (35) |
| − Fever, diarrhea with oligofructose 2 g/d during 3 wk (36) |
| + IgG measles Ab with oligofructose /inulin (70:30) 4 wk prior to vaccine (41) |
| Other |
| Softer stools with oligofructose 0.74–3 g/d (37), with oligofructose 1.5 and 3 g/L (32), or with oligofructose 3 g/L (30) |
| No effect on diarrhea with oligofructose 1.1 g/d (35,39) or with oligofructose/inulin 2.25 g/d (40). |
| − Flatulence with oligofructose 2 g/d 3 wk (36) |
| Stable growth and water balance with oligofructose 1.5 and 3 g/L (32,30) |

[1] + or – correspond to significant increase or reduction, respectively.

Clostridia counts dropped and both shifts subsided after a 2-wk washout period (36). Moore showed that an average daily consumption of 0.74 g oligofructose (max 3 g) succeeds in softening stools but observed no alterations in other GI symptoms (37).

The inulin/GOS mixture administered to healthy toddlers in amounts of 4.5 g/d resulted in SCFA patterns with higher acetate and lower butyrate (38).

Prebiotics have been tested in disease states such as diarrhea. In breast-fed Peruvian children, no effect was seen on the incidence of diarrhea by adding oligofructose to cereals, with or without zinc (39).

A mixture of oligofructose and inulin (70/30 Prebio 1) at 2.25 g/d for 3 wk is protective of the Bifidus flora during amoxicillin treatment. Prebiotic treatment did not cause any GI symptoms but also did not alter stool frequency or consistency (40). The same Prebio 1 mixture was shown to enhance antibody response to measles vaccination when given 4 wk before. No effect was seen on GI tolerance (41).

### Effects of inulin and oligofructose in adolescents

Adolescents have so far inspired few clinical studies with prebiotics. An important, well-proven effect of oligofructose and inulin is improved calcium absorption in this age group.

Oligofructose at 15 g/d to 14- to 16-y-old boys improves fractional Ca absorption (42). A mixture of inulin and oligofructose (Synergy) at 8 g/d to 11- to 13.9-y-old girls on high Ca intake improves fractional Ca absorption. After 1 y of supplementation, the same treatment also improved significantly bone mineral density in adolescents (43). For a more detailed account on the positive effects of inulin and oligofructose in adolescents, please refer to the article by Abrams et al. in this supplement issue.

Biomarkers with stable isotopes, such as 13C- and 15N-labeled lactose ureide, can be used in children to mark the metabolism of intestinal bacteria (44). Expired $^{13}CO_2$ indicates the hydrolysis of $^{13}C$ lactose ureide by intestinal flora. Urinary $^{15}N$ excretion indicates the accumulation of ammonia. Pre- and probiotics increase bacterial N incorporation, resulting in reduced urinary $^{15}N$ excretion in healthy adults (45). We recently performed a study with 13C- and 15N-labeled lactose ureide in adolescents with Crohn's disease. The results indicated that a synbiotic (Synergy + lactobacillus rhamnosus and acidophilus) induced a significantly favorable effect on colonic NH3 metabolism, implying a lower production of potentially toxic metabolites (46).

### Brief reflections on probiotics vs. prebiotics

Probiotics, living health-promoting bacteria, have also been added to infant formula and milk-based nutritional products for all age groups. An excellent and exhaustive review of published placebo-controlled trials on the effect of probiotics in children and adults was recently published (47). The benefit of some specific probiotic strains for clinical problems has predominantly been demonstrated for acute infectious diarrhea. Some strains are protective against necrotizing enterocolitis in the intensive care nursery (48). Lactobacillus GG taken by mothers prepartum and by infants at risk for atopy in the early postnatal period appeared to lower the risk for atopic dermatitis for an extended period of up to 7 y (49). It is important to stress that the demonstrated effects were strain specific.

Despite the established bifidogenic effects of the prebioitics that we have discussed, it would be erroneous to assume that all probiotic effects can or may be duplicated by prebiotics. Not all probiotic effects are reproduced by the bifidogenic effects of prebiotics and conversely their effects are not limited to those of probiotics. Furthermore, safety issues are not comparable. A key benefit of prebiotics is that they are easier to include in formula and transition food than probiotics. This is why they perhaps have a greater market potential for infant and toddler foods that must be sterilized.

### Conclusions and future directions

The interest and number of reports on applications of inulin and oligofructose in pediatrics since our last review in 2005 (16) is impressive. It is now dogma that the inulin/GOS mixture in formula is bifidogenic. Oligofructose alone or in combination with inulin also has the potential to increase Bifidus counts in young children.

Clinical studies report encouraging data on immune mediated effects of prebiotic supplementation: less fever, fewer GI and respiratory infections, and less atopic dermatitis at an early age. It is probable that the bifidogenic factor is essential to achieve these desirable goals.

However, there is more to the story. The demonstrated bifidogenic effect on intestinal flora is not the only mechanism involved. Compared with probiotics, prebiotics may have a different or more pronounced influence on the infant's intestinal metabolism, because they are the very substrate for fermentation. Different mechanisms of action such as the contribution of osmotic effects in the lumen probably make pre- and probiotics very different agents. The importance of the osmotic factor and alterations of SCFA profiles should be determined. Pediatricians welcome the laxative effect of inulin and oligofructose because constipation and abdominal cramping is a frequent complaint. No concerning effects on water balance have been reported.

Are prebiotics to be considered protective, against infections, against allergy, or will they also be therapeutic? For treatment of acute infectious diarrhea, probiotics are proven effective (47) but not (yet?) prebiotics. Unwanted changes in intestinal ecology contribute to numerous intestinal diseases. It is challenging to explore how nutritional intervention may alter the intestinal milieu, possibly alter the expression of certain genes, and be pivotal in the early development of GI diseases.

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