

Oral Administration of Probiotic *Escherichia coli* after Birth Reduces Frequency of Allergies and Repeated Infections Later in Life (after 10 and 20 Years)

Rája Lodinová-Zádníková^a Božena Cukrowska^c
Helena Tlaskalova-Hogenova^b

^aInstitute for Care of Mother and Child and ^bDepartment of Immunology and Gnotobiology, Institute of Microbiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic;

^cDepartment of Pathology, Children's Memorial Health Institute, Warsaw, Poland

Key Words

Escherichia coli colonization, neonatal ·
Allergy, long-term prevention · Probiotics

Abstract

Background: The development of allergies is a complex in which both composition and influence of the intestinal flora play an important role. We observed in earlier studies that the presence of an orally administered probiotic *Escherichia coli* strain in the intestine stimulated both a serum and local antibody response, decreased the presence of pathogens, the number of infections and the need for antibiotics. **Methods:** The preventive effect of oral colonization after birth with a probiotic *E. coli* strain was assessed by evaluating the results of a questionnaire both 20 years (150 full-term infants) and 10 years (77 preterm infants) after colonization. **Results:** Differences in occurrence of allergies in colonized and control subjects were statistically significant both after 10 and 20 years ($p < 0.01$). Specific serum IgE antibodies confirmed the presence of allergies in 100% of 10-year-old and 91% of 20-year-old patients with clinical symptoms of allergy. Ten years after colonization, the occurrence of repeated infections was significantly lower in colonized subjects

than it was in controls ($p < 0.01$); 20 years later, no differences were found in these groups. **Conclusions:** Intentional colonization of the intestine with *E. coli* after birth (offering the advantage of the first colonizer) was found to decrease the incidence of allergies and repeated infections in later life.

Copyright © 2003 S. Karger AG, Basel

Introduction

Attempts were made by various authors [1] to substitute a randomly acquired intestinal flora with a non-pathogenic bacterial strain. Recently, the preventive effect on early atopic disease in high-risk children was ascribed to a probiotic *Lactobacillus GG* strain [2].

In earlier studies, we used a well-described nonpathogenic *Escherichia coli* strain, serotype 083:K24:H31, in the oral colonization of infants after birth. The strain remaining dominant in the intestine over several months stimulated both serum and local antibody, thus replacing an absent secretory IgA in maternal milk particularly in formula-fed infants [3].

Our results indicated that a preventive colonization of high-risk infants with *E. coli* after birth decreased the inci-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2003 S. Karger AG, Basel
1018–2438/03/1313–0209\$19.50/0

Accessible online at:
www.karger.com/iaa

Correspondence to: Dr. Rája Lodinová-Zádníková
Institute for Care of Mother and Child
Podolské nábreží 157
CZ–147 10 Prague 4 (Czech Republic)
Tel. +420 2 9651 1111, Fax +420 2 4143 2572, E-Mail mojziso@upmd.cz

dence of pathogens both in the intestine and other parts of the body. In addition, it decreased the number of infections and reduced the administration of antibiotics [4].

In the present retrospective study, we evaluated the incidence of allergies and repeated infections in two groups of subjects colonized intentionally after birth 10 and 20 years earlier with a nonpathogenic strain of *E. coli*.

Subjects and Methods

Groups A1, A2: Born as Full-Term Infants 20 Years Earlier

Group A1 (n = 640). All infants born over a period of 4 months in the maternity hospital were colonized orally with *E. coli* 3 times during their 1st week of life (1 ml of suspension contained 5×10^8 microbes).

Group A2 (n = 640). All infants born 4 months later in the same maternity hospital were used as controls. (The 4-month interval between the two groups was a measure preventing against contamination with a life strain.) There was no selection in either group.

Group B1, B2: Born 10 Years Earlier as Premature Infants

Group B1 (n = 230). Premature infants born over a period of 6 months and not treated with antibiotics were orally colonized with *E. coli* – 3 times a week over a period of 4 weeks.

Group B2 (n = 204). Premature infants born 6 months after those of group B1 (to avoid possible contamination) were used as controls.

Twenty years later, questionnaires prepared by specialists (pediatricians, immunologists, microbiologists, allergologists) were mailed to all subjects. Questions were focused on general topics, such as family history, birth parameters, breast-feeding, vaccination, health condition, occurrence of repeated infections (2 or more infections 6 or more times a year) and allergies.

The χ^2 test in Mantel-Haenszel modification was used for statistical evaluation.

Results and Discussion

The number of questionnaires which could not be delivered was 150 in group A1, 120 in group A2, 40 in group B1, and 38 in group B2. The number of questionnaires which were answered was 150 (31%) in group A1, 144 (28%) in group A2, 77 (40%) in group B1, and 55 (33%) in group B2.

Evaluation

Questionnaire 1

There were insignificant differences in the family history including the incidence of allergies and general parameters (birth weight, birth length, gestational age, breast-feeding, vaccination, surgery).

Table 1. Effects of oral colonization after birth with a probiotic *E. coli* strain on the frequency of allergic diseases and repeated infections assessed after 10 and 20 years

Groups of infants	Allergy (clinical symptoms)	Repeated infections
<i>After 10 years</i>		
B1 (colonized infants, n = 77)	12 (9)*	23 (18)*
B2 (control infants, n = 55)	33 (18)	58 (32)
<i>After 20 years</i>		
A1 (colonized infants, n = 150)	16 (24)*	59 (89)
A2 (control infants, n = 144)	32 (46)	60 (86)

Figures represent percentage with the number of patients.

* $p < 0.01$.

After 10 years, differences in the occurrence of allergies in colonized and control subjects were statistically significant and remained equally significant after 20 years ($p \leq 0.01$, table 1).

Most allergies involved respiratory and skin symptoms (rhinitis, conjunctivitis, bronchitis, asthma, eczema) (table 2).

The occurrence of repeated infections after 10 years was significantly lower in colonized than in control subjects ($p \leq 0.01$); after 20 years, no difference was observed in these groups (table 1). Results of a later etiology are not available.

Questionnaire 2

Details about allergies were obtained under medical supervision at checkup visits. A diagnosis of allergy was confirmed both by results of specific IgE tests against the most common antigens, of earlier skin tests, manifestation of clinical symptoms and long-term follow-up at allergy departments.

Specific serum IgE antibodies confirmed the presence of allergy in 100% of 10-year-old and 91% of 20-year-old patients with clinical symptoms of allergy. Most subjects reacted to house dust, timothy, pollen, mould and birch; few subjects only reacted to food allergens.

Our results support the hypothesis that the composition of the intestinal flora plays an important role in the development of immunity including immunopathologic consequences (allergy) [5, 6].

Possible reasons for the long-lasting effect of colonization on immune reactions could be (1) advantages of the

Table 2. Types of allergies and repeated infections in colonized and control infants

Group of infants	Type of allergy, %			Type of repeated infections, %				
	respiratory	skin	combined	n	respiratory	otitis	tonsillitis	combined
<i>After 10 years</i>								
Colonized infants (n = 9)	44 (asthma 11)	66	11	18	72	28	33	72
Control infants (n = 18)	44 (asthma 12)	72	33	32	100	47	37	97
<i>After 20 years</i>								
Colonized infants (n = 24)	71 (asthma 35)	50	25	89	65	22	27	22
Control infants (n = 46)	70 (asthma 28)	56	26	86	62	22	31	25

first colonizer and (2) an unusual persistence of the *E. coli* strain in the intestine.

The effect of intentional colonization of the intestine with *E. coli* after birth was immediately beneficial to infants resulting in a lower incidence of pathogens, a lower incidence of infections, less need for antibiotics [4], a decrease in the incidence of allergies and repeated infections later in life.

Acknowledgment

The project was approved by the Ethical Committee and was supported by the Czech Ministry of Health (grant No. NI/7525-3) and by the Grant Agency of the Academy of Sciences of the Czech Republic (grant No. A5020205).

References

- 1 Lari AK, Gold F, Borderon JC, Laugier J, Lafont JP: Implantation and in vivo antagonistic effects of antibiotic-susceptible *Escherichia coli* strains administered to premature newborns. *Biol Neonate* 1990;58:73–78.
- 2 Kalliomaki M, Salminen S, Arvilommi H, Koro P, Koskinen P, Isolauri E: Probiotics in primary prevention of atopic disease: A randomized placebo-controlled trial. *Lancet* 2001; 357:1076–1079.
- 3 Lodinova-Zadnikova R, Slavikova M, Tlaskalova-Hogenova H, Adlerberth I, Hanson LA, Wold A, Carlsson B, Svanborg C, Mellander L: The antibody response in breast-fed and non-breast-fed infants after artificial colonisation of the intestine with *E. coli* 083. *Pediatr Res* 1991; 29:31–39.
- 4 Lodinova-Zadnikova R, Tlaskalova H, Bartakova Z: The antibody response in infants after colonisation of the intestine with *E. coli* 083. Artificial colonisation used as prevention against nosocomial infections. *Adv Exp Med Biol* 1991;310:329–333.
- 5 Tlaskalová-Hogenova H, Tuckova L, Lodinova-Zadnikova R, Stepankova R, Cukrowska B, Funda DP et al: Mucosal immunity: Its role in defense in allergy. *Int Arch Allergy Immunol* 2002;128:77–89.
- 6 Cukrowska B, Lodinova-Zadnikova R, Enders C, Sonnenborn U, Schulz J, Tlaskalova-Hogenova H: Specific proliferative and antibody responses of premature infants to intestinal colonization with non-pathogenic probiotic *E. coli* strain Nissle 1917. *Scand J Immunol* 2002; 55:204–209.