

EDITORIAL

Clinical & Experimental Allergy

Infantile wheeze and maternal gut microbes – is there a connection?

This editorial discusses the findings of the paper in this issue by N. E. Lange et al. [14], pp. 901–908.

A. K. Kukkonen and M. Kuitunen

Pediatric Department, The Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland

The human gut is estimated to harbour 700–1000 bacterial species numbering 10^{14} cells. These bacteria live in a symbiotic balance with the host and a healthy gut microflora is a prerequisite for a normal homeostasis of the human. Commensal bacteria in the intestinal tract have metabolic activities, protect the host from pathogen invasion and are required for intestinal epithelial development and for the maturation of a fully competent immune system. They are also involved in the development of oral tolerance to ingested foods. Disruption of this balance might give rise to gastrointestinal diseases, such as inflammatory bowel disease and atopic diseases.

Initially the gastrointestinal tract of a fetus is sterile. Moreover, diversity of bacteria in meconium is very low compared with a mature type of gut microbiota. The maturation of the immune system requires commensal microbes and no oral tolerance develops in germ-free environments [1]. Immature fetal immune system in the germ-free milieu of uterus is characterized by dominance of T helper cell type 2 signals and weakness of T helper cell type 1 signals. The T helper 2-skewed immunity is pivotal in protecting normal pregnancy, however, pronounced T helper type 2 responsiveness at birth predisposes for the development of atopy [2]. Maturing of the neonatal immune system towards non-allergy and to a fully developed T helper 1 type defence against viruses and bacteria is strongly stimulated by commensal bacteria that are in a complex

continuous cross-talk between with the host immune system.

Vaginally born infants acquire microbes resembling those found in their mother's vagina. In contrast, a neonate born by caesarean section is not exposed to vaginal microbes and is first colonized by *Clostridium* species or bacteria that are typically located on the skin, such as *Staphylococci*. Later and less frequent colonization of *Bifidobacteria*, *Bacteroides* and *E. coli* has been observed in children born by caesarean section [3]. Therefore, exposure to vaginal and to perineal bacteria seems to be important in the early colonization of an infant gastrointestinal tract. Furthermore, host genetics and a plethora of environmental factors, such as environmental microbial diversity, diet and exposure to antibiotics may affect both maternal and infantile gastrointestinal microbiota.

Diversity of the gut microbiota may, more than absence or presence of certain species, be crucial to the maturing of competent immunity. In today's Westernized world, where the allergy epidemic is evident, gut flora has changed and become poorer. The newborn gut is rapidly colonized by *Staphylococci* instead of the traditional fecal enterobacteria, which are acquired later [4]. This is in contrast to communities where greater environmental microbial diversity prevails. For example, Pakistani infants have a high turnover of *E. coli* strains and the strains found in mothers persist in their infants' flora [5]. Changing bacterial strains offer a stronger stimulus for the developing immunity and forms the basis for the modified "hygiene hypothesis", where the imbalanced intestinal microbiome is linked with allergies and autoimmune diseases. Other than relative lack of certain bacterial species, such as *Bifidobacteria* and *Bacteroides*, low diversity of gut microbiota has been observed in neonates who will later develop atopic eczema [6]. In a combined albeit heterogeneous cohort from Gothenburg, London and Rome, no association was found between early intestinal colonization

Correspondence:

Dr Anna Kaarina Kukkonen, Helsinki University Central Hospital, the Skin and Allergy Hospital, Meilahdentie 2, P.O.Box 160, 00029 HUCH Helsinki, Finland. E-mail: kaarina.kukkonen@hus.fi

Cite this as: A. K. Kukkonen and M. Kuitunen, *Clinical & Experimental Allergy*, 2012 (42) 814–816.

of any particular commensal bacteria and development of atopic eczema or sensitization to foods [3]. However, in this same cohort, reduced diversity in early fecal microbiota was found in infants who later developed atopic eczema [7].

Interventional studies on probiotics have shed light on the importance of early gut colonization on the development of atopic diseases and resistance to respiratory infections. Short-term prenatal administration of probiotics to pregnant mothers has modulated the colonization of neonatal gastrointestinal tract with beneficial *Bifidobacteria*. However, such intervention has failed to have any effect on the diversity of the infant gut microbiota during the first week of life [8]. When probiotics were given to pregnant mothers and to their newborn children during the first 6 months of life, the same probiotic species grew in the stools of the supplemented infants during the intervention. However, later in the follow-up, after stopping the supplementation, there was no difference in the quality or quantity *Lactobacilli* and *Bifidobacteria* between supplemented and non-supplemented children. Although manipulating gut microflora seem not to result in persistent colonization [9], early innate immune responses in the gut associate with the emergence of atopy [10]. In high-risk populations, giving probiotics both to mothers before delivery and to their neonates immediately after birth has reduced the incidence of atopic eczema [9, 11]. Interestingly, the late colonization of caesarean-delivered infants by *Bifidobacteria* can be corrected by probiotic and prebiotic supplementation leading to fewer IgE-associated allergy later in childhood [12]. Although probiotics have given us the opportunity to study in a randomized setting the effect of commensal bacteria on shaping the newborn immune system, not all studies on probiotics have shown an effect. We have learned that timing of the bacterial exposure may be critical since giving probiotics only to mothers [13] or only to newborn infants has failed to have any allergy preventive effect. In light of our current knowledge of the importance of gut microbial diversity, it seems likely that a stronger and broader bacterial supplementation, possibly with a constantly changing bacterial stimulus could be more effective than with just one strain.

In this issue, Lange et al. present their study on the influence of maternal intestinal flora during late pregnancy on infantile wheeze and eczema [14]. They cultured maternal fecal samples and used questionnaires at

the age of 2 and 6 months to assess wheeze or eczema as their primary outcomes. The investigators found that higher counts of anaerobes and enterococci in maternal stools increased the risk for infantile wheeze but had no effect on eczema. This interesting finding leads us to speculate on the significance of this association.

Given that 60% of mothers and 18% of fathers in the current study were atopic, the majority of infants were at high risk for atopy. Infants, who are genetically at risk for developing atopic diseases, may have more immature immune responses already at birth. Their delayed immune maturation may also express as weaker antibody responses to vaccines [15], and as compromised resistance to respiratory infections [16]. That among atopy-prone infants those supplemented with probiotic bacteria had fewer respiratory infections, improved vaccine antibody response and required fewer antibiotics than those not supplemented, indicates a vital role for commensal bacteria in defence against pathogens [17]. Therefore, the immune stimulation provided by microbes may be more important to atopy-prone infants than to those not having the genetic predisposition for atopy.

Although wheezing in childhood is associated with atopic diseases in the study by Lange et al., wheezing during infancy may not be an indicator of atopic phenotype [18]. Infant wheeze is frequent in viral infections and is associated with small calibre of airways, and with the exposure to both pre- and postnatal tobacco smoke. Furthermore, a history of infantile wheeze obtained by questionnaires may not always represent true wheeze. Parents may confuse blocked nose, inspiratory and expiratory wheeze to what the physician means by expiratory wheezing. That certain bacteria in maternal stools associated with more infantile wheeze in these atopy-prone infants may reflect susceptibility to common viral infections due to delayed development of Th1 type immune responses against viruses and bacteria. Wheeze in viral infections may be caused by this genetic predisposition. The same hereditary risk may later predispose these infants to the development of atopy, an outcome that could be assessed during a longer follow-up. Whether maternal fecal colonization has any effect on development of atopy may be studied by following these infants later in the childhood. The study published by Lange et al. raises interesting questions that hopefully will be explored in future studies.

References

- 1 Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 1997; 159:1739–45.
- 2 Marschan E, Honkanen J, Kukkonen K, Kuitunen M, Savilahti E, Vaarala O. Increased activation of GATA-3, IL-2 and IL-5 of cord blood mononuclear

- cells in infants with IgE sensitization. *Pediatr Allergy Immunol* 2008; 19: 132–9.
- 3 Adlerberth I, Strachan DP, Matricardi PM *et al.* Gut microbiota and development of atopic eczema in 3 European birth cohorts. *J Allergy Clin Immunol* 2007; 120:343–50.
 - 4 Lindberg E, Adlerberth I, Hesselmar B *et al.* High rate of transfer of *Staphylococcus aureus* from parental skin to infant gut flora. *J Clin Microbiol* 2004; 42:530–4.
 - 5 Adlerberth I, Jalil F, Carlsson B *et al.* High turnover rate of *Escherichia coli* strains in the intestinal flora of infants in Pakistan. *Epidemiol Infect* 1998; 121:587–98.
 - 6 Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. *J Allergy Clin Immunol* 2012; 129:434–40, 440.e1–2.
 - 7 Wang M, Karlsson C, Olsson C *et al.* Reduced diversity in the early fecal microbiota of infants with atopic eczema. *J Allergy Clin Immunol* 2008; 121:129–34.
 - 8 Ismail IH, Oppedisano F, Joseph SJ, Boyle RJ, Robins-Browne RM, Tang ML. Prenatal administration of Lactobacillus rhamnosus has no effect on the diversity of the early infant gut microbiota. *Pediatr Allergy Immunol* 2011; doi: 10.1111/j.1399-3038.2011.01239x. [Epub ahead of print].
 - 9 Kukkonen K, Savilahti E, Haahtela T *et al.* Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2007; 119: 192–8.
 - 10 Savilahti EM, Kukkonen AK, Haahtela T, Tuure T, Kuitunen M, Savilahti E. Intestinal defensin secretion in infancy is associated with the emergence of sensitization and atopic dermatitis. *Clin Exp Allergy* 2012; 42:405–11.
 - 11 Wickens K, Black PN, Stanley TV *et al.* A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2008; 122:788–94.
 - 12 Kuitunen M, Kukkonen K, Juntunen-Backman K *et al.* Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol* 2009; 123:335–41.
 - 13 Boyle RJ, Ismail IH, Kivivuori S *et al.* Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. *Allergy* 2011; 66:509–16.
 - 14 Lange NE, Celedón JC, Forno E *et al.* Maternal intestinal flora and wheeze in early childhood. *Clin Exp Allergy* 2012; 42:901–8.
 - 15 Prescott SL, Sly PD, Holt PG. Raised serum IgE associated with reduced responsiveness to DPT vaccination during infancy. *Lancet* 1998; 351:1489.
 - 16 Paunio M, Peltola H, Virtanen M, Leinikki P, Makela A, Heinonen OP. Acute infections, infection pressure, and atopy. *Clin Exp Allergy* 2006; 36: 634–9.
 - 17 Kukkonen K, Savilahti E, Haahtela T *et al.* Long-term safety and impact on infection rates of postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. *Pediatrics* 2008; 122: 8–12.
 - 18 Linneberg A, Simonsen JB, Petersen J, Stensballe LG, Benn CS. Differential effects of risk factors on infant wheeze and atopic dermatitis emphasize a different etiology. *J Allergy Clin Immunol* 2006; 117:184–9.