Allergology International 66 (2017) 529–538

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited review article

Bugging allergy; role of pre-, pro- and synbiotics in allergy prevention

Christina E. West [a, b, *], Majda Dzidic [b, c, d], Susan L. Prescott [b, e], Maria C. Jenmalm [b, c]

[a] Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden
[b] inFLAME Global Network (Worldwide Universities Network), West New York, NJ, USA
[c] Division of Neuro and Inflammation Sciences, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden
[d] Institute of Agrochemistry and Food Technology, Spanish National Research Council (IATA-CSIC), Department of Biotechnology, Unit of Lactic Acid Bacteria and Probiotics, Valencia, Spain
[e] School of Paediatrics and Child Health, University of Western Australia and Princess Margaret Hospital for Children, Perth, Australia

ARTICLE INFO

Article history:
Received 23 June 2017
Received in revised form
2 August 2017
Accepted 2 August 2017
Available online 1 September 2017

Keywords:
Asthma
Biodiversity
Eczema
Microbiome
Probiotic

Abbreviations:
GRADE, Grading of Recommendation Assessment Development and Evaluation; HMO, Human milk oligosaccharide; NCD, non-communicable disease; RCT, randomized controlled trial; RR, relative risk; SCORAD, Scoring Atopic Dermatitis; SCFA, short-chain fatty acid; Treg, regulatory T-cell; TLR, Toll-like receptor; WAO, World Allergy Organization

ABSTRACT

Large-scale biodiversity loss and complex changes in social behaviors are altering human microbial ecology. This is increasingly implicated in the global rise in inflammatory diseases, most notably the "allergy epidemic" in very early life. Colonization of human ecological niches, particularly the gastrointestinal tract, is critical for normal local and systemic immune development and regulation. Disturbances in composition, diversity and timing of microbial colonization have been associated with increased allergy risk, indicating the importance of strategies to restore a dysbiotic gut microbiota in the primary prevention of allergic diseases, including the administration of probiotics, prebiotics and synbiotics. Here, we summarize and discuss findings of randomized clinical trials that have examined the effects of these microbiome-related strategies on short and long-term allergy preventative effects – including new guidelines from the World Allergy Organization which now recommend probiotics and prebiotics for allergy prevention under certain conditions. The relatively low quality evidence, limited comparative studies and large heterogeneity between studies, have collectively hampered recommendations on specific probiotic strains, specific timing and specific conditions for the most effective preventive management. At the same time the risk of using available products is low. While further research is needed before specific practice guidelines on supplement probiotics and prebiotics, it is equally important that the underlying dietary and lifestyle factors of dysbiosis are addressed at both the individual and societal levels.

Introduction

The epidemic rise in allergic diseases and asthma is inexorably linked to complex environmental and modern lifestyle changes. Urbanization and global decline of environmental biodiversity are directly implicated in changes in human commensal microbiota, which are critical for both normal immune maturation and subsequent immune function. While these global effects are likely to vary widely across both macro-scale geographic environments and micro-scale human microbial habitats, there is growing evidence that 'dysbiosis' is a major factor in the global increase in inflammatory non-communicable diseases including allergic disease.[1–3] The ecological pressures on microbial diversity are multifaceted and reflect changes in individual exposures such as nutritional patterns (increased processed foods, less fresh and fermented foods), sedentary indoor living (vitamin D insufficiency, reduced nature relatedness and exposure to environmental biodiversity) as well as the wider social and economic drivers of 'dysbiotic drift'.[4–6]

Thus while it is important to develop strategies for individuals to restore personal biodiversity for disease prevention, as is the subject of this review, it is equally important to address the fundamental drivers of dysbiosis and nutritional supplements must be viewed in this broader ecological context.[7]

* Corresponding author. Department of Clinical Sciences, Pediatrics, Umeå University, SE 901 85 Umeå, Sweden.
E-mail address: christina.west@umu.se (C.E. West).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2017.08.001

The establishment of commensal microbiota in the gastrointestinal tract is critical to provide the tolerogenic microenvironment necessary for optimal development of both innate and adaptive immunity.[8] Adverse influences on early colonization may have long-lasting consequences, exemplified by numerous examples of early compositional and functional differences in early life gut microbiota that precede the onset of eczema and asthma.[9–20] While it has been logical to explore the role of probiotics,[21] prebiotics[22] and combinations of these (synbiotics) (Table 1), to favorably modulate gut microbiota, it is also important that such interventions are considered in tandem with other strategies that address the perinatal practices and environmental factors that are contributing to dysbiosis in the first place. Thus, although this review is concerned with the specific impact of prebiotics and probiotics in the perinatal setting, we underscore that, even if effective, such products are only one aspect of the solutions.

The importance of gut microbiota establishment in the development of oral tolerance and immune competence

The ambient conditions during initial antigen exposure, typically when the gastrointestinal immune system is still immature, are important for the success of oral tolerance. The mechanisms that initiate and maintain tolerance to dietary antigens are still being defined, however early microbial exposure appears essential in promoting an appropriate regulatory milieu during this period of dynamic development (Fig. 1).[23–25] Delivery method, antibiotic usage, breastfeeding, perinatal environmental factors and numerous factors that influence maternal microbiota in pregnancy and lactation are important in this early colonization processes – many of these now implicated in altered patterns of early colonization which may predispose to allergy and possible other early onset NCDs.[3] For example, reduced gut microbial diversity and an elevated *Enterobacteriaceae/Bacteroidaceae* ratio in early life appears associated with an increased risk of developing food sensitization and atopic eczema.[13,14,26,27] Moreover, gut microbiota composition at age 3–6 months was recently associated with milk allergy resolution at 8 years of age.[28]

Table 1
Definitions.

Probiotics	"live microorganisms, which when administered in adequate amounts confer a health benefit on the host"[21]
Prebiotics	"substrate that is selectively utilized by host microorganisms conferring a health benefit"[22]
Synbiotics	The combination of probiotics and prebiotics

New insights into how the gut microbiota influences food allergy have been provided by experimental animal models, clearly demonstrating that absence of microbiota during a short time interval in early life can result in defects in immune regulation.[29] While this extreme microbial depletion does not resemble the more subtle disruptions observed in humans, it nonetheless indicates that the high microbial content in the gut is crucial for sustaining the homeostatic host-microbiome relationship and preventing intestinal inflammation and allergies by inducing mucosal IgA and regulatory T-cell (Treg) responses.[8,25,29,30] The main mechanisms of induction of oral tolerance are mediated by Foxp3+ Treg, known to mediate suppressive reactions thus avoiding excessive immune activation.[24] IgA, as the most abundant mucosal immunoglobulin isotype, is important in the establishment of composition of intestinal microbiota[31] and may reinforce oral tolerance by strengthening the mucosal barrier function.[32] In line with this hypothesis, aberrant IgA responses to the gut microbiota during infancy were recently observed to precede allergy development during the first seven years of life.[33]

The lack of intestinal microbiota in germ free mice is associated with a Th2-skewed immune response, with enhanced IgE responses to food antigens, and/or a defect in mounting proper regulatory T-cell responses.[8,34,35] Thus, an early exposure to microbial symbionts occurring during certain time windows of developmental plasticity, potentially also during the prenatal period (either directly or indirectly through maternal immunomodulation), might be beneficial in preventing development of Th2- mediated allergic disease.[36] Preliminary evidence that reduced fecal diversity of Bacteroidetes in pregnancy is associated with increased risk of atopic eczema in their young children gives further support for a

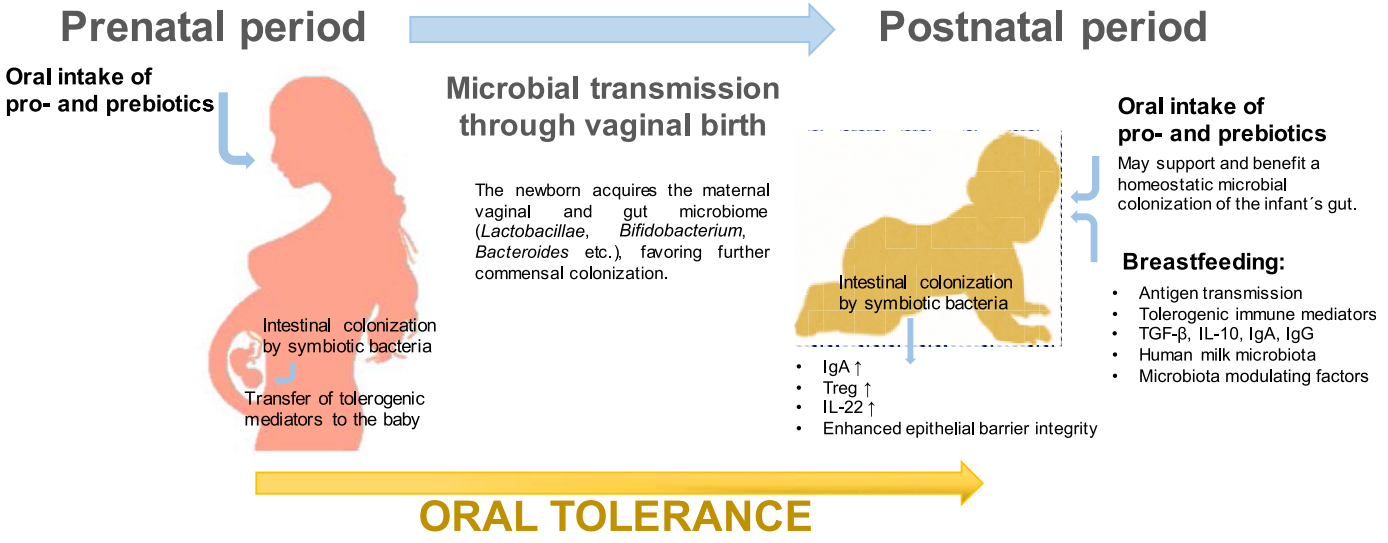

Fig. 1. Possible prenatal and postnatal mechanisms for induction of oral tolerance. Pro- and prebiotics administration during pregnancy can influence mother's gut microbiome potentially resulting in transmission of tolerogenic mediators (such as regulatory cytokines, antibodies and growth factors) through the placenta instructing foetal immune system development. Following vaginal delivery, the newborn's gut acquires the maternal vaginal (including *Lactobacillae* and *Bifidobacterium*) and gut (*Bacteroides*) microbiome favouring initial microbial colonization. Postnatally, oral administration of pro- and prebiotics together with breastfeeding and high-fibre diet might support ongoing intestinal colonization by symbiotic bacteria (including *Clostridium* spp. and *Bacteroides fragilis*) sustaining the homeostatic host-microbiome relationship. This might in turn prevent intestinal inflammation and decrease susceptibility to food allergies by inducing mucosal IgA and regulatory T-cell (Treg) responses.