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OPINION: Primary prevention of allergy: will it soon become a reality?

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ABSTRACT

It is generally accepted that allergic diseases are not curable and not preventable, but mainly controllable using pharmacotherapy (i.e. symptomatic medication). Recent research, however, demonstrated that a number of specific interventions can lead to (partial) primary prevention of allergy, especially of atopic dermatitis (AD) and food allergy (FA). Three types of primary prevention strategies have been successfully studied: early administration of bacterial products (most studies are on probiotics), early moisturizing in infants at risk for AD, and early exposure to allergenic foods (peanut and egg). Results of these studies indicate that the stage might have been set. Surely, much more research needs to be done before advice can be given in clinical practice. This opinion article discusses the three types of beneficial interventions, and gives ideas for future research, which might show the way for better strategies in primary prevention of allergic diseases.

BACKGROUND

The increase of allergic diseases, such as asthma, rhinitis, atopic dermatitis (AD) and food allergy (FA), during the last decades seems to be greatly influenced by changes in life style, including in sanitation and hygienic practices, as recently reviewed by Platts-Mills (1). While the end of the twentieth century was hallmarked by an increase in mainly respiratory allergy (asthma, rhinitis) and AD, in recent years a second wave of increasing allergy has occurred, mainly in AD and FA, especially peanut allergy, while respiratory allergies have more or less reached a plateau-phase. This was elegantly covered in recent reviews by Prescott et al (2,3). Whether the second wave is a consequence of the first wave is still unclear (i.e. the children in the second wave are the children of the parents who made up the first wave), and needs further study, which might elucidate specific genetic patterns of allergy, involving epigenetic mechanisms and the role of microbiota.

In the past, prevention of FA was mainly focussed on avoidance of allergens, including allergenic food. More recently, however, it has been suggested that early exposure, rather than avoidance, might have a protective effect on the development of FA. Moreover, there is now evidence that airborne food particles, including peanut and egg, can predispose to

sensitisation through the skin in children suffering from AD, making complete avoidance of foods hard to achieve, sometimes impossible (1,4).

Generally, it is accepted that allergic diseases cannot be prevented (total breast feeding during 4 to 6 months is still the best) (5). However, recent studies on AD and FA have shown that a number of interventions might be the way to go in primary prevention, and it seems that opportunities and evidence is mounting. More studies are needed, but the stage might have been set, and the direction in which to go has become more obvious.

The aim of this opinion is to give an overview of important recent developments in primary prevention and to suggest future studies. In short, 3 types of interventions on primary prevention give preliminary evidence that primary prevention, or at least partial primary prevention, may soon become a reality. Improving the interventions (or combining the interventions) in new studies might result in better (near absolute) primary prevention.

The 3 types of studies are:

1. Studies on bacterial products
2. Studies on early moisturizing
3. Studies on early food exposure

Another field of great interest for primary prevention is immunotherapy (IT), mainly sublingual immunotherapy (SLIT) and oral immunotherapy OIT). IT can be specific, using allergens, or non-specific, using Th1 or regulatory T cell (Treg) stimulatory interventions. Combining the two might result in the strongest effect, as shown in an animal model (6). Unfortunately, till today, no human studies on early IT have been published, but there are indirect indications that IT, at least, deserves to be studied in primary prevention of allergy.

1. STUDIES ON BACTERIAL PRODUCTS

In a large number of studies the pivotal contribution of gut microbiota in the early development of both local and systemic immune maturation and programming has been documented (7). In view of differences that were found in perinatal colonisation patterns in

association with changing lifestyle, including “westernisation” of diet and increasing hygiene, research focus has been shifted towards the immunomodulatory effects of microbiota in the development of allergic disease. Therefore, the effects of beneficial bacteria (probiotics) or resistant starches (prebiotics) that selectively have a positive influence on the growth of beneficial bacteria, have been studied in a large number of allergy prevention studies (8). Although the focus initially has been on perinatal administration, there is an ongoing shift in studying the effect of microbiota through pregnancy (9).

In a large number of studies effectiveness of bacterial products in preventing AD was shown, through a variety of mechanisms (**FIGURE**) (10-12). Moreover, it looks like a mixture of probiotics is more effective than one single probiotic, as recently reviewed by Zuccotti et al (13). However, not all studies were positive, more data on probiotics than on prebiotics are available, and it is mainly probiotics started prenatally and in combination with breast feeding, showing the best effectiveness (14). In a recent study, effectiveness on AD was shown till the age of 6 years, however, without any impact on respiratory allergy (15). In 2015, the World Allergy Organisation concluded that using probiotics is recommended in pregnant women, breastfeeding mothers at high risk of allergy in their children, and infants at high risk of developing allergies, as there was evidence of benefit in prevention AD (8).

There is encouraging evidence that prebiotics are effective in preventing allergy (16). However, there are no definitive recommendations with regard to prebiotics, mainly because of limited number of studies and lack of conclusive evidence. There is scope for more research in this arena to understand how to optimise the usage of prebiotics in preventing allergic diseases (8).

Taken together, it is very likely that bacterial products, mainly probiotics, will become an established part of primary prevention of allergy. More studies are needed to refine the various applications of bacterial products. However, it is likely that bacterial products are very appropriate targets of research in primary allergy prevention (17).

2. STUDIES ON EARLY MOISTURIZING

Key features in the pathophysiology of AD are skin barrier genetic defects, such as filaggrin deficiency, and abnormal immune responses, in which the environment is strongly involved (18). The observation that there is a role for transcutaneous sensitization to allergens, and that AD is not present at birth, but has its onset in the first months of life, lead to the study concept of aiming to prevent AD through the creation of an artificial barrier on skin, restoring the skin barrier, by intensive moisturizing from birth (before the onset of AD) (4). Till today (September 2015), two studies on the subject have been published.

A multinational, multicentre (in US and UK), randomised controlled pilot trial of 124 neonates tested the efficacy of using emollients soon after birth in the prevention of AD (19). The intervention group consisted of term infants who were considered to be of high risk of developing eczema (i.e. one parent or sibling has/had physician diagnosed AD/asthma or allergic rhinitis). Infants of mothers who had taken probiotics were excluded. Parents in the intervention group were given a choice of 3 emollients - oil, a cream/gel or a skin barrier restoring ointment - for application daily until 6 months of age. The primary outcome was the feasibility of this approach in prevention AD. Filaggrin mutation testing was done evaluating the loss of four function mutations common in European populations. A statistically significant protective effect was found with the use of daily emollient on the cumulative incidence of atopic dermatitis with a relative risk reduction of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; $p = .017$). Even though this was the first randomised controlled trial showing evidence that full body emollient therapy from birth may prevent AD, the study had some shortcomings: the infants were not screened for any underlying allergic sensitisation, and the follow-up of the subjects is relatively short.

A similar study from Japan studied the daily application of an emulsion moisturizer in 116 infants of high risk of developing AD (first degree relative with AD) till 32 weeks of life (20). The primary outcome was the cumulative incidence of AD at 32 weeks of life with as a secondary outcome allergic sensitization based on allergen specific IgE against egg white. The authors concluded that daily application of moisturizer during the first 32 weeks of life was associated with reduced risk of AD, but without statistically significant effect on allergic sensitization.

Taken together, the two studies strongly suggest that regular emollient application from birth reduces the incidence of AD, at least during the first 6 months of life. However, there is a need for larger confirmatory trials, which was acknowledged by the authors of both trials. It is certainly possible that regular emollient application masked onset of mild AD and that discontinuation of regular moisturizing would cause a rebound increase of AD development. However, there's little or nothing to lose, as emollients are inexpensive, easy to apply, have little or no side effects, and at the very least, seem to reduce eczematous lesions during the first months of life.

3. STUDIES ON WEANING

Despite a number of prevention recommendations, FA has been increasing since the late part of 20th century, as mentioned earlier. The age of introduction of food seems to be of importance in the prevention and evolution of food allergy. Earlier recommendations in the West promoted food avoidance, but were later withdrawn as studies failed to show beneficial effects of avoidance measures (21). In one study it was found that the risk of peanut allergy was 10 times higher among Jewish children in UK, compared to Israeli children of similar ancestry, which was attributed to the early introduction of peanuts in the Israeli children (22).

The recent British LEAP study (Learning Early About Peanut Allergy) study, which is a very interesting and excellent study, involved 640 “high-risk” babies – defined as those with egg allergy, severe eczema, or both (23). The infants were assigned to two groups: those whose parents were to regularly feed them peanut and those whose parents were told to have their children avoid peanut altogether. The children, enrolled between the ages of 4 and 11 months, were given a conclusive peanut food challenge at age 5. At that age, on average, only 3.2 percent of the “consumption” group had developed a peanut allergy, compared to more than 17.2 percent in the “avoidance” group. They reported that in the peanut consumption group, at a high risk of developing allergy, showed a reduction of the odds that a peanut allergy will develop by a remarkable 70% to 80%. The results of the study have huge implications on the early introduction of allergic foods in order to prevent FA. The American Academy of Allergy, Asthma and Immunology (AAAAI) and others already

implemented the study in their new guidelines on allergy prevention (24). The study only has a few minor weaknesses: it was an open labelled trial which did not incorporate a placebo regimen and only high risk, symptomatic infants were enrolled into the study, which makes it non-justified to extrapolate its results to the general population, or a population at risk, in particular to the Asian subcontinent. Therefore, more data on the subject are certainly desirable.

Another randomised controlled study from Australia evaluated early introduction of egg in high risk infants with AD (egg was introduced daily from age 4 to 8 months), looking at the timing of egg introduction into the infant's diets, and whether it was related to egg allergy in early childhood (25). A high proportion (31%) of infants randomized to receive egg had an allergic reaction to the egg powder and did not continue powder ingestion. At 4 months of age, before any known egg ingestion, 36% of infants already had egg-specific IgE levels (> 0.35 kU/L). The authors concluded that children introduced to egg in the first 12 months of life were 51% less likely to have a confirmed or suspected egg allergy at one year of age (5.2% vs. 11.5%, RR 0.49, 95% CI, 0.25 to 0.97, $p<0.05$) and 48% less likely to have a confirmed or suspected egg allergy between one and three years of age (7.0% vs. 14.5%, RR 0.52, 95% CI, 0.28 to 0.98, $p<0.05$). Egg exposure in the first year of life did not predict egg sensitisation (i.e. a positive skin prick test to egg) at any age. There was also no significant association between egg exposure in the first 12 months and AD with egg sensitisation at either one year of age or at one or three years of age.

Even though both the studies have implications on the early introduction of allergic foods in order to decrease allergic sensitisation, it is noted that both studies were performed in well-defined high-risk infants (and not in infants at risk, but without symptoms), and it might be that generalization of the results is not recommended for the moment.

It is also worth mentioning that breast feeding is still first choice in preventing allergy, and that studies are needed to improve the anti-allergic effects of breast milk, which seem to be dependent of immunomodulating substances, including TGF- α and IgA (26) The role of hypo-allergenic (HA) milks (i.e. extensively or partially hydrolysed) in primary prevention also needs further attention and more study, and is another interesting field of research

(especially in mothers who are unable to breastfeed), as suggested by their preventive effect upon AD in the GINI study and in others (27,28).

4. IDEAS FOR FUTURE STUDIES

It seems that, for the moment, there are three different approaches (i.e. administration of probiotics, early moisturizing, and early exposure to allergenic foods) that might have, at least partially, a preventive effect on allergic sensitization, mainly on AD and on FA. However, results of the studies, mainly of the weaning studies, cannot be generalized, which includes extrapolation to at risk infants who are still symptomfree, or extrapolation to other foods. Based on the three approaches, more studies are needed before applying in daily practice. Furthermore, it is very unlikely that one intervention (or even a combination of interventions) will be the optimal intervention for all newborns, having different genetic profiles, and different degrees of allergic constitution. Therefore, it is expected that, in the future, different preventive recommendations will become available, which will be tailored on the allergic genotype of the baby (i.e. from no allergy to extremely allergic, with different degrees in between). Moreover, combining the 3 approaches might lead to a more successful intervention. Ideas for future studies could be:

- On bacterial products (probiotics, prebiotics, synbiotics)

1. Comparative studies on optimal dose, duration, onset and type of probiotic. Perhaps probiotics need to be started earlier in pregnancy (from the onset?), as the dynamics of the own microbiota, changing from the beginning of pregnancy, have been shown. Especially, the phyla Actinobacteria (which includes Bifidobacteria) and Proteobacteria seem to undergo a significant distributive change in the last trimester of pregnancy, and it could be that focussing on Bifidobacteria is a better way to go (29). Unfortunately, there are no comparative studies of microbiota during pregnancy between allergic and non-allergic women.

2. Studies on combining probiotics with other preventive interventions, such as in combination with early moisturizing and/or tailored weaning procedures (even with early IT).

- On early moisturizer

The idea of early moisturizing preventing AD is a very appropriate idea for more research. Moreover, it seems to be a safe intervention. However, before recommending this intervention in daily practice, better studies are needed: studies with longer follow-up, and in which allergic sensitization is assessed. It would also be of interest to perform studies with moisturizers containing bacterial products, or in combination with oral probiotics (30).

- On weaning to food

The two studies that were discussed were performed in a specific allergic phenotype of infants (i.e. infants with AD and allergic sensitization). More studies are needed, especially in infants at risk (but non-symptomatic) from allergic families. Weaning procedures in different types of allergic children (with and without eczema), and with other allergenic foods (such as cow's milk) also deserve further study. In one study, it was found that early exposure to cow's milk, as a supplement to breast feeding, might promote tolerance to cow's milk (31).

5. ON EARLY IMMUNOTHERAPY

Studies on early IT deserve an important place in research on primary prevention, but, unfortunately, have not been performed till today for a number of reasons, including ethical issues, and issues of safety and feasibility. In a large number of studies effectiveness of IT has been shown in children and adults suffering from asthma, rhinitis and food allergy, and in a few studies IT was effective in children with AD (32). In a limited number of studies, it was shown that IT is also able to prevent new sensitizations in children, which, therefore, makes it a suitable candidate for primary prevention (33). Furthermore, sublingual IT (SLIT) has an excellent safety profile, and is a child-friendly way of administration (34). Oral IT (OIT) also is becoming more and more an established treatment, mainly for FA, such as peanut allergy, although has a less favourable safety profile than SLIT (35). In a recent study from Australia, a combination of OIT and probiotics was shown to have a success rate exceeding 80%, highlighting the favourable effect of combining anti-allergic treatments (36).

Research on IT for infants, as a primary preventive intervention, should only be considered if optimal conditions of safety and feasibility are fulfilled. Both injection (subcutaneous) IT and OIT have too many potential side effects, while SLIT is not feasible for infants (no infant can keep an extract under the tongue, unless it is glued or rubbed).

Transcutaneous (or epicutaneous) IT, on the other hand, could become a candidate in primary prevention, as it is effective, has a good safety profile, and is suitable for infants (37). However, for the moment, no studies in infancy have been performed. In a murine model, it was shown that epicutaneous IT prevents sensitization to new allergens through a Treg cell-dependent mechanism (38).

Apart of allergen IT, non-specific IT, using Th1 or Treg cell stimulants, such as bacterial antigens, should also become a subject of research in primary prevention. One example is the anti-inflammatory and inhibitory effect on RSV replication of the golden needle mushroom (*Flammulina velutipes*) (39).

In research on IT, the adjuvant effect of helminths or helminthic proteins, as immunomodulating agents, deserves further study, as it was found that in early life helminths are able to induce strong regulatory mechanisms. In a clinical study, anti-helminthic treatment of Ugandan mothers increased the prevalence of infantile AD and wheezing compared with seen in a placebo-controlled group (40). Straubinger et al. have shown that immune responses provoked by worm infections in a pregnant mouse model, protect offspring against the development of allergic airway inflammation after birth, and found that INF-gamma was crucial in this process (41). The studies on the modulating role of helminths in allergy are of great interest, and might provide new approaches of primary prevention. It would certainly be worthwhile to study the additive effect of helminths in an IT study in early life or in pregnant allergic women.

6. RESPIRATORY ALLERGY: not preventable soon?

Primary prevention of allergic asthma and allergic rhinitis still has a long way to go. Previous studies on early avoidance of inhalants, such as house dust mite, have largely failed or only showed borderline results, as reviewed by Martinez (42). This seems to be due to the huge

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role of respiratory viruses, such as rhinoviruses and respiratory syncytial virus, in the onset of asthma, even in the onset of allergic sensitization (43). Recent studies have shown that asthma is the consequence of an initial viral insult enhancing immune responses to allergens, mainly in subjects predisposed to Th-2 type of responses. New evidence suggest that, in early life, complex interactions occur between viral respiratory infections and aeroallergen sensitization in genetically susceptible subjects (i.e. overlapping inflammatory reactions), triggering immune responses and airway inflammation that are characteristic of persistent asthma (43). Martinez suggested that primary prevention of asthma might become possible through bacterial products, such as oral lyophilized extracts of respiratory bacteria, based on studies in children raised on farms, showing a diminished asthma prevalence during school years, which might be due to activation of regulatory T cells (42). In parallel with this, Larsen et al. found an abnormal immune response to pathogenic bacteria colonizing the airways in early life in children suffering from asthma at school age, highlighting the role of early bacterial immune responses (44). However, scientific data on this postulation are still not available, and it might be that more intense or combined interventions will be needed to prevent allergic asthma, such as preventive usage of anti-viral treatments, including specific anti-viral antibodies and vaccinations.

DISCUSSION AND CONCLUSION

Recent research on primary prevention of allergy has revealed that certain, specific interventions are, at least, partially successful in preventing allergy, mainly AD and FA (TABLE). It seems we now have the availability of feasible tools that might show us the way on how to prevent certain types of AD and FA. This is in contrast with aims to prevent respiratory allergy, such as asthma and rhinitis, for which prevention seems to be harder to achieve, and is still far away, mainly because of the central role of respiratory viruses in its onset.

Time has come now to build on obtained results, and to set up new and more robust studies, based on current knowledge. Three types of intervention have been shown to be successful: usage of bacterial products (mainly probiotics), early moisturizing, and targeted weaning interventions. Although the studies were not perfect, at least, they showed the

way. Combining interventions could now be the next research phase to set up. Finally, adding new approaches, such as the usage of IT, or immunomodulatory interventions, might result in better outcomes.

Taken together, it looks like certain types of AD and FA will be preventable soon, which might diminish or even halt the onset of the Allergic March in a number of children, and thereby indirectly preventing asthma and rhinitis. Perhaps the right way to go now is to focus on FA and AD, and less on asthma and rhinitis. Perhaps future studies on primary prevention of AD and FA will teach us how to set up research in primary prevention of asthma and rhinitis.

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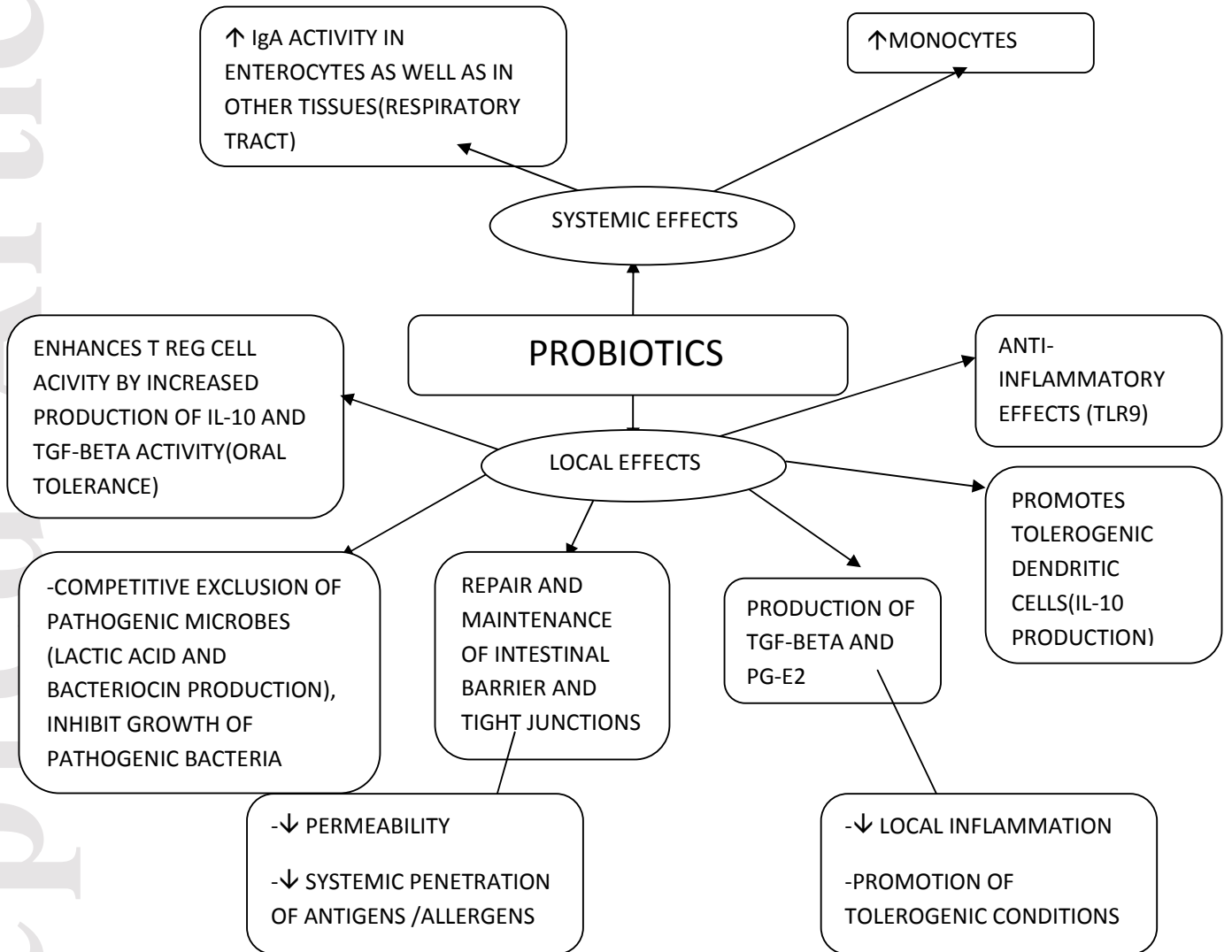
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FIGURE: Mechanisms of probiotics in allergy



Inspired by Prescott and Björkstén B (2007) and on Bermudez-Brito M, et al, 2012.

Table: Primary prevention of allergy (mainly for AD and FA)

INTERVENTION	EFFECT
1. Breast feeding during 4 – 6 months	To all infants (especially those at risk for allergy)
2. Probiotics (best is to start during pregnancy, and to continue in combination with breast milk)	Prevents AD (might prevent FA) no effect on respiratory allergy (asthma – rhinitis)
3. Early moisturizing	Prevents AD (in short follow-up studies)
4. Early introduction of peanut - egg	Prevents FA (in specific at risk infants)
5. Extensively or partially hydrolysed formula	In cases where breast feeding is impossible. Prevents AD and cow's milk allergy (more evidence is needed)
<i>FUTURE RESEARCH</i> 1. Combination of interventions 2. Exploring the role of early IT 3. Exploring the role of immunomodulatory treatments (helminths, bacterial products) – in combination with IT.	