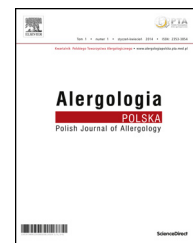


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Review/Praca pogładowa

Probiotics for the prevention of atopic dermatitis and other allergic diseases: What are the real facts?



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ARTICLE INFO

Article history:

Received: 20.08.2017

Accepted: 28.08.2017

Available online: 05.09.2017

Keywords:

- Probiotics
- Synbiotics
- Prevention
- Atopic dermatitis

ABSTRACT

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases diagnosed all over the world. The course of this complicated disease is chronic and relapsing and there have been many variants both endogenic and phenotypic already described and despite of our better understanding of AD we have no well “structured” therapeutical approach to many of our patients. Mainly because we do not understand it in an adequate way and complexity of treatment must be highly individualized. Recent studies suggest prevention of AD can be achieved through early intervention to protect the disturbed skin barrier. While the skin lesions are developed AD requires appropriate control of local and systemic immune activation for optimal management which obviously may cause the whole variety of adverse events. Therefore it seems that early intervention might improve long-term outcomes of AD and reduce the risk of development of systemic sensitization that leads to associated allergic/atopic diseases within the gastrointestinal and respiratory tract. For some time probiotics have been suggested as an intervention to prevent allergic diseases such as AD. Therefore besides many publications, a systematic review of randomized trials assessing the effect of any probiotics administered to pregnant women breast-feeding mothers, and/or infants have been analyzed in this review paper in order to state what is the “real truth” about this type of preventive approach.

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Introduction

Atopic diseases are on increase and cause more and more burden on health care because of potentially life threatening

acute allergic reactions, reduced quality of life and relatively high direct and indirect costs, [1–3]. Atopic dermatitis (AD) often precedes the development of food allergy, asthma and allergic rhinitis. Recent insights into AD reveal abnormalities in the terminal differentiation of the epidermal epithelium

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<http://dx.doi.org/10.1016/j.alergo.2017.08.001>

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leading to a defect stratum corneum, which allows enhanced allergen penetration and systemic IgE-sensitization. Atopic skin is also predisposed to colonization or infection by pathogenic microbes, mainly *Staphylococcus aureus* and simplex virus. Causes of abnormal skin barrier structure and function are highly complex and driven by a combination of genetic, environmental and immunologic factors [4]. These factors likely account for the heterogeneity of AD onset and the severity and natural history of this fascinating skin disease. Recent studies suggest prevention of AD can be achieved through early intervention to protect the skin barrier. It seems that early intervention might improve long-term outcomes for AD and reduce the systemic sensitization that leads to associated diseases of atopic characteristics [4].

At the same time the composition of skin and gastrointestinal microbiota have driven attention of many researchers working in the field of prophylactic measures in AD [5]. It seems that the composition of gastrointestinal microbiota has been postulated to play an important role in the development of allergy because it promotes potentially antiallergenic processes: Th1-type immunity generation of TGF. Which is known to be a strong suppressor of Th2-induced allergic inflammation and induction of oral tolerance), as well as IgA production, an essential component of mucosal immune defense [6]. The relatively new gut microbiota hypothesis suggests that alternations within those microbiota, the early and highly massive source of microbial exposure, might underline the contemporary allergic epidemic.

Up till now publications concerning this problem were either evaluating individual outcomes or are already outdated. The most recent reviews on prevention do assess the use of probiotics individually on the outcomes of sensitization [7] asthma [8] and atopic dermatitis [9]. These studies have proven a modest reduction in AD, and provided evidence of a mild effect in reducing sensitization. On the other hand for other types of allergic diseases there are insufficient data to provide any real conclusions.

A Cochrane systemic review [10] was published more than 7 years ago and therefore it seems to be tempting to analyze the new data released in the last years.

Questions to be asked:

1. Should supplementation of probiotics versus no such supplementation be used in pregnant women to prevent development of allergy in their children?
2. Should supplementation of probiotics versus no such supplementation be used in breast-feeding mothers to prevent development of allergy in their children?
3. Should supplementation of probiotics versus no such supplementation be used in infants to prevent development of allergy? [5]

What do our patients think?

- In case of AD most of the patients or the parents of AD children are sure that the disease is related to the food allergy. Very often this is not only the question of parents' idea but also, unfortunately doctors who diagnose AD in all children presenting with inflammatory skin problems localized within the facial location. In general such children are immediately put on a strict elimination diet, without any logical supplementation and the gut microbiome is even more "confused" than before.

- Later on, seeing no improvement after administration of the elimination diet patients consult with the dermatologist (usually pediatricians, general doctors and allergologists take care of AD/not AD children) and the whole structure of complex treatment approach is being changed.
- Patients/parents of AD children sometimes have some knowledge about the proper supplementation of the diet but in general it is of a very "poor" quality.
- Patients/parents of AD patients are confused and often misunderstand the term PROBIOTIC, PREBIOTIC and SYMBIOTIC

What is the daily practice?

- Information provided by doctors are not of a "good quality"
- Very often these information are misleading and unclear
- Not all probiotics are the same and patients should be informed about it
- The pharmaceutical market is "overloaded" with probiotics of inadequate quality
- Parents of patients suffering from AD spend a lot of money for treatment of the disease and on "top of the bill there are probiotics", which also costs
- There is not enough data to state that probiotics will stop development of any allergy or allergic disease at the moment (although the logic is behind) and more studies are necessary
- There is much more to be done in terms of research and clinical observations before we can draw the final conclusion

What are the real, true data?

The last systematic review and meta-analysis of randomized controlled trials on the topic of "Probiotics for the prevention of allergy" has been published in 2015. Considering the fact that the microbiome/microbiota of skin and gut are very much under research at the moment, there may be some different opinions coming soon. Anyhow, we would like to present the data which have been carefully analyzed and should be taken into consideration in our practical, clinical performance as specialists in the field of allergology [5].

2403 unique bibliographic citations have been identified, of which 178 have been selected for full-text assessment comparing at least 1 probiotic with placebo and obviously meeting the inclusion criteria [11-35]. Different populations, and periods when probiotics were administered (e.g. during pregnancy only or during pregnancy and breast feeding) have been analyzed.

All necessary details and tables are available in the original paper and due to the so will not be presented in this paper. We will only concentrate on the conclusions driven from this interesting review and point out some "dangerous points", which might be confusing for the allergologist with no dermatological speciality.

Conclusions and summary

This systematic review revealed that supplementation with probiotics during pregnancy, in breast-feeding period or in infants decreases the risk of eczema (including AD) in infants. And here comes the first confusion: **What is eczema?**

- AD presents classical clinical pictures of eczema, but there is a wide variety of eczematous skin lesions which might be similar to AD although being something completely different. Therefore here we can see the first possibility of making a mistake influencing the results.

“However the certainty in the evidence is very low because of the risk of bias across trials, indirectness of the evidence inconsistency of results among studies and imprecision of the pooled estimates...” [5]. Therefore we should be very careful with our interpretation of this review paper.

Concerning other diseases and allergy itself there was no evidence suggesting that supplementation of probiotics may reduce the possible risk.

Adverse events were mild and similar in all investigated populations.

But there is so much logic behind in terms of gut microbiota and prevention of AD. Obviously more, properly designed studies are necessary as well as better probiotics composed of carefully selected ingredients.

The key messages of this systematic review is as follows:

- Probiotics given to pregnant women, breast-feeding mothers, and/or infants reduced the risk of eczema in infants.
 - VERY WEAK EVIDENCE!
- Currently available evidence does not indicate that probiotics prevent the development of other allergies.
 - ATOPIC DERMATITIS IS NOT ALWAYS ALLERGIC!
- Design of future studies should consider the weaknesses identified regarding the risk of bias and indirectness of the evidence.
 - ABSOLUTELY OBVIOUS!

Considering the whole content of this review one should be very careful in drawing conclusions and in our opinion at the moment probiotics should not be really considered currently as a prophylactic measure, at least in terms of AD.

Anyhow, as mentioned before we are clearly sure that gut microbiota plays a very important role in the development and the course of AD. Obviously there is such a variety of types of the disease that not in all cases this might be successful, but recently it has been noticed that **synbiotics in AD might be of a great value.**

In *Dermatology News* from February 2016 a meta-analysis of 8 studies involving nearly 1700 children have been performed. Investigators analyzed the SCORAD index in 6 treatment studies involving 369 children, and the relative risk of AD in 2 prevention trials involving 1320 children.

The results obtained in the treatment studies were as follows:

- Change in SCORAD index in those treated with synbiotics at 8 weeks was –6.56.
- Heterogeneity was significant
- Significant effect was seen only when using mixed strains of bacteria (average score difference –7.32), and when used in children aged 1 year or older

In the prevention studies, those taking synbiotics were 56% less likely than those taking placebo to develop AD.

These results are highly interesting and for sure further studies will make this interesting issue more clear for all of us, patients and doctors.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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