

---

# The implications of nomenclature

Sten Dreborg, MD, PhD

---

**Background:** To be able to draw the right conclusions from clinical research, it is essential that words have the same meaning to all researcher and clinicians.

**Objective:** To present the new nomenclature for allergy and discuss its influence on conclusions drawn from clinical studies with one example illustrating that conclusions change with the use of definitions and nomenclature.

**Methods:** To review one recent study at odds with the new allergy nomenclature. Atopy is defined as a personal or familial tendency to produce immunoglobulin (Ig)E antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis. Allergy is defined as a hypersensitivity reaction initiated by immunologic mechanisms and divided into IgE-mediated and non-IgE-mediated allergy. What has been called atopic diseases, eg, infantile eczema, can be caused by both IgE-mediated allergy (atopy) and non-IgE-mediated mechanisms. In the study, two groups of mothers/infants were given either *Lactobacillus* GG or placebo with the incidence of infantile eczema as primary outcome parameter.

**Results:** The study analyzed concludes that probiotic bacteria supplied to mother and child prevents infantile eczema development caused by both IgE-mediated (atopy) and non-IgE-mediated allergic mechanisms. The study also shows that IgE sensitization was similar in the two groups. Thus, "atopic disease" was prevented (subjective evaluation), whereas atopy, ie, IgE induction was not prevented.

**Conclusions:** Nomenclature is of utmost importance to interpret results in allergy research. If preventive measures, such as oral treatment with *Lactobacilli*, have an effect, this should be tested against a single mechanism of disease rather than against a disease caused by several mechanisms. However, in the study *Lactobacilli* are said to prevent atopic disease, and also that *Lactobacilli* do not hinder development of IgE sensitization, one of the mechanisms causing this disease.

Ann Allergy Asthma Immunol 2002;89(Suppl):83–85.

## INTRODUCTION

The definition of atopy, atopic disease, and allergy has been changing over the years. To reach a consensus on the nomenclature, European Academy of Allergology and Clinical Immunology (EAACI) formed a Task Force on Nomenclature, which has been working for some years. The results of that work were presented this year in the journal *Allergy*.<sup>1</sup> In summary, we defined some terms of great importance for future work as given in Table 1.

The connection between hypersensitivity, allergy and immunoglobulin (Ig)E-mediated allergy and atopy is illustrated in Figure 1.

Atopy means a tendency to produce IgE antibodies. However, it must be stressed that not all diseases in which IgE is present are not atopic. Some examples are helminth infestation, eg, ascaris and *Schistosoma* infestations; virus infections, eg, cytomegalovirus, "chemicals," eg, tobacco smoke; "superantigens," eg, staphylococcal enterotoxins, graft-versus-host disease, and Wiscott-Aldrich syndrome.

There have been two difficulties during the discussions:

1) Atopic dermatitis. We felt it most important to rename *atopic atopic* dermatitis and *nonatopic atopic* dermatitis, as

the word "atopic" involves the involvement of IgE. The disease can not be both atopic and especially not nonatopic but called atopic! The present solution for the time being is to call the disease atopic eczema/dermatitis syndrome (AEDS).

2) To convince clinicians to restrict the qualifier atopic to cases with proven IgE antibody mechanism. There are many papers on the natural course of atopy, the atopic march, epidemiologic studies on risks for different groups of children with "atopic disease" and intervention studies evaluating symptoms, ie, clinical signs of so-called "atopic diseases" rather than atopy. Many of these papers do not define atopy the way we<sup>1</sup>, or Jack Pepys, did in 1974,<sup>2</sup> by failing to ask for proof of an IgE-mediated disease/reaction. Thus, this group of clinically defined diseases can not be called atopic, but allergic diseases, because they are all allergic, as we defined it, including both cases with IgE antibody involvement and cases with other less well defined mechanisms (Fig 1).

In asthma or AEDS without IgE antibody involvement, the pathology is the same as in a case when IgE is involved.

## METHODS

To illustrate the difficulties involved in the evaluation of otherwise excellent clinical research, I will discuss an example from the allergy field. I will discuss the role of the so-called probiotics, ie, foods thought to modify the immune response, in a paper that is outside the new EAACI nomenclature for allergy.

---

Lerum, Sweden.

This article is based on the recent EAACI position paper.

Received for publication April 30, 2002.

Accepted for publication in revised form June 10, 2002.

Table 1. Definitions According to the EAACI<sup>1</sup> Position Paper

|                              |                                                                                                                                                                                                                                         |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hypersensitivity             | "Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects"                                                                                |
| Allergic hypersensitivity    | Because of immunologic mechanism                                                                                                                                                                                                        |
| Nonallergic hypersensitivity | No immunologic mechanism involved                                                                                                                                                                                                       |
| Allergy                      | Allergy is a hypersensitivity reaction initiated by immunologic mechanisms                                                                                                                                                              |
| IgE-mediated allergy         | IgE antibodies are involved in the reaction                                                                                                                                                                                             |
| Non-IgE-mediated allergy     | IgE antibodies are not involved in the reaction, which is caused by cell interaction, IgG, etc                                                                                                                                          |
| Atopy                        | Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins and, as a consequence, to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis |
| Atopic disease               | Diseases caused by IgE antibodies in atopic individuals. Thus, some cases of asthma and eczema in children are not atopic. Asthma, rhinoconjunctivitis, and AEDS (AD) should not be lumped together                                     |
| Atopic eczema                | Atopic eczema/dermatitis syndrome (AEDS) = earlier called atopic dermatitis (AD)                                                                                                                                                        |

## Analysis

Last year, Erika Isolauri et al<sup>3</sup> published an interesting study in *The Lancet*. In that study they found convincing evidence that probiotic *Lactobacilli* GG prevented the development of atopic dermatitis/eczema syndrome (AEDS), ie, the clinical entity as defined by clinicians, in this case Dr Kalliomäki.<sup>3</sup>

However, atopy was not prevented. Instead, they found no difference between mothers/children taking *Lactobacilli* GG capsules and not regarding the formation of IgE antibodies as measured by radioallergosorbent and skin prick tests (Table 2). Thus, probiotic food protects children from "infantile eczema," ie, AEDS, but not from atopy, ie, IgE antibody formation, one of two or more mechanisms causing AEDS.

## DISCUSSION

This approach can be used with many other papers within the area of allergy. The paper cited is just a recent one that has raised questions.

There are many research questions that can be raised when considering the difference between atopic and nonatopic and allergy subgroups, eg:

1) Are the so-called atopic diseases without IgE involvement predominantly reduced in children given probiotics, as IgE sensitization is not prevented?

2) Is there a link between IgE-mediated AEDS in infants with more urticarial presentation in some cases and the AEDS in preschool children and adults with the typical features of AEDS?

3) It is a clinical fact that some children with asthma appear to be nonatopic but after some years develop IgE antibodies and clinical reactions to pollens, mites, and animal dander? With the new nomenclature they will be regarded as nonatopic but as allergic who turn into atopic. Thus, they will be classified differently at different ages. But are several mechanisms involved or is it only our diagnostic tools that should be refined?

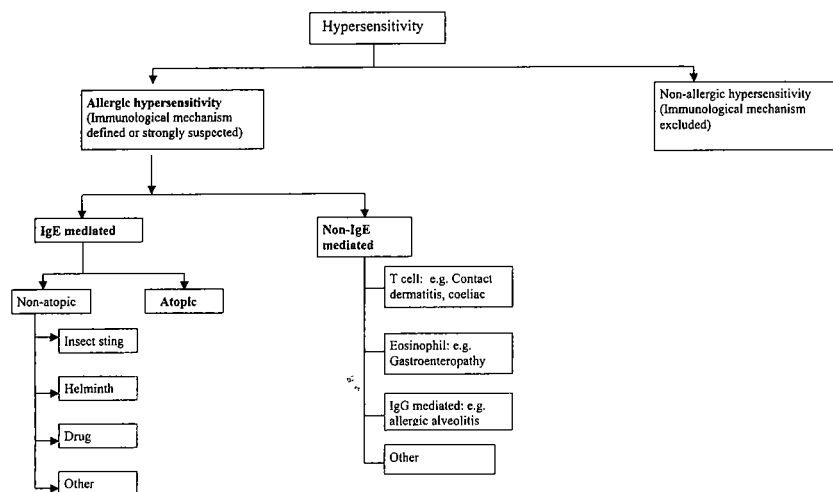


Figure 1. Hypersensitivity and its subgroups. It should be noted that all allergic IgE-dependent diseases are not atopic according to the proposed nomenclature. Further, all allergic diseases are not atopic but depend on other mechanisms.<sup>1</sup>

Table 2. Total IgE and Cow's Milk Specific IgE Antibodies in 2-Year-Old Children

| At 2 years of age          | Placebo (n = 68) | <i>Lactobacillus</i> GG (n = 64) | P                      |
|----------------------------|------------------|----------------------------------|------------------------|
| Total IgE (kU/L) > + 1 SD  | 32.7 (22.6–47.3) | 31.3 (22.8–43.0)                 | 0.85 <sup>†</sup> test |
| ≥1 RAST result > 0.35 kU/L | 16/64 (25%)      | 17/62 (27%)                      | 0.76 <sup>×2</sup>     |
| ≥1 SPT reaction > 3 mm D   | 9/65 (14%)       | 11/61 (18%)                      | 0.52 <sup>×2</sup>     |

In vitro and skin prick tests were administered to 2-year-old children given either *Lactobacillus* GG or placebo. No significant differences were found.<sup>3</sup> RAST, radioallergosorbent test; SPT, skin prick test.

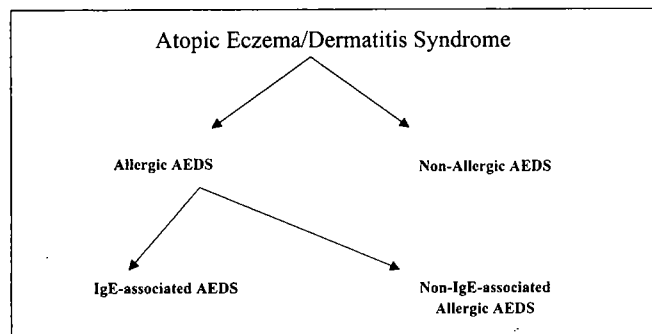


Figure 2. The revised nomenclature applied to AEDS

4) In most published trials, atopic and atopic disease are used interchangeably. This is confusing, as the so-called atopic diseases are probably caused by different mechanisms in different individuals and maybe also depend on different mechanisms in the same individual at different ages.

5) Are those who do not respond with IgE but are with an atopic disease at risk of developing other atopic diseases—with or without atopy?

6) Is there a progression over time from IgE-mediated allergy to cellular mechanisms both in AEDS and airway atopic diseases, explaining that pediatricians find more atopic children than do chest physicians?

7) Sensitization, ie, induction of IgE antibodies, does not mean disease, but sensitization at an early age indicates future atopic disease.<sup>4,5</sup>

By correctly using the terminology, we will learn more for epidemiologic and genetic studies but also from intervention studies, as shown by the Finnish group.<sup>3</sup>

## CONCLUSION

In the future it will be important to use the proposed nomenclature.<sup>1</sup> Vague classification on the basis of vague symptoms can but entangle scientific exchange. Only by strictly classifying each case is it possible to improve on current knowledge. Therefore, it is of the greatest importance that chairmen of scientific sessions and editors of scientific journals support the correct use of the new nomenclature.

## REFERENCES

1. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813–824.
2. Pepys J. Atopy. In: Gill PG, Coombs RR, Lachmann P, editors. *Clinical Aspects of Immunology*. Oxford: Blackwell Scientific, 2002:877–902.
3. Kalliomäki M, Salminen S, Arvilommi H, et al. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357:1076–1079.
4. Hattevig G, Kjellman B, Johansson SG, Björkstén B. Clinical symptoms and IgE responses to common food proteins in atopic and healthy children. *Clin Allergy* 1984;14:551–559.
5. Nickel R, Kulig M, Forster J, et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997;99:613–617.

Requests for reprints should be addressed to:

Sten Dreborg, MD, PhD

Alingsåsvägen 11

SE-443 35 Lerum, Sweden

E-mail: sten.dreborg@telia.com